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REVIEW

Mechanisms of Sodium-glucose Cotransporter 2 Inhibitors in Heart Failure

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Abstract

Heart failure is an end stage cardiac disease that has been associated with high mortality and rehospitalization rates in previous decades, in spite of standard anti-heart failure therapy, thus posing a major social and economic burden on public health. Several studies have demonstrated that sodium-glucose cotransporter 2 inhibitors (SGLT2i), anti-hyperglycemic drugs whose function is independent of islet function, have significant positive effects on prognosis and quality of life, by decreasing mortality and readmission rates in patients with heart failure. To increase general clinicians' understanding and facilitate the practical application of SGLT2i in the treatment of heart failure, the mechanisms through which SGLT2i alleviate heart failure is reviewed herein.

Keywords: Heart failure; Sodium-glucose Cotransporter 2 inhibitors (SGLT2i); Mechanisms

Introduction

Heart failure (HF) is a clinical state caused by anatomical or functional abnormalities in ventricular filling or ejection [1]; the most common causes include myocardial ischemia, hypertension, cardiomyopathy, valve injury, pulmonary hypertension, and congenital heart disease. More than 50 million people are believed to be affected by HF worldwide, thus resulting in substantial negative effects on society and the economy [2]. Therefore, the quest for new affordable ways to treat HF warrants attention. Numerous clinical trials [3–6] in recent years have demonstrated that sodium-glucose cotransporter 2 inhibitors (SGLT2i) have cardioprotective effects, and confer advantages in improving prognosis and quality of life in patients with HF. These drugs have achieved consistent cardiovascular benefits in the treatment of patients with HF with or without diabetes. Moreover, they have been found to reduce readmission rates and mortality in patients with HF [7]. The outcomes of various sizable clinical trials including patients with HFpEF and HFrEF, with and without diabetes, are shown in Table 1. Some drugs have been found to control blood glucose or blood pressure, but without conferring the beneficial cardiovascular effects of SGLT2i. Exactly how SGLT2i decrease cardiovascular risk factors remains unclear; however, the hypoglycemic effect appears unlikely to explain the full extent of benefits of SGLT2i. Here, the mechanisms underlying the amelioration of HF through SGLT2i treatment are reviewed.

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Table 1 Contributions of SGLT2i to HF Treatment in Major Clinical Trials.

Study title	Drug	Number of patients	Inclusion Criteria	Follow-up duration	Outcomes
DECLARE-TIMI58 [8]	Dapagliflozin	17,160	Patients with T2DM with combined ASCVD or high risk of ASCVD; HbA1c between 6.5% and 12%; and creatinine clearance ≥ 60 ml/min at enrollment	4.2 years	The rate of cardiovascular death or hospitalization for heart failure was 4.9% in the dapagliflozin group compared with 5.8% in the placebo group. Therefore, dapagliflozin decreased the rate of cardiovascular death or hospitalization for heart failure.
EMPEROR-Reduce [9]	Empagliflozin	3730	Patients with chronic heart failure with LVEF ≤ 40% and NYHA II–IV	16 months	A 25% decrease in the risk of cardiovascular death or heart failure hospitalization as a composite endpoint, and 31% decrease in the risk of hospitalization for heart failure, were observed.
EMPEROR-Preserve [10]	Empagliflozin	A total of 5988 cases, 67% of which were HFpEF	LVEF > 40% in patients with chronic heart failure	2.2 years	Empagliflozin decreased the probability of hospitalization for heart failure in patients with heart failure by 27% while decreasing the composite endpoint of mortality or hospitalization by 21%.
DAPA-HF [11]	Dapagliflozin	4744	Patients with LVEF ≤ 40%, NYHA II–IV, with or without T2DM, and elevated NT-proBNP	8 months	Dapagliflozin reduced the risk of cardiovascular death by 18% and the risk of hospitalisation for HF by 30% compared to placebo; patients without DM may also benefit.
DEFINE-HF [12]	Dapagliflozin	263	Patients with HFrEF with LVEF ≤ 40%, NYHA II–III, and elevated BNP	6–12 weeks	Although dapagliflozin treatment for longer than 12 weeks had no effect on mean NT-proBNP, it increased the percentage of patients with clinically significant improvements in their health or levels of a natriuretic peptide associated with heart failure.
Empire-HF [13]	Empagliflozin	391	Patients with LVEF ≤ 40%, NYHA I–III, treated according to heart failure treatment guidelines for at least 30 days before the randomized trial	2 years	After 12 weeks, empagliflozin decreased measured GFR, estimated extracellular volume, and estimated plasma volume.

