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REVIEW

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SGLT2 Inhibitor: an Emerging Pillar in Heart Failure Therapeutics?

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ABSTRACT

Heart failure (HF) is a worldwide pandemic that affects at least 26 million people and is becoming more prevalent. Heart failure health expenditures are substantial and will considerably increase with population aging. Newer medications for treating type 2 diabetes include sodium-glucose cotransporter-2 inhibitors (SGLT2). Recent clinical studies and research have shown the efficacy of this class in treating heart failure by lowering the risk of cardiovascular events, hospitalization, and mortality. In addition, there is undeniable evidence that SGLT2 inhibitors have a beneficial effect on metabolic function, even though the mechanisms responsible for these drugs' practical consequences have not been completely elucidated. In this narrative review, we discuss the effects of SGLT2 inhibitors on the provision of cardiac energy by ketone bodies, pathological remodeling of the ventricle, arterial stiffness, and inflammation in patients with HF.

Keywords: heart failure, SGLT2 inhibitors, cardiovascular disease.

INTRODUCTION

Heart failure (HF) is a significant healthcare issue associated with high resource utilization and cost of care. Although HF incidence has remained stable or slightly decreased, its prevalence is increasing due to improved HF treatments and longer life expectancy. Despite significant improvements in HF treatments, morbidity and mortality remain elevated. Even though cardiovascular (CV) mortality is declining over time, it remains the leading cause of death in HF patients (1). In the 2019 Heart Failure Association (HFA) ATLAS study, the median prevalence of HF was estimated to be 17 *per* 1000 people in 13 European countries that supplied data, ranging from 12 *per* 1000 people in Greece and Spain to >30 *per* 1000 people in Lithuania and Germany (2).

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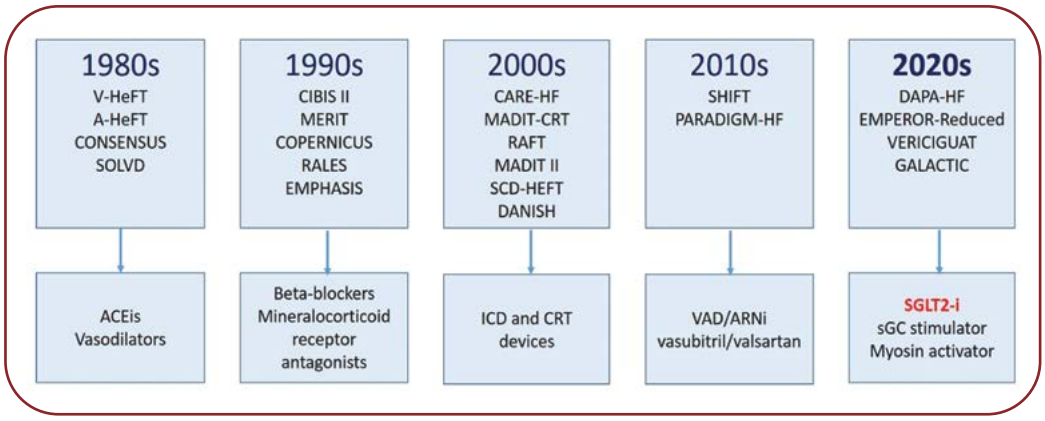

FIGURE 1. Evolution of the treatment of Heart Failure with reduced ejection fraction. (ACEi=angiotensin-converting enzyme inhibitor; ICD=implantable cardiac-defibrillator; CRT=cardiac resynchronization therapy; VAD=long-term ventricular assist device; ARNi=angiotensin receptor-neprilysin inhibitor; sGC=soluble guanylate cyclase)

Pharmacotherapy remains the cornerstone of HF treatment, and several powerful new therapeutic opportunities have recently emerged, including angiotensin-neprilysin receptor inhibitors (ARNi), sodium-glucose cotransporter-2 (SGLT2) inhibitors, omecamtiv mecarbil (INN) and vericiguat. However, SGLT2 inhibitors have arguably provided the most impressive and consistent benefits across the HF spectrum, coupled with an exceptional safety profile (3). Consequently, SGLT2 inhibitors are now considered one of the four foundational drugs for managing HF in patients with reduced ejection fraction (HFrEF) (4). Moreover, its efficacy is currently being investigated over a wide range of ejection fraction (EF). Figure 1 provides a visual representation of the most critical research and chronological order of events that have shed light on these drugs' effects on HFrEF.

