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Emerging Concepts in Sodium-Glucose Cotransporter 2 Inhibitors in the Management of Heart Failure: From Clinical Evidence to Potential Mechanisms

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Abstract

Heart failure (HF) is a major public health problem with an increasing prevalence among aging populations and individuals with type 2 diabetes. The pathophysiology of HF is complex and results from various detrimental pathways (inflammation, oxidative stress, endothelial dysfunction, adverse remodeling, and decreased autophagic flux, among others) that contribute to a failure of cardiac output. While the introduction of sodium-glucose cotransporter 2 inhibitors (SGLT2is), originally designed as antidiabetic medications for the treatment of T2D, has revolutionized the treatment of HF and are currently formally recommended for its treatment, according to relevance to the societal guidelines. No other oral antidiabetic medications except SGLT2is to date have shown the significant benefit on HF events. However, despite SGLT2is' possible wide clinical implications, there are lots of questions to unravel the mechanisms underlying their mode of action. This article provides an overview of the major cardiovascular outcome trials assessing the effectiveness of SGLT2is in the management of HF and of the diverse mechanisms of action through which SGLT2is exert their benefits in this setting. These mechanisms will be mainly focused on the "off-target" direct cardiac effects of SGLT2i, which may help explain the beneficial effects of SGLT2is on patients with HF, irrespective of their diabetes status. Nevertheless, given notably absence of SGLT2 in the cardiac myocardium, the evidence suggests that SGLT2-independent effects of this drug class likely occurs through off-target effects in the myocardium. Thus, further research is required to investigate the potential mechanisms underlying the effect of SGLT2is on cardiac cells and to provide mechanistic and additional clinical evidence regarding the various effects of SGLT2is across the spectrum of HF.

Key Words: Sodium-glucose cotransporter 2 inhibitors; heart failure; cardioprotection; cardiovascular outcome trials; mechanisms.

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Introduction

Heart failure (HF) is a clinical condition caused by the heart's inability to pump sufficient blood to meet the body's needs. Despite considerable progress in HF management, it remains a major public health and clinical problem worldwide[1]. The pathophysiology of HF is complex and involves various detrimental mechanisms such as inflammatory and oxidative stress processes, endothelial dysfunction, fibrosis, altered cardiac sodium transporters and ionic homeostasis, and metabolic/mitochondrial pathways[2]. Despite being initially developed as antidiabetic medications for patients with type 2 diabetes (T2D), sodium-glucose cotransporter 2 (SGLT2) inhibitors (SGLT2is) have demonstrated unexpected benefits in reducing hospitalization for HF (HHF), atherosclerotic events, and mortality rates as well as delaying chronic kidney disease (CKD) progression[3]. Because SGLT2 receptors are not expressed in the heart, these beneficial cardiorenal effects of SGLT2is in patients with HF may not be explained by lowering blood glucose alone. Numerous mechanisms related to diuresis/natriuresis, the sympathetic nervous system, erythropoiesis, autophagy, endothelial function, energetics, adverse remodeling, ionic homeostasis, circulating provascular progenitor cells, and anti-inflammatory, antifibrotic, antioxidant, hemodynamic, and metabolic effects have been proposed to explain the beneficial effects of SGLT2is both on diabetic and nondiabetic patients with HF[4,5].

This review mainly focused on the direct SGLT2is effects on the heart that are independent of effects on the kidney and provides an overview of the major cardiovascular (CV) outcome trials (CVOTs) that have assessed the beneficial effects of SGLT2is in both diabetic and nondiabetic patients with HF. This review also analyzed the latest mechanistic evidence of the benefits of SGLT2is, which may provide an explanation of the benefits of this drug class in HF. The pleotropic effects of SGLT2is may provide hope that these drugs can be administered to a wide range of HF patients, regardless of their diabetic status, to maximize the therapeutic benefits.

Clinical Evidence in HF Pharmacotherapy: SGLT2is

Early CVOTs evaluating the effects of SGLT2is on patients with T2D and a high risk of cardiovascular disease (CVD)—such as the empagliflozin cardiovascular outcomes event trial in type 2 diabetes (EMPA-REG OUTCOME)[6], canagliflozin and cardiovascular and renal events in type 2 diabetes (CANVAS)[7], dapagliflozin and cardiovascular outcomes in type 2 diabetes (DECLARE-TIMI 58)[8], and cardiovascular outcomes with ertugliflozin in type 2 diabetes (VERTIS-CV)[9]—have provided valuable insights. These 4 trials have reported reductions in the relative risk of HHF of 30%, 33%, 27%, and 35%, respectively[6-9]. A meta-analysis of 11 CVOTs, including more than 70 000 patients with T2D (without HF) or with established HF (50% of whom did not have diabetes), reported that SGLT2is led to a consistent reduction in the HHF risk of approximately 30%[10]. The beneficial effects of SGLT2is on HHF risk have been observed early in the course of treatment, regardless of the specific drug within the class. Additionally, when combined with other established drugs for HF such as neprilysin inhibitors, SGLT2is may have additional incremental benefits[11].

On the basis of these results, dedicated large-scale clinical trials investigating the effects of SGLT2is in patients with HF have been conducted. The dapagliflozin and prevention of adverse outcomes in heart failure (DAPA-HF) trial, which was the first trial to investigate the effects of SGLT2is on 4744 patients with New York Heart Association class II to IV HF and an ejection fraction (EF) of <40%, reported that dapagliflozin significantly reduced the risk of worsening HF or CV mortality by 26% (hazard ratio [HR] = 0.74; $p < 0.001$)[12]. These benefits were

consistent, regardless of whether the patient had diabetes[12]. Similar results were observed in the empagliflozin outcome trial in patients with chronic heart failure with reduced ejection fraction (EMPEROR-Reduced), and it reported that empagliflozin markedly reduced the risk of HHF or CV mortality, irrespective of diabetes status (HR = 0.75; $p < 0.001$)[13]. Compared with placebo, empagliflozin was associated with a lower HHF (HR = 0.70; $p < 0.001$)[13]. On the basis of these results, SGLT2is have been included as a Level of Evidence A recommendation in the current clinical guidelines for the management of HF with reduced ejection fraction (HFrEF) [14].