Glucose-lowering Mechanisms of SGLT2i

SGLT1/2 are enriched primarily in the kidneys, SGLT2 is a member of the SLC5 family and is expressed in the S1 section of the proximal tubule, where approximately 90% of renal glucose reabsorption is performed by SGLT2 [14]. SGLT2i are anti-diabetic medications that decrease blood glucose levels through direct binding to SGLT2 receptors and subsequent prevention of the kidney's proximal tubules from absorbing glucose (Figure 1). This mechanism is unlikely to result in hypoglycemia, because it does not affect endogenous insulin or the insulin pathway [15, 16].

Potential Mechanisms Underlying the Benefits of SGLT2i in Patients with HF

Natriuretic and Antihypertensive Effects

Blood pressure and body blood volume are closely linked. Peripheral vascular afterload and resistance

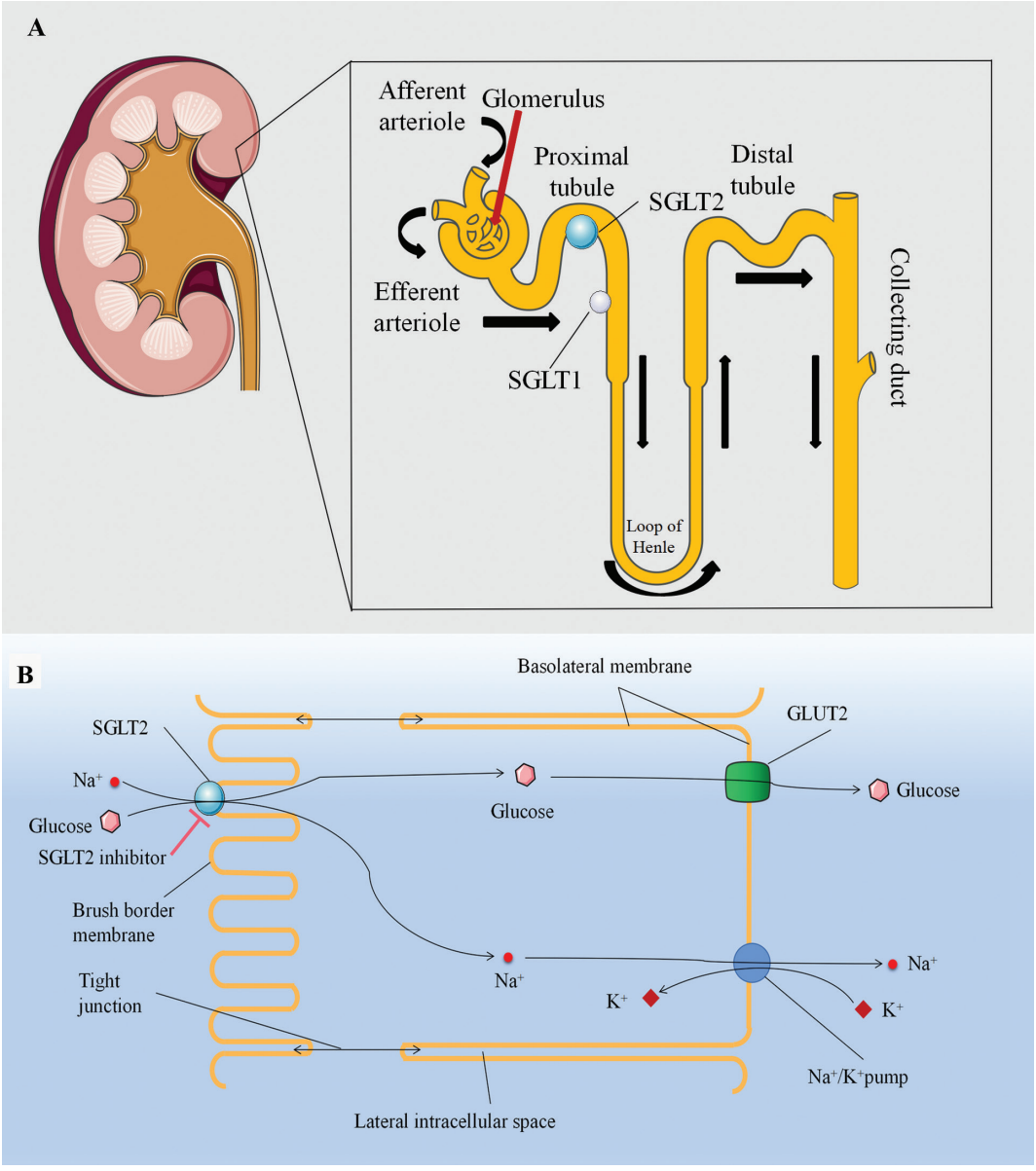

Figure 1 Hypoglycemic Mechanism of SGLT2i.
(A) To maintain glucose homeostasis, glucose and Na^+ can be reabsorbed at proximal tubule sites under normal circumstances.
(B) SGLT2i inhibit glucose reabsorption in proximal tubules by binding SGLT2 receptors, thus decreasing blood glucose.

increase as a result of hypertension and subsequently trigger left ventricular remodeling. Left ventricular remodeling worsens over time, and decompensation ultimately results in HF. Therefore, lowering blood pressure ameliorates HF. Because SGLT2i decrease glucose reabsorption, more glucose and the Na^+ that is associated with it are excreted from the body, thereby decreasing blood volume, circulation blood pressure, and extracellular fluid osmolality [17]. However, SGLT2i administration does not significantly lower blood pressure in the presence of volume changes or urinary salt excretion [18], thus indicating that additional processes may be involved in the antihypertensive response. Natriuresis decreases blood volume through a mechanism similar to that of thiazide diuretics. However, these diuretics have not been demonstrated to benefit the course of HF. Therefore, the antihypertensive mechanism of SGLT2i may involve a