SGLT family

Initially, SGLT2 inhibitors were developed as diabetes treatments. Yet, they have acquired broad usage not just as a drug with the potential to reduce blood glucose but also for their unique kidney protective actions, improvement in cardiovascular (CV) outcomes, and other physical benefits. Long-term SGLT2 inhibition generated a consistent 20% to 25% lowering in the combined risk of CV death or hospitalizations for HF in 12 large-scale trials involving >70,000 patients (5).

This drug class derives its name from its pharmacological target, "the SGLT2". Sodium-glucose cotransporter is a membrane protein that can transport sodium ions (Na^+) and glucose into cells. There are six types of SGLT in humans; types I and II are primarily responsible for glucose absorption. SGLT1 is located mainly in the intestinal mucosa. It facilitates galactose absorption, whereas SGLT2 is primarily located in the proximal tubule of the renal nephron and is responsible for 90% of renal glucose reabsorption (6-7). These drugs were initially derived from the apple tree bark compound phlorizin (phloretin-2-B-glucoside), a non-selective competitive inhibitor of the SGLT2 protein, initially known for its anti-malarial activity (8). SGLT2 inhibitors were first developed in Japan in 1996 as analogs of phlorizin (*i.e.*, 4'-dehydroxyphlorizin).

Synthetic analogs of phlorizin with increased selectivity for SGLT2, a longer half-life (>12 hours) and enhanced oral bioavailability were developed. This class of antihyperglycemics is distinct from all others in that they have a significant glucose-lowering effect independent of insulin (8-9). These drugs can be used in monotherapy or in combination with other hypoglycaemic agents.

We intend to summarise the underlying molecular mechanism of these impacts. ❑

MECHANISMS TARGETED BY SGLT-2 INHIBITORS

Blood pressure

In individuals with T2DM, SGLT2 inhibitors have been shown to reduce systolic blood pressure (SBP) by 2.46 mm Hg and diastolic blood pressure (DBP) by 1.46 mm Hg (10). Likewise, ambulatory blood pressure monitoring supported these findings, demonstrating that SGLT2 inhibitors caused a substantial reduction in 24-hour systolic blood pressure by 3.76 mm Hg and 24-hour diastolic blood pressure by 1.76 mm Hg compared to the controls (11).

Recent research indicates that SGLT2 inhibitors reduce SBP by 1.68 mm Hg in patients with

HF but have no effect on DBP levels (12). As a result, the diuretic and natriuretic effects of SGLT2 provide beneficial effects on the CV system. These benefits include a reduction in blood volume, a reduction in blood pressure, and an improvement in ventricular load. However, in the meantime, it regulates the central nervous system and influences the paraventricular nucleus of the hypothalamus, which both contribute to it affecting the CV system.

Volume regulation

The homeostatic mechanisms that maintain body fluid volume are essential to the renal safety of SGLT2 inhibitors. (13). As observed in the DAPASALT study, acute therapy with SGLT2 inhibitors may not significantly affect plasma volume and intracellular volume status in patients with intact renal function; however, it is associated with a significant drop in extracellular volume status (14). For example, 12 weeks of treatment with an SGLT2 inhibitor versus placebo resulted in a substantial decrease in estimated extracellular and plasma volumes in patients with established HFrEF (15). Additionally, early treatment with an SGLT2 inhibitor in patients with a recent acute myocardial infarction, preexisting T2DM, and established HF was demonstrated to result in a significant decrease in plasma volume status after 24 weeks of medication (16).

SGLT2 inhibitors significantly increase urine volume, resulting in an acute reduction in body weight and an exponential decrease in interstitial fluid volume. However, in patients who receive treatment for an extended period, their plasma volume status and extracellular volume are reduced.

Cardiac function and remodeling

SGLT2 inhibitors have been shown to substantially increase left ventricle (LV) ejection fraction (LVEF) by 2.458% and decrease LV mass (LVM) by 6.319 g, LV end-systolic volume (LVESV) by 8.44 mL and LV end-diastolic volume (LVEDV) by 9.134 mL, while causing a significant decrease in left atrial volume index (LAVI) by 2.791 mL/m (17). Another relevant meta-analysis demonstrated similar results, confirming the positive effect of SGLT2 inhibition on cardiac remodeling (18). Notably, SGLT2 inhibitors tend to exert more substantial beneficial effects on LV function than other kinds of anti-diabetic drugs, such as dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists (18-19).

