Role and molecular mechanisms of SGLT2 inhibitors in pathological cardiac remodeling (Review)

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Abstract. Cardiovascular diseases are caused by pathological cardiac remodeling, which involves fibrosis, inflammation and cell dysfunction. This includes autophagy, apoptosis, oxidative stress, mitochondrial dysfunction, changes in energy metabolism, angiogenesis and dysregulation of signaling pathways. These changes in heart structure and/or function ultimately result in heart failure. In an effort to prevent this, multiple cardiovascular outcome trials have demonstrated the cardiac benefits of sodium-glucose cotransporter type 2 inhibitors (SGLT2is), hypoglycemic drugs initially designed to treat type 2 diabetes mellitus. SGLT2is include empagliflozin and dapagliflozin, which are listed as guideline drugs in the 2021 European Guidelines for Heart Failure and the 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America Guidelines for Heart Failure Management. In recent years, multiple studies using animal models have explored the mechanisms by which SGLT2is prevent cardiac remodeling. This article reviews the role of SGLT2is in cardiac remodeling induced by different etiologies to provide a guideline for further evaluation of the mechanisms underlying the inhibition of pathological cardiac remodeling by SGLT2is, as well as the development of novel drug targets.

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Contents

1. Introduction

In the event of external triggers, cardiac insufficiency responds to adaptive alterations in both the structure and function of the heart, commonly referred to as cardiac remodeling. These alterations include changes in genomic expression levels, cell morphology and abnormal interstitial secretion (1,2). Cardiac remodeling is divided into physiological and pathological types. Physiological cardiac remodeling is a reversible adaptive reaction that primarily occurs during growth, exercise and pregnancy (3). Where pathological cardiac remodeling is an irreversible adaptive response caused by numerous conditions, including myocardial infarction (MI), ischemia/reperfusion (I/R) injury, pressure loading, inflammation and oxidative stress (4,5). Direct manifestations of cardiac remodeling include myocardial hypertrophy and cardiac fibrosis and continued poor remodeling can lead to heart failure (6-8). Thus, determining the mechanisms that lead to cardiac remodeling and preventing undesirable remodeling is essential.

Sodium-glucose cotransporter type 2 inhibitors (SGLT2is) are hypoglycemic medications that inhibit SGLT2 in the renal tubules, decreasing glucose reabsorption, lowering the renal glucose threshold and initiating glucose excretion in the urine (9). Compared with other traditional hypoglycemic drugs, SGLT2is are primarily used for treating type 2 diabetes but have also been reported to exert cardiovascular benefits. According to cardiovascular outcome studies, SGLT2is reduce the incidence of hospitalization due to heart failure (10-14). The 'new tetrad' of cornerstone heart failure medications has replaced the original 'golden triangle' and

now includes beta-blockers, aldosterone receptor antagonists, renin-angiotensin system inhibitors and SGLT2is (15,16).

The four SGLT2 inhibitors widely used in clinical treatment are Empagliflozin (EMPA), Dapagliflozin (DAPA), Canagliflozin (CANA) and Ertugliflozin; these have been approved by the US Food and Drug Administration and the European Medicines Agency (17). EMPA and DAPA are widely used for heart failure prevention and treatment (15,16). Existing studies have confirmed the lack of SGLT2 expression in cardiac tissue, thereby necessitating the investigation of the myocardial protective effect of SGLT2is (18). It has been suggested that SGLT2is exerts a diuretic effect via glomerular reabsorption, reducing blood volume and cardiac load and protecting the heart by reducing myocardial oxygen consumption. However, as this diuretic effect is dependent on blood glucose concentration, the cardiac benefit in non-diabetic patients has not been determined (19). Therefore, the protective effect of SGLT2is on the myocardium may be exerted directly on the heart. Several studies have shown that the anti-heart failure effect of SGLT2is may be mediated by inhibiting or reversing cardiac remodeling (20-22).