In addition to the benefits of SGLT2is in patients with HFrEF, trials have investigated whether SGLT2is would provide benefits in patients with HF with a preserved ejection fraction (HFpEF). The empagliflozin outcome trial in patients with chronic heart failure with preserved ejection fraction (EMPEROR-Preserved) trial reported that empagliflozin markedly reduced the combined risk of HHF and CV death in patients with HFpEF (HR = 0.79; $p < 0.0001$), irrespective of diabetes status**[15]**. This trial established SGLT2is as the first effective treatment modality against HFpEF with left ventricular (LV) ejection fraction (LVEF) ≤ 65% and that empagliflozin reduced HHF with a similar magnitude for HFpEF (−29%) as for HFrEF (−31%) patients**[15,16]**. Similarly, the dapagliflozin in heart failure with mildly reduced or preserved ejection fraction (DELIVER) trial, which involved 6263 patients with HF and an LVEF of >40%, reported that dapagliflozin led to a 18% reduction in the primary outcome (defined as the composite of CV death, hospitalization, or urgent visit for HF; HR = 0.82; $p < 0.001$)[17]. These findings suggest that in terms of the management of HF events, SGLT2is have broad applicability across the spectrum of LVEF, regardless of the presence or absence of T2D. Table 1 summarizes the effects of SGLT2is on HF outcomes in the major CVOTs.

Potential Cardiovascular Mechanisms of SGLT2is in HF

Although SGLT2is were initially designed to target SGLT2 in the kidney and facilitate glycosuria in patients with T2D, SGLT2is have revealed unexpected beneficial effects on the reduction of HHF, atherosclerotic events, and mortality rate as well as CKD progression[3]. Although many commentaries and review articles have discussed the mechanisms underlying the renoprotective effects of SGLT2i[18,19], given that SGLT2 receptors are not expressed in the heart, these beneficial cardiac effects of SGLT2i, specifically, that on HF, cannot be attributed to reduction in blood glucose alone. In addition, despite dedicated large-scale clinical trials strongly supporting the effectiveness of SGLT2is in HF[6-9, 12,13,15], the improvement in outcomes cannot be solely explained by the control of conventional risk factors such as improved glycemia, reduced body weight, lowered blood pressure (BP), and improved cholesterol[20]. For this reason, the study explored the underlying mechanisms and pathways through which SGLT2is exert their cardioprotective effects in HF pathophysiology. The potential mechanisms of cardioprotection by SGLT2is in HF are summarized in Figure 1.

Inflammation

Inflammation plays a crucial role in the development and progression of HF, and elevated levels of proinflammatory biomarkers have been observed in patients with HF, indicating the association between HF severity and inflammation[2,4]. This association is evident in patients with both HFrEF and HRpEF[21]. Inflammatory cytokines can both increase extracellular matrix turnover and fibrosis and lead to endothelial dysfunction. Dapagliflozin has been reported to ameliorate diastolic function in rats, possibly through attenuation of markers of cardiac inflammation, fibrosis, and endothelial activation[22]. Dapagliflozin is also associated with a decrease in the

Table 1. Summary of the effects of SGLT2is on HF outcomes reported by major cardiovascular outcome trials

Clinical trial	Intervention	Enrollment	Main inclusion criteria	Mean eGFR (mL/min/1.73 m^2)	Diabetes (%)	HF (%)	Primary endpoint	Findings (HR [95% CI]; p)
EMPA-REG OUTCOME[6]	Empagliflozin 10 or 25 mg QD vs. placebo	N=7202	T2D Age ≥ 18 y ASCVD; eGFR ≥ 30 mL/min/1.73 m^2 BMI ≤ 45 kg/m^2 HbA1c: 7.0%-9.0% without GLDs or HbA1c: 7.0%-10.0% with stable GLDs	74	100	10.1	MACE (CV death, nonfatal MI, or nonfatal stroke)	*Secondary outcomes:* CV death or HHF: 0.66 (0.55-0.79); $p < .001$ HHF: 0.65 (0.50-0.85); $p = .002$
CANVAS[7]	Canagliflozin 100 mg QD vs. placebo	N=10142	T2D ASCVD or age ≥ 50 y with 2 or more risk factors for CVD	76.7	100	14.4	MACE (CV death, nonfatal MI, or nonfatal stroke)	*Secondary outcomes:* CV death or HHF: 0.78 (0.67-0.91); p = NA HHF: 0.67 (0.52-0.87); p = NA
DECLARE-TIMI-58[8]	Dapagliflozin 10 mg QD vs. placebo	N=17160	T2D Age ≥ 40 y ASCVD or multiple risk factors for ASCVD eGFR ≥ 60 mL/min/1.73 m^2	85.4	100	10	MACE (CV death, MI, or ischemic stroke)	*Secondary outcomes:* CV death or HHF: 0.83 (0.73-0.95); $p = .005$ HHF: 0.73 (0.61-0.88); p = NA
VERTIS-CV[9]	Ertugliflozin 5 or 15 mg QD vs. placebo	N=8246	T2D CVD Age ≥ 40 y eGFR ≥ 30 mL/min/1.73 m^2	76	100	24	MACE (CV death, nonfatal MI, or nonfatal stroke)	*Secondary outcomes:* CV death or HHF: 0.88 (0.75-1.03); $p = .11$ for superiority HHF: 0.70 (0.54-0.90); p = NA
DAPA-HF[12]	Dapagliflozin 10 mg QD vs. placebo	N=4744	Age ≥ 18 y EF ≤ 40% NYHA class II, III, or IV NT-proBNP ≥ 600 pg/mL eGFR ≥ 30 mL/min/1.73 m^2	66	41.8	100	First occurrence of CV death or worsening HF (HHF or emergency visit resulting in intravenous therapy for HF)	*Primary outcome components and secondary outcomes:* CV death or first HHF: 0.75 (0.65-0.85); $p < .001$ CV death or total HHF: 0.75 (0.65-0.88); $p < .001$ HHF: 0.70 (0.59-0.83); p = NA HHF or an urgent visit for HF: 0.70 (0.59-0.83); p = NA

Clinical trial	Intervention	Enrollment	Main inclusion criteria	Mean eGFR (mL/min/1.73 m^2)	Diabetes (%)	HF (%)	Primary endpoint	Findings (HR [95% CI]; p)
EMPEROR-Reduced[13]	Empagliflozin 10 mg QD vs. placebo	N=3730	Age ≥ 18 y LVEF ≤ 40% NYHA class II, III, or IV	61.8	49.8	100	First occurrence of CV death or HHF	*Primary outcome components and secondary outcomes:* CV death or first HHF: 0.75 (0.65-0.86); $p < .001$ CV death or total HHF: 0.76 (0.65-0.89); $p < .001$ HHF: 0.69 (0.59-0.81); p = NA
EMPEROR-Preserved[15]	Empagliflozin 10 mg QD vs. placebo	N=5988	Age ≥ 18 y LVEF ≥ 40% NYHA class II, III, or IV	60.6	49	100	First occurrence of CV death or HHF	*Primary outcome components and secondary outcomes:* HHF: 0.71 (0.60-0.83); p = NA HHF or emergency visits for HF: 0.69 (0.59-0.80); p = NA
DELIVER[17]	Dapagliflozin 10 mg QD vs. placebo	N=6263	Age ≥ 40 y LVEF > 40% (including prior LVEF ≤ 40%) NYHA class II, III, or IV	61	44.7	100	Composite of CV death or HF exacerbation (HHF or urgent visit)	*Primary composite outcome:* HHF or an urgent visit for HF: 0.79 (0.69-0.91); p = NA HHF: 0.77 (0.67-0.89); p = NA Urgent visit for HF: 0.76 (0.55-1.07); p = NA Secondary outcomes: Total number of worsening HF events and CV deaths: 0.77 (0.67-0.89); $p < .001$