decrease in arterial stiffness and suppression of sympathetic activity [19]. The precise pathophysiological mechanisms underlying the antihypertensive effects of SGLT2i have not yet been fully elucidated. This level of blood pressure decrease, although advantageous in the context of cardiovascular disease, is unlikely to have substantial benefits in decreasing cardiovascular morbidity and mortality.

Weight Loss and Regulation of Adipokines and Epicardial Adipose Tissue

HF can result from coronary heart disease, which can develop as a result of hyperglycemia. In addition, adipose-induced inflammation has a wide range of adverse effects, including coronary and systemic microvascular endothelial dysfunction, thus making excess adipose tissue crucial for the emergence and development of HF [20]. Therefore, weight loss and glycemic control are essential to ameliorate HF. SGLT2i therapy is believed to decrease mortality in HF at least partly through the weight loss that results from an increased ratio of glucagon to insulin, which consequently increases lipid mobilization [21]. In addition, in response to the loss of calories from glucose excretion, fat stores in adipose tissue are mobilized [22], thereby leading to weight loss of approximately 1–4 kg, according to various experiments [23–25]. Moreover, SGLT2i improve insulin responsiveness in the hypothalamus [26], thus decreasing total fat mass, subcutaneous fat, visceral fat, and liver fat content [27–31]. However, the benefit of weight loss is not permanent but reaches a plateau between 24 and 52 weeks, thus prompting questions regarding the involvement of weight loss in decreasing HF mortality [32]. In patients with HF without diabetes, no evidence indicates that SGLT2i decrease weight. Furthermore, conclusive evidence is lacking regarding how weight loss affects cardiac function, quality of life, and exercise tolerance in people with HF, despite the high prevalence of obesity among people with this condition [33]. Therefore, the advantages of SGLT2i in patients with HF cannot be attributed only to weight loss.