The data from studies suggest that SGLT2 inhibitor-mediated improved performance in LV diastolic function leads to lower filling pressures. This, combined with induced improvements in myocardial stiffness and fibrosis, results in improved LV performance, which may partially explain the beneficial effects of this class in HF (20). In addition, a cross-comparative study between various SGLT2 inhibitors showed that empagliflozin was linked with a more significant improvement of LV mass, LV mass index, LVESV, LVESV index, LVEDV, and LVEDV index with statistical significance (20).

Arterial stiffness

Increased arterial stiffness corresponds to increased afterload, the reduction of which is a significant treatment objective for patients with HF, including those with acute HF. Therefore, it was theorized that SGLT2 inhibitors ameliorate arterial stiffness, and this is one of the mechanisms implicated in the cardioprotective effects observed with this drug class (21).

Some newly released data support the hypothesis that SGLT2 inhibitors do not significantly impact vascular aging (22). However, it must be acknowledged that after six months of treatment, empagliflozin significantly decreased pulse wave velocity in HFrEF patients without diabetes mellitus at baseline compared to placebo (23). As a result, patients diagnosed with HF who take medications from this class may experience lessening arterial stiffness.

Myocardial fibrosis

Empagliflozin was found to reduce myocardial fibrosis and induce a significant reduction in extracellular volume, as measured by cardiac magnetic resonance imaging, in a recent meta-analysis that included all relevant trials (21-23). Myocardial fibrosis may predict adverse outcomes in participants with recent episodes of acute HF (22). Still, ameliorating myocardial fibrosis by SGLT2 inhibitors may not provide a significant benefit in the acute setting of HF. It has recently been shown in a diabetic mouse that the anti-fibrotic benefits are exerted partly through inhibition of collagen formation and ac-

cumulation via the canonical TGF-β/Smad pathway and by decreasing oxidative stress via activation of Nrf2/ARE signaling (23). The involvement of such key pathways in inflammation and oxidative stress further explains the pleiotropic benefits of this class of therapeutics.

Myocardial energetics

Experimentally and clinically, SGLT2 inhibitors improve myocardial energetics, LV remodeling and function in patients with chronic HF. In addition, SGLT2 inhibitors are known to reduce the insulin/glucagon ratio, which leads to a preference for lipids and ketone bodies (KBs) as metabolic substrates and creates a cardioprotective metabolic switch in HF.

In the treatment of HF, SGLT2 inhibitors optimize the usage of KBs by many routes, including increasing hepatic synthesis of KBs, modulating mitochondrial metabolism, activating the nutritional deprivation signaling system, and enhancing the utilization of cardiac KBs (24). In addition, SGLT2 inhibitors can ameliorate hypoxia and inflammation and allow myofibroblasts to return to erythropoietin-producing fibroblasts, increasing oxygen for energy metabolism in the heart. The ongoing EMPA-VISION trial is meant to assess the effects of empagliflozin medication on cardiac energy metabolism and physiology in individuals with HF (25).

Antiarrhythmic properties

According to the findings of a different meta-analysis that was just recently published (26), SGLT2 inhibitors do not affect the risk of ventricular arrhythmias or sudden cardiac death. However, it was successfully proved that prior use of SGLT2 inhibitors among the studied population resulted in significantly lower rates of atrial fibrillation, ventricular tachycardia, and ventricular fibrillation in the acute setting of myocardial infarction. Furthermore, the use of SGLT2 inhibitors was linked to a significant reduction in the chances of new-onset arrhythmia (26-27). Data from animal and cellular models support the hypothesis that SGLT2 inhibitors exert anti-arrhythmogenic effects.