Abbreviations: ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; CV: cardiovascular; CVD: cardiovascular disease; CI: confidence interval; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; GLDs: glucose-lowering agents; HbA1c: glycated hemoglobin; HF: heart failure; HHF: hospitalization for heart failure; MACE: major adverse cardiovascular event; MI: myocardial infarction; NA: not applicable; NYHA: New York Heart Association; NT-proBNP: N-terminal pro B-type natriuretic peptide; BNP: B-type natriuretic peptide; SGLT2is: Sodium-glucose cotransporter-2 (SGLT2) inhibitors ;T2D: type 2 diabetes.

¶ Worsening heart failure events were defined as hospitalization for heart failure or an urgent visit for heart failure. The total number of worsening heart failure events comprised first and recurrent events.

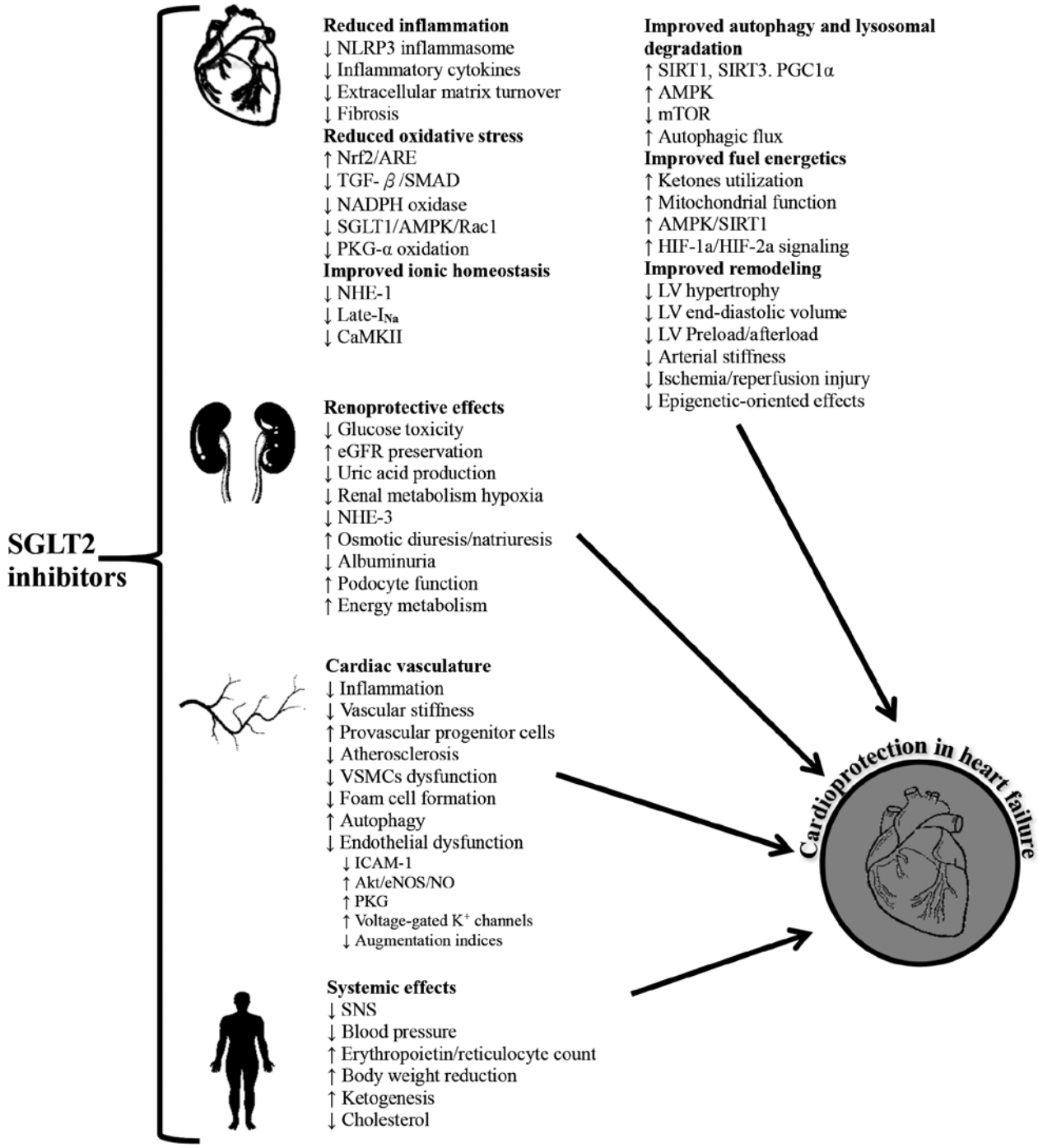

Figure 1. Potential mechanisms of cardioprotection by SGLT2is in heart failure

Abbreviations: SGLT2, sodium-glucose cotransporter 2; NLRP3, nucleotide-binding domain-like receptor protein 3 inflammasome; Nrf2/ARE, nuclear factor erythroid 2-like 2/antioxidant responsive element; TGF-β, transforming growth factor beta; AMPK, adenosine monophosphate-activated protein kinase; ICAM-1, intercellular adhesion molecule 1; NO, nitric oxide; eNOS, endothelial nitric oxide synthase; PKG, protein kinase G; K+, potassium; mTORC, mammalian target of rapamycin complex; SIRT1, sirtuin1; SIRT3, sirtuin3; PGC 1α; peroxisome proliferator-activated receptor-γ coactivator 1α; HIF-1a, hypoxia-inducible factor-1a; HIF-2a, hypoxia-inducible factor-2a; LV, left ventricular; NHE-1, sodium/hydrogen exchanger-1; NHE-3, sodium/hydrogen exchanger-3; late-INa, late sodium current; CaMKII, calcium/calmodulin-dependent kinase II; eGFR, estimated glomerular filtration rate; SNS, sympathetic nervous system; NADPH, nicotinamide adenine dinucleotide phosphate; VSMCs, vascular smooth muscle cells.

expression of inflammatory markers in the aorta in pigs with HFpEF[23]. Empagliflozin has been demonstrated to reduce the levels of proinflammatory cytokines, thereby contributing to the preservation of cardiomyocyte contraction and relaxation in a cellular model of endothelial dysfunction. This suggests that empagliflozin could be particularly beneficial in addressing the cardiac mechanical implications of impaired microvascular function in HF[24].