Epicardial adipose tissue concentration is associated with the risk of cardiovascular events [34]. Adipose tissue secretes a variety of bioactive molecules known as adipokines, including leptin and adiponectin [35, 36]. In contrast to lipocalin, which inhibits the development of myocardial inflammation [37], elevated serum leptin concentrations in people with HF are associated with cardiac fibrosis and inflammation-induced cardiac remodeling [38, 39]. Elevated serum leptin stimulates inflammatory responses and upregulates pro-inflammatory factors, such as TNF-α and IL-6 [40]. SGLT2i play crucial roles in maintaining the dynamic balance of pro- and anti-inflammatory adipokines, and also decrease serum leptin levels while increasing lipocalin concentrations; the above processes have vasoprotective effects on the heart and slow the onset of HF [41, 42]. In addition, SGLT2i benefit patients with HF by decreasing the amount of pericardial adipose tissue [43]. However, some researchers have questioned this finding, given that type 2 diabetic mice develop cardiac dysfunction even in the absence of leptin [44]; empagliflozin decreases hepatic steatosis in mice and humans, but has no direct effect on cardiac fat [27]; and SGLT2i antagonism of leptin action is only speculative, according to indirect associations reported in studies citing different models [45].

Improved Myocardial Energy Metabolism

The heart requires sufficient energy to support its ongoing contraction. In physiological conditions, the oxidation of glucose and fatty acids produces approximately 90% of the ATP, whereas the remaining 10% is derived from lactate, ketones, and amino acids

[46]. In HF, mitochondrial dysfunction, cell death, or apoptosis results from impaired cardiac energy metabolism and increased glucose uptake, primarily from anaerobic oxidation, which decreases glucose supply and consequently increases the production of reactive oxygen species in cardiomyocytes, thereby causing cardiac dysfunction and ventricular remodeling [47]. SGLT2i lessen the harmful effects of excess glucose on cardiomyocytes and decrease glucose overload in these cells [48]. In addition, because cardiomyocytes use less glucose, they become more dependent on the ketone bodies created through the oxidation of free fatty acids for energy. Among these compounds, beta-hydroxybutyric acid is considered a "super fuel" that boosts the effectiveness of cardiac metabolism [49]. Beta-hydroxybutyric acid has been shown to provide a direct energy source for cardiomyocytes in HF, and animal trials have demonstrated that steady infusion of beta-hydroxybutyric acid enhances cardiac function and metabolic efficiency [50]. The hepatic mobilization and oxidation of fatty acids by SGLT2i can raise blood levels of beta-hydroxybutyric acid [51], and the increases in intracellular ATP content, mitochondrial function, and reactive oxygen species production can all be significantly improved, together with cardiac energy metabolism and cardiac dysfunction [52, 53]. Treatment with empagliflozin improves left ventricular function; increases the utilization of free fatty acids, ketone bodies, and branched-chain amino acids as myocardial metabolic substrates; and increases myocardial energy use [47]. The cardiovascular advantages of treatment with SGLT2i have been proposed to be associated with changes in cardiac metabolism from the utilization of more oxygen-efficient ketone bodies to the glucose present at high levels, thus resulting in toxicity to cardiomyocytes. However, the need for beta-hydroxybutyric acid as a super fuel in failing hearts has been questioned [54]. In addition, studies in mice have shown that the oxidative efficiency of ketone bodies remains nearly unchanged after the application of SGLT2i, thereby suggesting that the increase in ATP production may not be dependent on ketone utilization [55], whereas elevated ketone bodies may cause diabetic ketosis.