Regulation of adipokines and epicardial adipose tissue

Adipose tissues secrete many biologically active substances known collectively as adipokines. Adipokines are in equilibrium; adiponectin and secreted frizzled-related protein 5 (SFPR5) can suppress the expression of many pro-inflammatory mediators and protect against a wide range of endocrine or CV diseases associated with obesity (28-30). Simultaneously, leptin can activate inflammatory responses and up-regulate pro-inflammatory elements such as tumor necrosis factor (TNF) and interleukin-6 (IL-6), which speeds up the beginning and progression of CV disease (31-32). Contrary effects are exerted by leptin and adiponectin on subclinical inflammation and insulin resistance (33). Meta-analysis demonstrates that SGLT2 inhibitors can effectively lower circulating leptin levels, raise circulating adiponectin levels, and inhibit the excretion of IL-6 and TNF- in animal aortas (34-35), resulting in cardiac vascular protection and a delay in the evolution of HF. Furthermore, SGLT2 inhibitors can lower the amount of epicardial adipose tissue in individuals by reducing systemic microinflammation (36) and adipose-related vascular disorders (37), which is advantageous for patients with HF.

Inhibition of Na^+-H^+ exchange protein

Empagliflozin inhibits the activity of NHE1 (Na^+/H^+ Exchange Protein 1) in the hearts of mice, rats, and rabbits, consequently decreasing the sodium and calcium levels in cardiomyocytes (38). Additionally, as a direct cardiac impact, it can suppress the NHE of the isolated intact heart and postpone the onset of ischemia contracture of the heart in the absence of insulin. Similarly, empagliflozin can decrease the calcium sensitivity of human cardiac myofilaments, ameliorating the myocardium's diastolic dysfunction and decreasing NHE in human bodies (39). Overall, SGLT2 inhibitors decrease the quantity of Na^+ entering cells by inhibiting NHE1 and improve contractile dysfunction in HF by correcting intracellular pH, resulting in CV benefits. However, there are dissenting opinions that the activity of cardiac NHE1 will not be influenced by empagliflozin or other SGLT2 inhibitors, as empagliflozin has no regulatory effect on the levels of Na^+ at therapeutic doses. They suggest that the SGLT2 inhibitor's role in HF should not be understood as being mediated by myocardial NHE1 or intracellular Na^+ (40).

In general, the function of SGLT2 inhibitors for NHE is contested due to the paucity of clini-

cal research data and the need for additional evidence.

Reduction of body weight and fat content

Excessive adipose tissue is essential in the development and progression of HF (41). Several studies have shown that SGLT2 inhibitors play a vital role in weight loss during their pharmacological activity in both kinds of diabetes (41–43). Due to the calorie loss caused by the excretion of glucose (44) and improved hypothalamic insulin responsiveness (45), the administration of SGLT2 inhibitors can reduce the weight of patients, resulting in a decrease in total fat mass, subdermal fat, visceral fat, and hepatic fat content (46-48).

Although SGLT2 inhibitors can not treat obesity permanently, reducing body weight and fat percentage may still benefit the CV system. This effect can be especially beneficial in patients with heart failure preserved ejection fraction (HFpEF), who often present with obesity or metabolic syndrome as associated comorbidity (49).

Renal benefits

The primary renal-protective mechanism for its renal protection is attributed to the tubuloglomerular change under the application of SGLT2. Na^+ and glucose reabsorption will be diminished when SGLT2 inhibitors are administered. To maintain homeostasis, the macula dense can then detect these changes, activating tubuloglomerular feedback and driving the contraction of the afferent arteriole. The expression of SGLT2 in the kidney is high, whereas in the healthy heart is low (50). Regardless of the underlying diabetes status, this class of medications has changed the therapy of chronic kidney disease (CKD) and HF, despite their moderate effect on glycemic control. Consequently, various pathological conditions, such as high perfusion, high load, and excessive glomerulus filtration, will be alleviated, resulting in robust renal protection (51-52). Initial CV outcome trials demonstrated the efficacy of SGLT2 inhibitors drugs in lowering CV mortality and hospitalization for HF in individuals with T2DM, and a 40% reduction in the likelihood of kidney disease progression (51-53). It is important to note that the group of patients who participated in these preliminary investigations had, for the most part, intact renal function and no severe albuminuria. In addition to reducing the metabolic burden of the kidney and helping oxidative stress or inflammation at that site *in vivo*, SGLT2 inhibitors have been described in previous sections as having the ability to reduce the kidney's metabolic burden (53). To evaluate the impact of SGLT2 inhibitors medicines on glomerular disorders, decreased estimated Glomerular Filtration Rate, non-proteinuric CKD, dialysis, and transplant populations, the outcomes of future trials are eagerly anticipated.