In humans, canagliflozin reduced serum levels of interleukin (IL)-6, tumor necrosis factor receptor, matrix metalloproteinase 7, and fibronectin 1 in patients with T2D, suggesting that canagliflozin treatment ameliorates inflammation and fibrosis[25]. Empagliflozin reduced serum levels of IL-10, high-sensitivity C-reactive protein, and myeloperoxidase in patients with T2D, suggesting evidence of the anti-inflammatory and antioxidant properties of empagliflozin treatment in humans, which may contribute to its beneficial CV effects[26]. Similarly, in patients with T2D at high risk of CVD, empagliflozin significantly attenuated nucleotide-binding domain-like receptor protein 3 (NLRP3) inflammasome activation and secretion of IL-1, which has a pathogenic effect on both T2D and CVD, potentially through increased serum β-hydroxybutyrate (β-OHB) levels and decreased serum insulin, glucose, and uric acid[27]. This study suggested that these mechanisms might help to explain the cardioprotective effects of SGLT2is in humans.

The anti-inflammatory properties of SGLT2is are associated with their ability to reduce the molecular processes related to inflammation including extracellular matrix turnover and fibrosis[4]. Empagliflozin has been demonstrated to significantly attenuate cell-mediated collagen production in the extracellular matrix, and dapagliflozin has been demonstrated to exert marked antifibrotic effects on postinfarct rat hearts through the suppression of collagen synthesis[4].

Several experimental studies have provided insights into the cellular effects of SGLT2is, particularly at the molecular level, and their impact on cardiac inflammation. One potential mechanism involves the reduction of the NLRP3 inflammasome activation by SGLT2is, thereby reducing cardiac inflammation and the production and secretion of proinflammatory cytokines[28]. The NLRP3 is also associated with chronic inflammation in HF[29]. SGLT2is can reduce the expression of NLRP3 inflammasomes in cardiac fibroblasts[30] as well as in human macrophages[31]. However, whether SGLT2is exert direct or indirect effects on the NLRP3 inflammasome remains unclear. Ketone β-OHB has been suggested to be able to block the NLRP3 inflammasome-mediated inflammatory process[32]. Because SGLT2is increase the circulating β-OHB levels, some of the beneficial effects of SGLT2 inhibition may occur secondarily to the ketone inhibition of the NLRP3 inflammasome[4].

Preliminary evidence suggests that SGLT2is may have a unique effect on the restoration of provascular progenitor cells in patients with T2D. Empagliflozin has been demonstrated to reduce the number of M1 cells (proinflammatory macrophages) while increasing the number of M2 cells (anti-inflammatory macrophages), promoting polarization. In addition, empagliflozin has been associated with a decrease in systemic granulocyte burden in patients with T2D and an increase in circulating $ALDH^{hi}SSC^{mid}$ monocytes, thereby inducing a transition from M1 to M2 polarization. These effects are associated with collateral vessel maturation during arteriogenesis[4]. Thus, by promoting the recovery of circulating provascular cells in patients with T2D, SGLT2is may considerably promote vessel homeostasis. Additional studies are warranted to evaluate whether this result is observed in patients without T2D.

Taken together, because inflammation is a key contributor to HF severity, the suppression of cardiac inflammation may be one mechanism through which SGLT2is provide benefits in HF. Although inflammation was previously believed to be a secondary symptom of HF development, emerging evidence

highlights the importance of inflammation and cytokines in the causal development and progression of cardiac dysfunction[33]. Therefore, if SGLT2is can reduce inflammation, this effect may contribute to the improvement of HF outcomes.

Oxidative stress

Oxidative stress has been implicated in several heart diseases, in particular, HFpEF. Oxidative stress can trigger a signaling cascade of inflammation, contributing to the development and progression of HFpEF[2]. Emerging evidence indicates that SGLT2is have antioxidant effects[34-39]. The impact of SGLT2is on myocardial oxidative stress has been investigated in various experimental studies[34-36]. In a modified T2D mouse model, empagliflozin significantly ameliorated myocardial oxidative stress injury and cardiac fibrosis by activating the Nrf2/ARE signaling pathway and suppressing the transforming growth factor-β (TGF-β)/SMAD pathway[34]. Dapagliflozin reduced cardiomyopathy and myocardial fibrosis in a diabetic rat model by reducing the production of reactive oxygen species (ROS) through the reversion of the upregulation of TGF-β/SMAD signaling[35]. Similarly, empagliflozin improved post-myocardial infarction mortality outcomes, possibly by modifying antioxidants and cardiac energy metabolism in diabetic rats[36].

Despite these benefits, limited clinical data are currently available regarding the antioxidant effects of SGLT2is. Although several clinical studies have demonstrated a significant reduction in the levels of oxidative stress markers such as 8-iso-prostaglandin F2a and 8-hydroxy-20-deoxyguanosine, the study designs were not powered to assess these observations accurately[37]. In a study involving human myocardial tissue, canagliflozin inhibited myocardial nicotinamide adenine dinucleotide phosphate oxidase activity and reduced endothelial nitric oxide synthase (eNOS) coupling through a SGLT1/adenosine monophosphate-activated protein kinase (AMPK)/ras-related C3 botulinum toxin substrate 1 (Rac1) pathway, leading to anti-inflammatory and anti-apoptotic effects[38]. Similarly, empagliflozin was significantly associated with the attenuation of cardiomyocyte and endothelial function through the inhibition of proinflammatory-oxidative pathways and protein kinase G oxidation in patients with HFpEF[39].

Taken together, these findings suggest that SGLT2is can reduce cardiac oxidative stress through multiple cellular pathways both in experimental and clinical settings, despite the absence of SGLT2 expression in cardiac cells. However, well-designed clinical studies with adequate power are needed to fully elucidate the impact of SGLT2is on oxidative stress in patients with HF.