Alleviation of Inflammation

Interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor (TNF), galectin-3, and other pro-inflammatory biomarkers are elevated in patients with HF [56], and the magnitude of the elevation correlates with the severity of the disease. This association is significant in patients with decreased or preserved ejection fraction [57, 58]. By decreasing myocardial macrophage infiltration and inflammatory factors, and enhancing anti-inflammatory factors, animal studies have demonstrated that SGLT2i decrease cardiac inflammation in models of diabetic cardiomyopathy, myocardial ischemia, and HF [59, 60]. Furthermore, SGLT2i have been found to decrease the inflammatory response in human patients [61, 62]. Inflammatory vesicles associated with Nucleotide-Binding Domain-Like Receptor Protein 3 (NLRP3) have been discovered to contribute to persistent inflammation in HF and to facilitate the progression of HF [63]. In patients with diabetes mellitus and coronary artery disease, empagliflozin dramatically decreases IL-1 release in macrophages and blocks the activation of NLRP3 inflammatory vesicles. Moreover, empagliflozin markedly decreases cell-mediated extracellular matrix collagen remodeling in individuals with coronary artery disease and diabetes mellitus; inhibits NLRP3 inflammasome activation; and decreases IL-1 release in human macrophages [64, 65]. In addition, SGLT2i increase levels of circulating -hydroxybutyric acid, which in turn inhibits the inflammatory processes caused by NLRP3 inflammasomes. Moreover, the AMPK pathway prevents the growth of inflammatory cells [66], and SGLT2i have been found to increase AMPK phosphorylation in lipopolysaccharide-treated cardiac fibroblasts, thereby preventing an increase in inflammation [67]. Numerous studies have shown that insulin decreases the release of pro-inflammatory cytokines, thus lessening the inflammatory response. Insulin is a crucial hormone regulating glucose through a physiological response [68, 69]. Insulin resistance is closely associated with pro-inflammatory and inflammatory states [70]. Studies have shown that SGLT2i decrease insulin resistance, and thus assist in preventing the progression of inflammation and increased inflammation [71].

Anti-fibrotic Effects and Improved Ventricular Remodeling

The pathogenesis of HF is closely associated with cardiac remodeling, and ventricular remodeling

can result in irreversible cardiac remodeling via pathological myocardial hypertrophy, extracellular matrix changes with fibrosis, fibroblast proliferation, increased myocardial extracellular matrix degradation, and apoptosis. By decreasing extracellular matrix synthesis and myocardial fibrosis in HF, SGLT2i can avoid unfavorable cardiac remodeling [72]. By preventing extracellular matrix remodeling and the development of pro-fibrotic markers, empagliflozin has a direct anti-fibrotic action on myofibroblasts, thereby preventing ventricular remodeling and slowing the progression of HF [73]. Dapagliflozin has been discovered to significantly decrease collagen synthesis, inhibit myofibroblast infiltration, and increase macrophage polarization in a rat model of myocardial infarction, by activating transcriptional activator 3 signaling pathways and reactive oxygen/nitrogen-dependent signaling [74]. SGLT2i suppress NLRP3 inflammasome activity after myocardial ischemia and help the heart recover after ischemia; none of these actions rely on hyperglycemia [75]. Empagliflozin also enhances ventricular remodeling in early stages of myocardial infarction, decreases the extent of myocardial infarction, attenuates interstitial fibrosis, and prevents cardiomyocyte death in non-diabetic animals [76]. Furthermore, Na^+/H^+ exchanger 1 (NHE-1) increases intracellular Ca^{2+} concentrations during HF, thereby resulting in cardiac hypertrophy and fibrosis in cardiac fibroblasts. Intracellular Ca^{2+} levels in cardiac myocytes are directly associated with cardiac hypertrophy [77]. NHE-1's abilities to decrease ventricular hypertrophy and myocardial fibrosis, and improve ventricular remodeling, are inhibited by SGLT2i. In addition, SGLT2i lessen cardiac remodeling by decreasing the expression or transcription of genes associated with cardiac hypertrophy and fibrosis [78].