Currently, the molecular mechanisms and signaling pathways of SGLT2is in cardiac remodeling are being investigated. The present review provides a foundation and supports the investigation of novel mechanisms of cardiac remodeling and heart failure, as well as the development of novel drug targets based on the function and molecular mechanisms of SGLT2is-mediated inhibition of pathological cardiac remodeling (Fig. 1).

2. Effects of SGLT2is on cardiac structure and function

Pathological cardiac remodeling is often manifested by changes in the morphology and size of the left ventricle. In addition, the left ventricular (LV) mass index (LVMI) and LV ejection fraction (LVEF) are used as evaluation indexes of cardiac structural function (23,24). Studies have reported that SGLT2isThe improved cardiac function is mainly manifested as increased LVEF and decreased LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), left atrial volume index (LAVI) and LVMI (22,25-35). However, LV diastolic dysfunction (LVDD) often manifests as altered LV diastolic filling and is assessed based on the peak mitral E wave velocity to early mitral or septal annular tissue Doppler velocity ratio (E/e'), peak mitral E wave velocity to A wave velocity ratio and LAVI (36). SGLT2is also improved ejection fraction, LVEDV, LVESV and diastolic dysfunction in animal models of heart failure (37-46).

Regarding cardiac structure, the LV mass (LVM), LV wall thickness and LV wall thickness-to-cavity radius can be used to determine the structural and morphological changes of the LV. Specifically, increased LVM has been considered a marker of clinical LV hypertrophy (47). Several studies have demonstrated that the cardiovascular benefits of SGLT2is may be achieved through reduced LVM, as it occurs without a decline in the volume, which reflects the decrease in ventricular wall thickness (26,29,30,48). However, the mechanisms of decreasing wall thickness are yet to be elucidated. In the present review, the effects of SGLT2is on cardiac structure and function in patients with cardiovascular disease and animal models were summarized (Tables I and II).

3. Effects of SGLT2is on myocardial hypertrophy in cardiomyocytes and cardiac fibrosis in cardiac fibroblasts

Pathological cardiac remodeling causes hypertrophy of cardiomyocytes and the proliferation of non-cardiomyocytes in numerous cardiovascular diseases, including hypertension, diabetic cardiomyopathy, aortic stenosis, MI, pathological stimulation, cardiomyocyte hypertrophy and cardiac fibrosis (3). The characteristics of cardiac hypertrophy are abnormal size and function of myocardial cells, often manifested as increased ventricular mass, myocardial cell volume and expression of fetal genes, such as atrial natriuretic peptide, brain natriuretic peptide and β-myosin heavy chain (49). Myocardial fibrosis, the excessive deposition of extracellular matrix, is closely associated with the severity of myocardial fibrosis. Type I collagen is the most abundant structural protein (50,51). Myocardial fibroblasts are the main cellular effectors that lead to cardiac fibrosis. Pathological stimuli can reduce the number of cardiomyocytes, which in turn stimulates inflammation. In order to compensate for the loss of cardiomyocytes, cardiac fibroblasts proliferate and differentiate into myofibroblasts, leading to scar formation (52).

Cardiac hypertrophy and cardiac fibrosis are the major pathological processes in cardiac remodeling and are closely related to the prognosis of cardiovascular diseases, making them the primary intervention targets for heart failure (53,54). Several studies have demonstrated that SGLT2is attenuates or inhibits cardiomyocyte hypertrophy and cardiac fibrosis by regulating multiple signaling pathways in numerous models, such as transverse aortic constriction (TAC), left coronary artery ligation MI and diabetes (39,40,55-63).

4. Role of SGLT2is in cellular pathophysiological processes

Apoptosis. Apoptosis is a type of programmed cell death that serves a key role in embryonic development and tissue homeostasis (64). Apoptosis is mediated by death receptors, also known as extrinsic apoptotic pathways and mitochondria, also called intrinsic apoptotic pathways, both of which can activate cysteine-dependent proteases (caspases) (65). Apoptosis serves a crucial role in the development of the heart and is associated with the occurrence and development of numerous cardiovascular diseases. Studies have reported that apoptosis is a pathological feature of MI and heart failure, and that the inhibition of apoptosis can prevent and treat post-MI remodeling and heart failure (66).