Endothelial Dysfunction

Endothelial dysfunction, characterized by increased chronic inflammation, increased oxidative stress, and reduced production of nitric oxide (NO), plays a role in the development of atherosclerosis and HF[40]. A growing body of evidence suggests that SGLT2is may play a role in the amelioration of endothelial dysfunction[40,41]. On the molecular level, SGLT2is have been demonstrated to increase NO bioavailability and suppress endothelial apoptosis, potentially through the elevation of hematocrit, modulation of AMPK, stimulation of the Akt/eNOS/NO pathway, activation of protein kinase G, and modulation of voltage-gated potassium channels[42]. Dapagliflozin has been demonstrated to ameliorate diastolic function in nondiabetic rats with HFpEF, potentially through the reversal of endothelial activation and eNOS deficit, reduction in cardiac inflammation, and attenuation of cardiac fibrosis[22]. Empagliflozin has been demonstrated to be associated with increased NO production and reduced oxidative stress in a cellular model of endothelial dysfunction. This preservation of endothelial dysfunction contributes to the maintenance of proper contraction and relaxation of cardiomyocytes, indicating a direct positive effect of empagliflozin on

the cardiac mechanical implications of microvascular dysfunction in HF[24]. Empagliflozin attenuated coronary microvascular function and structural abnormalities and protected cardiac pericytes in an animal experiment, suggesting that empagliflozin might be an effective drug for the treatment of diabetic coronary microvascular dysfunction[43]. In patients with uncontrolled T2D, add-on treatment of dapagliflozin significantly improved the peripheral microvascular endothelial dysfunction as assessed by reactive hyperemia peripheral arterial tonometry[44].

The effect of SGLT2is on endothelial function has been elucidated in clinical settings. Empagliflozin has been associated with improvements in arterial stiffness, as indicated by reductions in carotid radial pulse wave velocity and radial, carotid, and aortic augmentation indices[45]. Dapagliflozin has been demonstrated to improve micro- and macrovascular endothelial function in T2D patients with atherosclerotic disease, potentially through increased NO production[46]. In patients with T2D and established HF, dapagliflozin led to significant reductions in intercellular adhesion molecule 1 (ICAM-1), a surrogate marker of the endothelial function, compared with placebo[47]. However, no significant difference was observed in flow-mediated dilation after 12 weeks of treatment between the groups[47]. Similar positive effects were observed in several clinical studies, which have reported that SGLT2is improved the endothelial function in patient with or without HF[42]. However, conflicting results were presented in a study of drug-naïve patients with T2D that revealed that dapagliflozin did not improve markers of endothelial function (eg, nitrotyrosine, endothelin, and β2-microglobulin) after an 8-week treatment[48]. Another randomized controlled trial (RCT) in patients with T2D and coronary artery disease demonstrated no significant difference in flow-mediated dilation between the dapagliflozin treatment and placebo groups[49].

Aside from improved endothelial dysfunction and control of conventional risk factors, SGLT2is exert anti-atherosclerotic effects mainly through several mechanisms: increasing ketogenesis, reducing uric acid levels, inhibiting macrophage inflammation and foam cell formation, regulating autophagy, and improving vascular smooth muscle dysfunction[50], which may play an important role in reducing HF as well as its complications.

Taken together, although most studies have suggested that SGLT2is exert favorable direct effects against endothelial dysfunction such as increased NO production, reduced oxidative stress, and inhibited inflammation, further research is required to fully understand the complex mechanism by which SGLT2is benefit patients with endothelial dysfunction-related HF.

Autophagic Flux

HF is characterized by excessive amounts of nutrients within cardiomyocytes as a result of the accumulation of glucose, amino acids, and long-chain fatty acids. This accumulation in cardiomyocytes is caused by the blockade of oxidative metabolism due to mitochondrial dysfunction in HF[51]. Increased myocardial glucose uptake in HF has been associated with increased expression of glucose transporter 1 in conjunction with increased activity of phosphofructokinase 1, and glycolytic flux. Nevertheless, this increase in glycolysis is insufficient to completely compensate for the energy deficit in HF or to restore cardiac function[51]. Consequently, nutrient-deprivation pathways such as AMPK, sirtuin (SIRT) 1, SIRT 3, peroxisome proliferator-activated receptor-γ coactivator 1α (PGC1α) signaling are inhibited, whereas nutrient-surplus pathways such as Akt/mammalian target of rapamycin complex (mTORC) signaling are stimulated. This leads to increased endoplasmic reticulum stress and reduced activation of the degradative lysosomal enzymes responsible for removing metabolic waste through a process called "autophagy"[42,52].

These cellular wastes are constituents of the inflammasome, the hazardous damaged organelles and debris that SGLT2is could promote to clear off, providing a multi-directed cardioprotective action that deserves further investigation[53].

SGLT2 inhibition may mimic a fasting state characterized by caloric loss in the urine, shrinkage of fat depots, and ketogenesis at the systemic level[52]. At a cellular level, SGLT2 inhibition downregulates nutrient-surplus signaling pathways such as the mTOR signaling pathway and upregulates nutrient-deprivation signaling pathways such as AMPK, SIRT1, SIRT3, and PGC1α pathways[52]. Consequently, SGLT2is promote autophagic flux in the heart through the upregulation of these nutrient-deprivation signaling pathways, thereby reducing endoplasmic reticulum stress, inhibiting proinflammatory pathways, enhancing mitochondrial function, diminishing oxidative stress, and preventing cardiomyocyte apoptosis[52,54]. Therefore, the nutrient deprivation hypothesis can accurately recapitulate the highly distinctive pattern of molecular and cellular benefits of SGLT2is in the failing heart[52].

Numerous experimental studies have demonstrated that increased autophagy flux and nutrient-deprivation signaling pathways mediate the cardioprotective effects of SGLT2is[52]. The preservation of cell viability and reduction of cellular stress by SGLT2is are accompanied by an upregulation of autophagy flux and nutrient-deprivation sensors (e.g., SIRT2, SIRT3, and AMPK) in various models of cardiac injury[52]. These effects have been observed even in isolated hearts that do not express known SGLT2 receptors and were not influenced by changes in environmental oxygen, ketones, or glucose. Notably, the cytoprotective effects of these drugs disappear when SIRT1, SIRT3, and AMPK signaling and autophagy were blocked, indicating that these pathways mediate the benefits of SGLT2is observed in these experimental models[52]. SGLT2i-induced changes in nutrient signaling may be associated with a biologically driven inverse relationship between the expression of nutrient-deprivation sensors (e.g., SIRT1 and SIRT3) and SGLT2 expression, with changes in nutrient transport (e.g., blockage of glucose transporter 1 by SGLT2is) or with binding of SGLT2is directly to the active sites of SIRT1, SIRT3, or mTOR[52]. In silico analyses of drug–drug interactions and proteomic analyses of samples from clinical trials of SGLT2is provide further evidence supporting this framework[52]. However, because the heart does not express SGLT2, the effect of SGLT2 inhibition on cardiac AMPK/SIRT1 and SIRT3/PGC1α/Akt/mTORC pathways has yet to be fully elucidated. Subsequent studies are required to address this evidence gap.