Autophagy

Autophagy, an adaptive response to diverse metabolic and stressful situations, is a lysosome-dependent intracellular degradation mechanism that preserves cellular physiological homeostasis by eliminating potentially harmful components and circulating cellular components [79]. Autophagy activation decreases the heart remodeling and dysfunction caused by myocardial infarction [80]. Activation of sirtuin-1 (SIRT1), adenosine monophosphate-activated protein kinase (AMPK), and hypoxia-inducible factors (HIF-1α and HIF-2α) is the principal mechanism initiating the autophagic response. The expression of AMPK, SIRT1, and HIF-1α can also be elevated by SGLT2 inhibitors. Furthermore, deactivation of inflammatory vesicles results from the autophagy-mediated clearance of damaged organelles – a response that may partially account for the anti-inflammatory and antioxidant effects of SGLT2i [67, 81]. The cardiovascular advantages of SGLT2i may be explained by the aforementioned mode of action, which modulates autophagy phenomena.

Decreased Sympathetic Hyperexcitability

Overactivation of the sympathetic nervous system (SNS) is a key factor in the emergence of HF. Norepinephrine – which has myocardial toxic effects after long-term exposure to high concentrations, and can cause apoptosis and fibrosis – is secreted in large amounts by cardiac sympathetic nerve endings in people with HF [82]. Plasma catecholamine levels are markedly elevated in HF, thus negatively affecting cardiac function by increasing heart rate and altering heart rhythm, among other effects [83]. The ability of SGLT2i to decrease blood pressure without raising the heart rate suggests their potential to prevent cardiac SNS activation and hence confer cardioprotective effects [84, 85]. In a pig HF model, dapagliflozin therapy has been demonstrated to decrease serum norepinephrine concentrations and SNS tone, thus delaying cardiac remodeling [86]. In addition, dapagliflozin has been reported to dramatically enhance endothelial function and blood pressure in mice by lowering IL-6 and sympathetic nervous system excitability [87]. Moreover, SGLT2i indirectly decrease sympathetic excitement by preventing renal afferent sympathetic neurons from becoming activated [88]. Future research will focus on identifying the mechanism through which SGLT2 decreases SNS activity, given that little is known about how SGLT2i affect the sympathetic nervous system, and clinical evidence is notably lacking.

Direct Action on the Myocardium

Although SGLT2 expression in the heart is minimal, SGLT2 inhibition is closely associated with

cardiac sodium homeostasis, because of its profound effects on ion transporters. NHE1 plays an important role in myocardial ischemia and HF [89, 90]. The intracellular pH decreases in HF increase myocardial NHE1 activity in patients, and additionally increase Na^+ concentrations in the cytoplasm of cardiomyocytes, thus further activating Na^+/Ca^{2+} reverse transport and leading to intracellular Ca^{2+} overload in cardiomyocytes, accelerating HF, and increasing the risk of arrhythmias [91]. In studies in rabbits and rats [92, 93], SGLT2i have been shown to downregulate myocardial NHE1 activity and restore Na^+/Ca^{2+} homeostasis in the cytoplasm of cardiomyocytes, and to result in elevated concentrations of Ca^{2+} in mitochondria. These effects improve cardiac contractile activity and mitochondrial function; decrease oxidative stress; and might possibly decrease cardiac hypertrophy, fibrosis, and cardiac remodeling [94]. These responses may be direct regulatory effects of SGLT2i on cardiac myocytes. However, at therapeutic doses, empagliflozin has not been found to affect myocardial NHE1 activity, and the effects of SGLT2i in HF should not be interpreted as being mediated by myocardial NHE1 or intracellular Na^+ [95]. In addition, the effects of SGLT2i on NHE1 are controversial and must be confirmed by additional evidence, because SGLT2 receptors are minimally expressed in the heart, and NHE inhibitors have not shown a benefit in HF.

In addition, the expression and activity of Ca^{2+}/Calmodulin-Dependent Protein Kinase II (CaMKII) are upregulated in patients with HF; moreover, activation of CaMKII promotes myocardial necrosis, apoptosis, and fibroblast proliferation, which are associated with the development of arrhythmias and unfavorable myocardial remodeling [96]. Empagliflozin has been shown to decrease CaMKII activity in mouse ventricular myocytes, as well as to decrease CaMKII-dependent phosphorylation of RyR2 in murine and human ventricular myocytes, thereby significantly diminishing sarcoplasmic Ca^{2+} leakage and improving myocardial contractility [97]. However, the mechanism underlying the decrease in CaMKII activity is unclear.