Clinical value of SGLT2 inhibitors in HF

Due to their practical hypoglycemic impact, SGLT2 inhibitors are generally used to treat T2DM, and early clinical trials targeted diabetic patients primarily. Unexpectedly, the researchers discovered that SGLT2 inhibitors have excellent CV advantages for diabetic patients. Although SGLT2 inhibitors have been demonstrated to have numerous metabolic, hemodynamic, and organ-specific effects in HF, their mechanisms of action remain unknown.

The class of SGLT2 inhibitors includes five oral drugs: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, and sotagliflozin. In addition, the US Food and Drug Administration

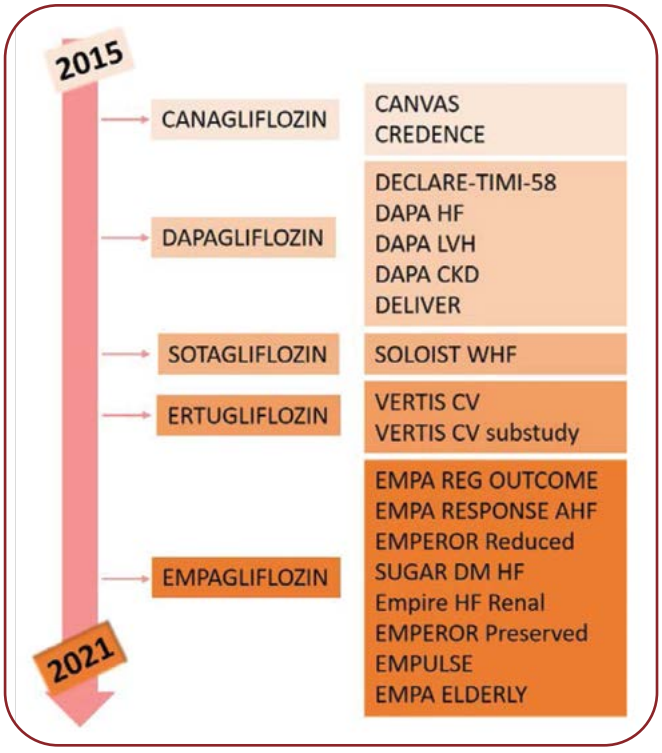

FIGURE 2. The development of clinical trials about SGLT2 inhibitors

(FDA) also approved bexagliflozin (Brenzavvy, TheracosBio), the sixth SGLT-2 inhibitor, for treating adults with T2DM. In chronological order, we summarize the clinical trials regarding the beneficial effects of SGLT2 inhibitors in the treatment of HF in Figure 2.

Empagliflozin

Compared to the placebo, empagliflozin reduced the relative CV-associated, HF hospitalization-associated and any cause-associated death rates by 38%, 35%, and 32%, respectively, in the EMPA-REG-OUTCOME trial (54). Furthermore, SGLT2 inhibitors lower the risk of death and hospitalization from HF. Those who received empagliflozin were less likely to experience poor renal outcomes than those who received a placebo (54).

Moreover, research on the impact of SGLT2 inhibitors on cardiac structure and function in HFrEF revealed that empagliflozin induces positive remodeling of the left ventricle (55).

Moreover, the EMPEROR PRESERVED trial, which focused on patients with HFpEF, demonstrated that empagliflozin lowered the cumulative risk of CV death or hospitalization for HFpEF patients, regardless of diabetes status (56).

Dapagliflozin

The DECLARE-TIMI-58 experiment yielded significant findings. After the use of dapagliflozin, the rate of hospitalization for HF with T2DM decreased by 27% (57).

The DAPA-HF trial was the first to assess the addition of SGLT2 inhibitors to conventional therapy for patients with HFrEF. Compared to a placebo, dapagliflozin significantly reduced the risk of CV death or worsening HF (defined as hospitalization for HF or emergency for HF) (58).

In addition, many patients treated with dapagliflozin demonstrated clinically meaningful improvements in HF symptoms and cardiac function. Moreover, dapagliflozin alleviated the symptoms of HF across all age categories, including the elderly (59). Patients treated with dapagliflozin had a decreased mortality risk from renal or CV causes than those treated with placebo (60).