Fuel Energetics

Several studies have demonstrated dramatic changes in energy metabolism in the failing heart[4]. As HF progresses, a persistent decline in mitochondrial oxidative metabolism is observed, leading to an increased reliance of the heart on glycolysis as an energy source. The reduced capacity for mitochondrial glucose oxidation in the failing heart results in decreased energy production and a fuel-starved heart. In addition, a failing heart exhibits uncoupling between glycolysis and glucose oxidation, which results in increased proton production, which, in turn, causes a decrease in cardiac efficiency (cardiac work/O_2 consumed). This decrease in cardiac efficiency occurs not only in patients with HFrEF but also in patients with HFpEF with left ventricular (LV) hypertrophy. In both the cases, the LV mechanical efficiency is reduced[4].

Fuel efficiency is measured by the P/O ratio, which reflects the number of adenosine triphosphate (ATP) molecules (P) generated per oxygen atom (O) consumed by the mitochondrial electron transport chain. The P/O ratio of ketones is 2.56 for ATP production compared with 2.58 for glucose and 2.28 for palmitate, so their efficiency for ATP generation per

oxygen atom is higher than that of fatty acids and lower than that of glucose [55]. Table 2 summaries the fuel energy generated of various substrates.

Emerging evidence suggests that ketones are favorable substrates that generate more free energy per mole of oxygen to fuel ATP production than do free fatty acids metabolism or glycolysis in the failing heart[56]. The failing heart is primarily energy starved because of reduced mitochondrial oxidative metabolism, and an increase in ketone oxidation has been proposed to be an adaptive metabolic process in the failing heart[4]. It was reported that blood ketones were almost double in patients with HF compared to the controls without HF (median 0.27 vs. 0.15 mmol/L, respectively; p <0.05)[57]. SGLT2is induce calorie loss through increased urinary excretion, resulting in glycosuria, which is accompanied by increased glucagon synthesis, enhanced fatty acid oxidation, and the increased mobilization of adipose tissue, leading to increases in circulating ketone levels[4]. The low ketonemia levels induced by SGLT2is have been suggested to fuel the metabolic state of the heart and thus improve cardiac energetics[55]. In a post hoc analyses of a 52-week open-label Japanese study in ~ 1300 patients with T2D, fasting ketones were >1mmol/L in 12–20% of patients treated with 100 or 200 mg canagliflozin daily[58]. Unfortunately, there was no control group in this study. In another study, 25 mg empagliflozin daily rose fasting β-OHB levels from 0.25 to 0.56mmol/L (p < 0.01) over 4 weeks of treatment in patients with T2D[59].

SGLT2is may enhance the utilization of ketones during the treatment of HF through multiple pathways, including increasing hepatic production of ketones, promoting the utilization of cardiac ketones, regulating mitochondrial metabolism, activating the energy sensor AMPK to restore energy metabolism, and restoring normal numbers of mitochondria in diseased hearts[2,60]. Notably, these ketone-induced improvements in cardiac energetics may not increase cardiac efficiency[60]. SGLT2is can attenuate inflammation and hypoxia and facilitate the conversion of myofibroblasts to erythropoietin-producing fibroblasts, which can provide an increased oxygen supply for energy metabolism in the heart[60].

The effects of SGLT2is on ketone utilization, their interaction with other potentially adverse pathways, and their relevance for cardiac function and CV benefits remain controversial[61]. Rather than superfueling the heart, SGLT2is have been hypothesized to induce a dormancy state characterized by energy preservation and high resistance to environmental stressors. This state, similar to animal hibernation, involves fuel storage and the suppression of metabolic rates[62]. However, this hypothesis is largely based on experimental data from animal models. Therefore, dedicated studies, including those in humans, are required to test this hypothesis. SGLT2is have also been hypothesized to exert their effects by activating low-energy sensors, which mimic a fasting tran-

Table 2. Fuel energy generated of various substrates

Substrate, complete oxidation of one molecule	Adenosine triphosphate generated	Atoms of oxygen consumed	P/O ratio*	Energy liberated, kJ/mol of 2-carbon units
Glucose	31	12	2.58	935.5
β-hydroxybutyrate	23	9	2.56	1019.2
Palmitate	105	46	2.28	1246.8
Pyruvate	15	6	2.50	776.9

*P/O ratio is the number of adenosine triphosphate molecules generated per oxygen atom consumed by the mitochondrial electron transport chain.

scriptional paradigm and lead to cardiac benefits[63]. SGLT2is may deceive cells into perceiving a fasting and hypoxic state. Oxygen deprivation stimulates the activation of the SIRT1 and AMPK signaling pathways, which are adaptive responses to starvation and cellular stress. AMPK helps preserve mitochondrial function, thereby leading to a reduction in ROS formation and attenuation of the resulting proinflammatory and proapoptotic responses. SIRT1 activates hypoxia-inducible factor-2 a (HIF-2a) and possibly hypoxia-inducible factor-1 a (HIF-1a) under certain conditions, which are the principal stimuli for erythropoietin synthesis. This relationship may explain why statistical mediation analyses of large-scale trials have indicated that erythrocytosis is the most powerful predictor of the action of SGLT2is in reducing HF events[63]. The enhancement of HIF-1a/HIF-2a signaling by SGLT2is may amplify the autophagic flux already augmented by AMPK/SIRT1, thereby contributing to the remarkable cardiac benefits of these drugs[63].

Taken together, SGLT2is may enhance the energy supply to the failing heart through a shift in fuel energetics; however, further research is required to explore their roles in cardiac fuel energetics.

Adverse Remodeling

Cardiac remodeling refers to changes in the geometry, size, mass, and function of the heart that result from interstitial, cellular, and molecular changes. Adverse cardiac remodeling is characterized by decreased autophagy, increased apoptosis and necrosis, altered energy metabolism, and impaired myocardial oxygen supply and demand[64]. Cardiac remodeling plays a critical role in the development and progression of HF. Therefore, reversing adverse cardiac remodeling is a plausible central mechanism underlying the cardioprotective benefits of SGLT2is[64].

Several studies have demonstrated that SGLT2is may be involved in the reversal of cardiac remodeling. For example, an analysis of echocardiograms in a small uncontrolled study of T2D patients with established CVD demonstrated that empagliflozin led to a regression of LV mass and improvement in diastolic function[65]. Dapagliflozin has been reported to significantly reduce LV mass in T2D patients with LV hypertrophy along with reductions in adipose tissue, body weight, systolic BP, insulin resistance, and high-sensitivity C-reactive protein[66]. Similarly, a retrospective study on T2D patients with or without HF demonstrated that SGLT2is significantly reduced the echocardiographic LV end-diastolic diameter[67]. The SGLT2i-induced improvements in LVEF and diastolic function were more prominent in HF patients, especially in those with HFrEF[67]. Large-scale clinical trials such as DAPA-HF[12], EMPEROR-Reduced[13], and the randomized trial of empagliflozin in nondiabetic patients with HF and reduced EF (EMPA-TROPISM)[68] have consistently demonstrated that SGLT2is counteract and improve adverse cardiac remodeling in patients with HFpEF and HFrEF, which could explain the observed CV benefits[69]. However, in a RCT of patients without diabetes and significant HF who were at risk for adverse cardiac remodeling, treatment with empagliflozin did not lead to a significant reduction in LV volumes or EF after 6 months[70].