Further studies have reported that SGLT2is reduces cardiac remodeling and improves cardiac function by inhibiting the apoptosis pathways. EMPA inhibits cardiomyocyte apoptosis and improves cardiac remodeling in early MI in non-diabetic mice (67).

In mice with autoimmune myocarditis induced by α-myosin-heavy chain peptides, CANA markedly reduces the Bax/Bcl-2 ratio and the level of cleaved caspase-3 protein, followed by inhibition of apoptosis, which was reported to improve myocarditis (68). In cardiac I/R rats, DAPA-induced pre-ischemia upregulated the levels of anti-apoptotic protein Bcl-2 to protect cardiomyocytes from apoptosis, thereby alleviating cardiac mitochondrial dysfunction by reducing reactive oxygen species (ROS) production (43). DAPA

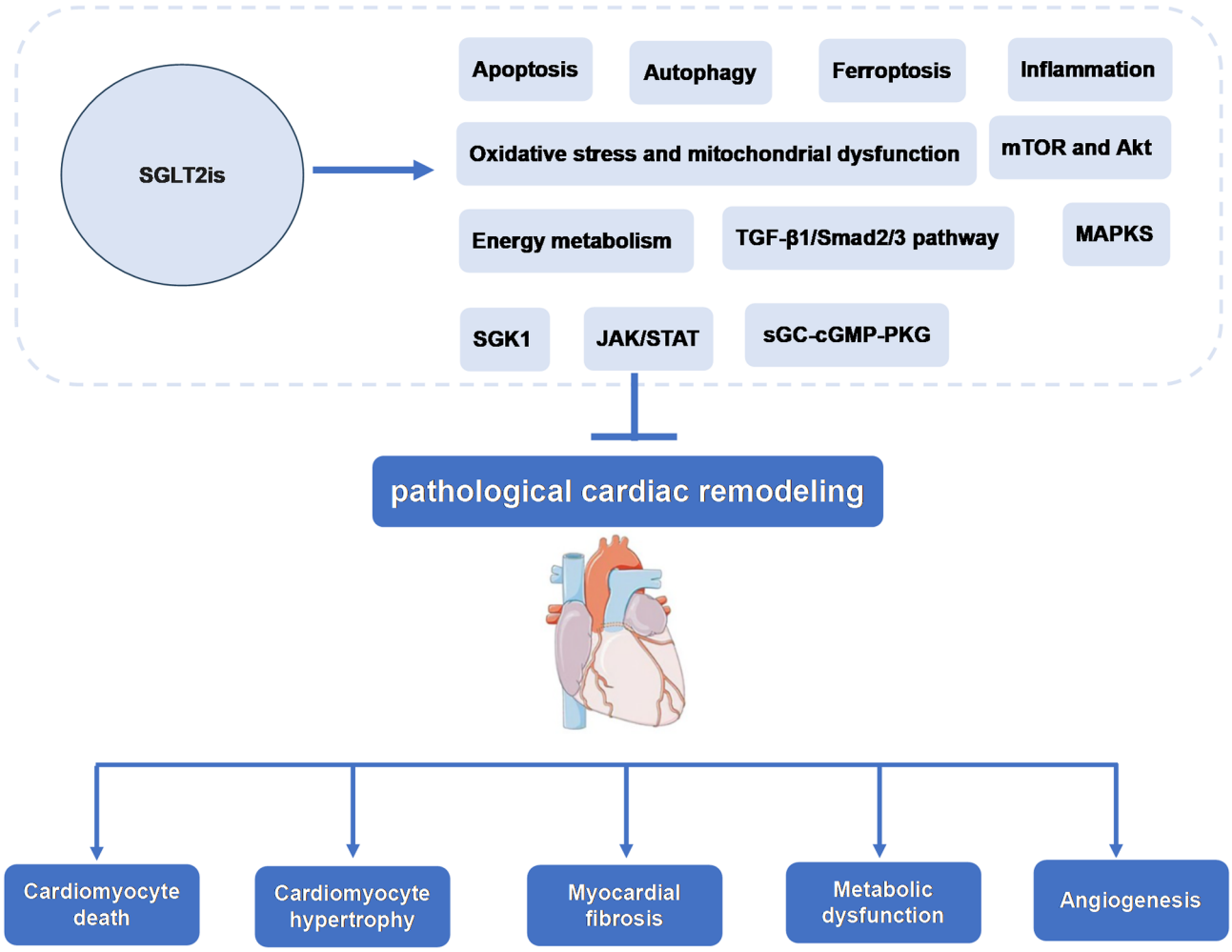

Figure 1. Possible role and mechanism of SGLT2is in inhibiting pathological cardiac remodeling. SGLT2is, sodium-glucose cotransporter type 2 inhibitors; JAK, Janus kinase; STAT, signal transducer and activator of transcription; SGK1, Serum/glucocorticoid regulated kinase 1; sGC, soluble guanylate cyclase enzyme; cGMP, cyclic guanosine monophosphate; PKG, cGMP-dependent protein kinase.

mediates the cardioprotective effect in diabetic rats by activating the phosphorylation of Akt, JAK2 and MAPK signaling cascades, increasing the erythropoietin levels and reducing apoptosis (69). DAPA also normalizes mitochondrial fission and reduces cardiomyocyte apoptosis by activating the phosphoglycerate mutase member 5 (PGAM5)/dynamin-related protein 1 (Drp1) signaling pathway, thereby improving cardiac remodeling after acute MI (70). However, this study did not use an agonist for the PGAM5/Drp1 pathway, so the relationship between DAPA and the PGAM5/Drp1 signaling pathway could not be assessed.