The ongoing DELIVER study may give additional information regarding the impact of adding dapagliflozin to standard therapy in HFpEF (61).

Canagliflozin

Canagliflozin has CV benefits and improves kidney function by lowering albuminuria and creatinine levels. This is its most notable effect. The CANVAS study has attracted the interest of numerous researchers. Following using canagliflozin, hospitalization for HF reduced the risk of proteinuria progression and renal insufficiency by 33%, 27%, and 40%, respectively (62). In addition, individuals on canagliflozin experience good cardiac and renal benefits, independent of whether they had T2DM, renal disease, or HF at baseline (62). Canagliflozin can also reduce levels of NT-proBNP, a particular indication of HF (63).

Sotagliflozin and ertugliflozin

Sotagliflozin and ertugliflozin have only been the subject of a few investigations. Sotagliflozin is a balanced SGLT1 and SGLT2 inhibitor, whereas empagliflozin is a selective SGLT2 inhibitor. In one study, patients with T2DM with worsening HF who received sotagliflozin had a significantly reduced number of CV-related fatalities and hospitalizations than those who received a placebo (64). There is a need for more extensive clinical trials better to understand the therapeutic impact of these two medications.

Benefits and safety concerns of SGLT2 inhibitors

SGLT2 inhibitors can lower blood glucose, blood pressure, uric acid, creatinine, and the development of albuminuria; promote weight loss; recover indicators of heart failure (NT-proBNP and cardiac troponin T (cTnT)); and maintain LVM

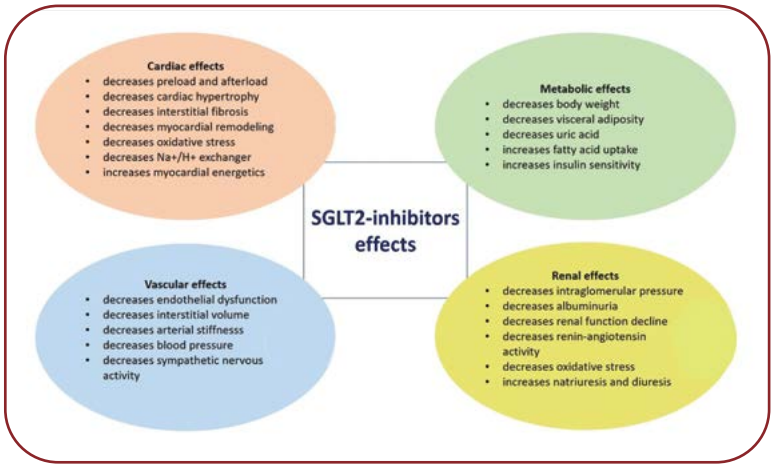

FIGURE 3. Cardiometabolic effects of SGLT2 inhibitors

and cross-sectional area of cardiomyocytes (65-67). While some trials have demonstrated a slight increase in low-density lipoprotein (LDL) cholesterol levels after administration of SGLT2 inhibitors, CV benefits were consistently independent of baseline LDL cholesterol levels (67). In Figure 3, we can observe the cardiometabolic effects of SGLT2 inhibitors.

In current clinical trials, SGLT2 inhibitors have been related to vaginal infections, hypoglycemia, acute renal failure, diabetic ketoacidosis, thromboembolic events, amputation, and fracture. ❑

CONCLUSION

Initially, SGLT2 inhibitors were developed solely as glucose-lowering drugs; however, their use has dramatically expanded since several large clinical trials demonstrated a significant reduction in primary CV outcomes. The clinical value of SGLT2 inhibitors in preventing and treating HF is beyond doubt. The updated HF therapy guidelines advocate dapagliflozin or empagliflozin for all patients with HFrEF, regardless of T2DM status. Inhibitors of SGLT2 have undeniable clinical utility in preventing and treating HF. We present a complete and systematic assessment of the mechanisms of SGLT2 inhibitors in HF, including ion-exchange regulation, volume regulation hypothesis, cardiac remodeling, and optimization of cardiac energy metabolism. Because of its wide range of cardioprotective mechanisms, molecular discoveries and data from clinical trials have combined to reclassify SGLT2 medicines from anti-hyperglycemic therapies to powerful HF therapeutics. ❑

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