Conclusion

SGLT2i have potent and cardioprotective effects, and have led to advancements in the treatment of cardiovascular disease. SGLT2i significantly decrease rehospitalization rates and mortality in HF

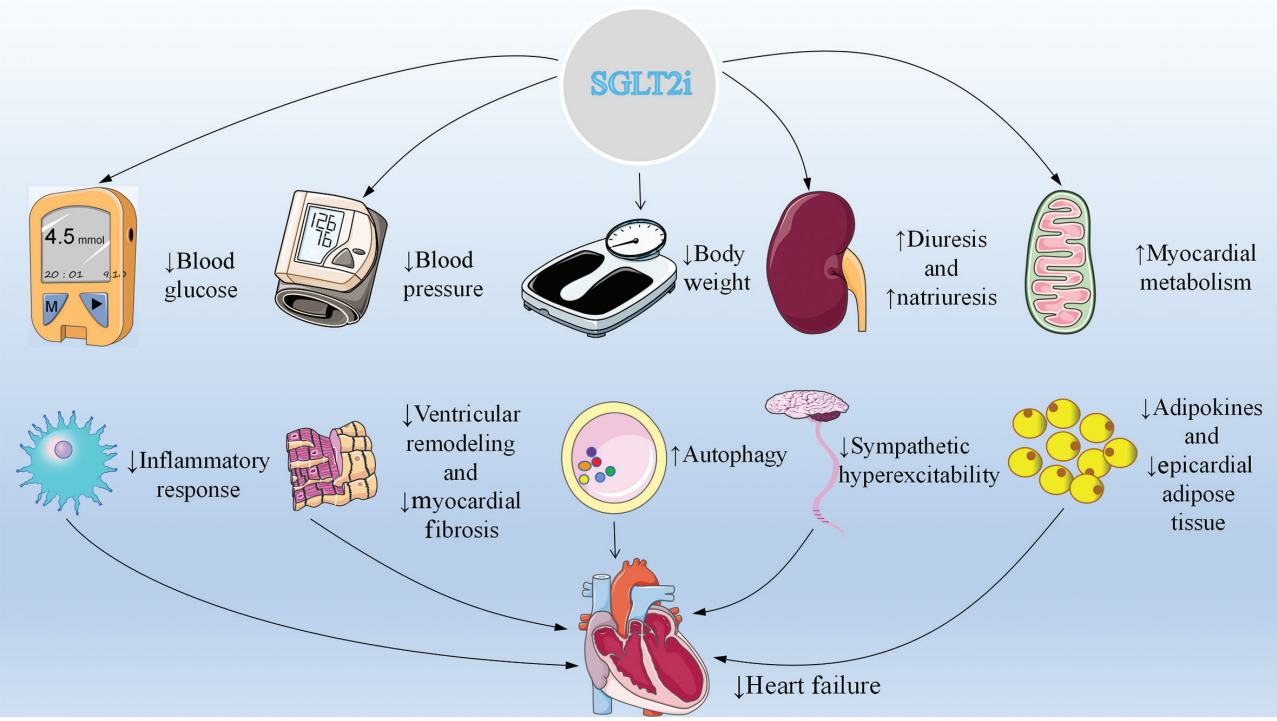

Figure 2 Cardioprotective Effects of SGLT2i in Patients with Heart Failure.

well beyond their initial glucose-lowering effects, on the basis of evidence from numerous large randomized controlled trials over the past few years. Many guidelines now recommend SGLT2i for the treatment of HF. Thus, the applications of these drugs have expanded from lowering blood glucose to treating HF. However, the exact mechanism through which SGLT2i ameliorate HF is unclear. This article has discussed several pathways through which SGLT2i help patients with HF (Figure 2), but many more paths of action must be thoroughly researched. In addition, any possible negative effects of these drugs must be explored in future trials.

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Conflicts of interest

The authors declare they have no conflicts of interest.

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