Although SGLT2is have been demonstrated to exert considerable beneficial effects on the reversal of cardiac remodeling, the exact underlying mechanisms remain unclear, and several hypotheses have been proposed. First, SGLT2is have been hypothesized to promote sustained reductions in intravascular volume through diuretic and natriuretic effects, leading to a decrease in LV stretch and wall stress, which contributes to a reduction of LV volumes[71]. This hypothesis was evaluated in the EMPA-TROPISM trial, which suggested that compared with placebo, empagliflozin led to a significant reduction of LV end-diastolic volume (−25.1 vs. −1.5 mL; $p < 0.001$) and LV end-systolic volume (−26.6 vs. −0.5 mL; $p < 0.001$) and significant improvements in LVEF

(6.0 vs. −0.1; $p < 0.001$) [68]. This hypothesis was supported by several studies, which suggests a direct beneficial effect of SGLT2is on patients with HF (HFpEF or HFrEF) through a significant reduction in pulmonary artery pressures[54]. Second, SGLT2is may lower LV afterload by reducing the BP and arterial stiffness[71]. This hypothesis was evaluated in a RCT of dapagliflozin on left ventricular hypertrophy in people with type 2 diabetes (DAPA-LVH trial), which suggested that dapagliflozin reduced LV mass assessed by cardiac magnetic resonance imaging in the intention-to-treat analysis (change in LV mass: dapagliflozin group –3.95 ± 4.85 g vs. placebo group –1.13 ± 4.55 g; $p = 0.018$), leading to an absolute mean difference of –2.82 g (95% confidence interval –5.13 to –0.51)[66]. Additionally, SGLT2is have been demonstrated to reduce cardiomyocyte passive stiffness by enhancing the phosphorylation levels of myofilament regulatory proteins in myocardial fibers from patients and rats with HFpEF, which has been speculated to partially contribute to LV hypertrophy regression and improvement in diastolic dysfunction[72]. Notably, the effects of SGLT2is on diastolic dysfunction were independent of diabetes[72]. Third, cardiac fibrosis may occur as a result of chronic inflammation, thereby exacerbating cardiac dysfunction and HF[28]. The ability of SGLT2is to reduce cardiac fibrosis has been well documented in experimental models of obesity/diabetes[28]. This hypothesis was evaluated in a rat model of mitral regurgitation-induced myocardial dysfunction, which suggested that dapagliflozin reduced LV fibrosis potentially through the attenuation of apoptosis and endoplasmic reticulum stress[73]. Similar results were reported in a study of infarcted animal hearts, which showed that dapagliflozin attenuated cardiac fibrosis by regulating the macrophage polarization via STAT3 signaling[74]. Fourth, the increase in levels of ketones following SGLT2is can ameliorate pathological remodeling[69]. This hypothesis was evaluated in animal models showing that the absence of the enzyme succinyl-CoA:3-oxoacid CoA transferase, which is necessary for the terminal oxidation of ketones, can contribute to the acceleration of pathological remodeling[69]. Similarly, greater pathological remodeling is evidenced in the SCOT knockout models[75], suggesting some benefits of ketones in cardiac remodeling. Fifth, The reversal of adverse cardiac remodeling with SGLT2is may be associated with improvements in myocardial energetics, a reduction in cardiac inflammation and oxidative stress, and the inhibition of the mTORC pathway[4]. This hypothesis was evaluated in experimental studies suggesting that SGLT2is exert cardioprotective effects against ischemia/reperfusion injury, which may be attributable to a decrease in calmodulin kinase II activity, leading to improved sarcoplasmic reticulum (SR) calcium flux and increased contractility[4]. Finally, SGLT2is may exert downstream epigenetic-oriented effects on cardiac cells, which may contribute to the reversal of cardiac remodeling[76]. This hypothesis was evaluated by several preclinical models of cardiac remodeling, which suggested that SGLT2is could improve vascular health and cardiac fibrosis by modulating specific molecular pathways, and, in part, through downstream epigenetic interference, especially for empagliflozin[76].

Taken together, the inhibition of SGLT2 may reverse adverse cardiac remodeling, thereby reducing LV wall stress and improving cardiac function[4]. However, further research is warranted to fully understand the complex mechanism underlying the effects of SGLT2is on cardiac remodeling.

Ionic Homeostasis

Voltage-gatedion channels play a crucial role in the maintenance of optimal cardiac contractile function. Disruptions in ionic homeostasis are associated with electrical disturbances that can contribute to the development of arrhythmias and insufficient cardiac output/relaxation, especially in HF[2]. Therefore, targeting the underlying ionic imbalances associated with HF is an attractive therapeutic strategy. Numer-

ous clinical studies have demonstrated that treatment with SGLT2is reduced the risk of ventricular arrhythmias and sudden cardiac death in patients with HF[2]. These results highlight the protective effect of SGLT2is against life-threating ionic imbalances in HF. Several cardiac mechanisms have been proposed to explain the effects of SGLT2is on ionic homeostasis during HF. Among these mechanisms, the inhibition of cardiac sodium/hydrogen exchanger-1 (NHE-1), reduction of the cardiac late sodium current (late-I_{Na}), and decrease in the cytosolic calcium/calmodulin-dependent kinase II (CaMKII) are particularly notable[54].

NHE-1 is associated with the regulation of sodium flux in cardiomyocytes, and its overexpression is associated with cellular sodium overload, which can contribute to the development and progression of HF[54]. Experimental studies have demonstrated that NHE-1 inhibition minimized cardiomyocyte injury and reduced HF severity, cardiac remodeling, hypertrophy, fibrosis, and systolic dysfunction[77]. The cardioprotective effects of SGLT2is have been hypothesized to be exerted through the inhibition of NHE-1. Several animal studies have demonstrated that SGLT2is can directly reduce the activity of NHE-1 by lowering cytoplasmic calcium and sodium concentrations in the myocardium[54], suggesting cardioprotective effects of this class of drugs through the mechanism of NHE-1 inhibition. In isolated human hearts, empagliflozin was observed to reduce the expression of NHE-1 in cardiomyocytes, which may help improve contractile dysfunction by reducing intracellular calcium and sodium load[78]. To date, no clinical trial has investigated the effects of SGLT2is on NHE-1 as a feasible therapy for the treatment of HF. Therefore, further research is warranted to examine the clinical efficacy of NHE-1 inhibition by SGLT2is, particularly in patients with HF.

Voltage-gated sodium channels in cardiomyocytes play a crucial role in initiating the action potential by enabling rapid sodium entry followed by rapid inactivation[2]. However, a small fraction of sodium channels may not become inactive, leading to the generation of late-I_{Na}[54]. Several studies have indicated that the induction of late-I_{Na} may contribute to the development of arrhythmias and HF by increasing cytoplasmic calcium concentration, prolonging the action potential within cardiomyocytes, and generating both early and delayed afterdepolarizations[54]. In addition, the upregulation of CaMKII plays a pivotal role in the stimulation of late-I_{Na} and the pathogenesis of HF[79]. In an experimental study, the long-term inhibition of SGLT2 with canagliflozin was demonstrated to attenuate myocardial ischemia/reperfusion injury, irrespective of diabetic status, potentially through a decrease of CaMKII levels[79]. Empagliflozin also reduced the CaMKII-dependent phosphorylation of cardiac ryanodine receptor type 2, a receptor involved in the disturbed regulation of calcium and pathogenesis of HF. This reduction in CaMKII-mediated calcium leak from the SR and the improvement in contractility have been observed in failing ventricular human and murine cardiomyocytes[80,81].

In failing ventricular human and murine cardiomyocytes, SGLT2is were reported to reduce late-I_{Na}, potentially inhibiting the dysfunction of the I_{Na} induced by HF[54]. This reduction in late-I_{Na} is believed to be a drug class effect of SGLT2is[2]. In a translational murine model of HFpEF, direct treatment with empagliflozin did not cause changes in late-I_{Na}; however preincubation (4 h) with empagliflozin reversed late-I_{Na} upregulation[82]. This suggests that empagliflozin inhibits late-I_{Na} in HFpEF through an indirect mechanism that may involve the suppression of CaMKII activity and therefore a reduction in the CaMKII-dependent phosphorylation of cardiac sodium channels, rather than through a direct inhibitory mechanism on cardiac sodium channels[54,82]. These novel findings provide important insights into a plausible molecular mechanism by which the SGLT2is contribute to the robust protection against HF. However, further research is necessary

to confirm these findings in clinical trials involving patients with HF and to investigate the potential interrelationship among these pathways.

Conclusions

The SGLT2is are relatively new class of antidiabetic medications that constitute a novel and promising treatment option for patients with HF based on current evidence. Now, SGLT2is have emerged as a prominent therapy for HF and are currently formally recommended as Level of Evidence A in patients with symptomatic chronic HFrEF irrespective of the presence of T2D by the American Heart Association, American College of Cardiology, and Heart Failure Society of America guideline for the management of HF in 2022. Additionally, SGLT2is are recommended as Level of Evidence A in patients with T2D and established HF (preserved or reduced ejection fraction) by the American Diabetes Association guidelines for diabetes care in 2023. Ongoing clinical trials are exploring the potential synergistic benefits of combining SGLT2is with other drugs such as mineralocorticoid antagonists and endothelin receptor antagonists.

This review mainly focused on the direct SGLT2is effects on the heart that are independent of effects on the kidney. While control of conventional risk factors seems unable to explain the significant benefit of these drugs on HF endpoints, several novel mechanisms of SGLT2is are proposed, including anti-inflammatory, antifibrotic, antioxidant, metabolic effects, improved cardiac remodeling, mediated fuel energetics, increased autophagic flux, and direct effects on cardiac ion-homeostasis. Given the beneficial effects of these drugs in HF, additional translational studies are needed to fully elucidate the biochemical alterations induced by SGLT2is in HF. In particular, human studies with sufficient power that have fully elaborated on the biochemical alterations caused by this drug class in HF are lacking. These data are crucial for understanding the therapeutic benefits of SGLT2is and their potential in reducing the need for multiple medications by targeting multiple pathways involved in HF pathogenesis.

Conflicts of interest

No conflicts of interest associated with this manuscript to declare.

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第2型鈉-葡萄糖共同轉運蛋白抑制劑在治療心臟衰竭的新概念：從臨床實證到潛在機轉

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摘　要

心臟衰竭是一個重要的大眾健康問題，其盛行率隨著人口老化和第 2 型糖尿病個體數的盛行而有增加的趨勢。心臟衰竭之病理生理學有著錯綜複雜的致病機轉，源自於各種有害的途徑（發炎、氧化壓力、血管內皮功能失調、心肌細胞逆向重塑、減少細胞自噬流動作用等等）最終導致心臟輸出功能的衰竭。儘管第 2 型鈉 - 葡萄糖共同轉運蛋白抑制劑的推出，起初是構思作為治療第二型糖尿病的一種抗糖尿病用藥，卻發現該藥物對於心臟衰竭治療有著突破性的變革，同時根據各個相關學會的治療指引，目前該藥物已正式推薦做為心臟衰竭治療的一種用藥。除了第 2 型鈉 - 葡萄糖共同轉運蛋白抑制劑之外，迄今並沒有其它的口服抗糖尿病用藥對於心臟衰竭之事件有此顯著的好處。然而，儘管第 2 型鈉 - 葡萄糖共同轉運蛋白抑制劑對臨床作用有潛在廣泛之影響，許多關於它們機轉的作用模式之疑問有待進一步去探討。本篇論文旨在提供彙整有關主要心血管結果試驗在評估第 2 型鈉 - 葡萄糖共同轉運蛋白抑制劑治療心臟衰竭的效能，同時探討該藥物藉由各式各樣的機轉來提供治療心臟衰竭的好處。這些機轉將主要集中在第 2 型鈉 - 葡萄糖共同轉運蛋白抑制劑直接對心臟的脫靶效應 (off-target effects)。不管是否有沒有糖尿病存在，這些機轉可以用來幫助解釋該藥物對於心臟衰竭病患有益之影響。儘管如此，鑒於心肌細胞格外地缺乏第 2 型鈉 - 葡萄糖共同轉運蛋白，研究證據顯示該類藥物之獨立的第 2 型鈉 - 葡萄糖共同轉運蛋白效應可能透過脫靶效應來影響心肌細胞。因此，未來仍需進一步研究來探討第 2 型鈉 - 葡萄糖共同轉運蛋白抑制劑作用在心肌細胞的潛在機轉，以期能提供其在機轉方面和額外的臨床證據來評估第 2 型鈉 - 葡萄糖共同轉運蛋白抑制劑跨越心臟衰竭各個層面之各種效應。