A recent study reported that in Doxorubicin-induced cardiac dysfunction, DAPA decreased the cardiac expression of Bax and cleaved caspase-3, but increased the expression of Bcl-2, as well as signal transducer and activator of transcription 3 (STAT3) that was subsequently inhibited by Doxorubicin (71). These findings indicate that DAPA activates the expression of sirtuin1 (SIRT1), which inhibits the protein kinase RNA-like endoplasmic reticulum (ER) kinase (PERK)-eukaryotic translation initiation factor 2α (eIF2α)-C/EBP homologous protein signaling pathway of the ER stress response in angiotensin II (Ang II)-treated cardiomyocytes to reduce cardiomyocyte apoptosis and improve TAC-induced cardiac remodeling in mice (72). Therefore, it may be suggested that SGLT2is improves damaged cardiac function by continual myocardial cell apoptosis.

Many of the mechanisms are effectuated through the mitochondrial pathway. However, only a small number of studies have assessed the role of SGLT2is in myocardial cell apoptosis induced by the death receptor pathway. Hence, this mechanism should be evaluated to understand the anti-apoptotic mechanism of SGLT2is.

Autophagy. Autophagy is a process that degrades and recirculates damaged organelles, misfolded proteins and other macromolecules through lysosomal-dependent pathways to maintain cell homeostasis and function (73). Previous studies have shown a crucial role of basal autophagy in cardiac development and in the maintenance of normal cardiac function (74-77). However, insufficient or excessive autophagy can affect the development of pathological cardiac remodeling (78-80). Furthermore, the activation of autophagy leads to the death of cardiomyocytes in MI and I/R injury and has been shown to have a dual effect in numerous research models, which may be related to the Beclin 1 (BECN1) or AMPK-mammalian target of rapamycin (mTOR) pathways (81-83). Several studies have

Table I. Effects of SGLT2 inhibitors on cardiac structure and function in patients with cardiovascular disease.

Author(s), year	Clinical trial number/type	Patient characteristics	SGLT2i	Dose and action time	Diagnostic method	Outcomes	(Refs.)
Soga *et al*, 2018	UMIN000019789	Patients with type 2 diabetes mellitus with chronic heart failure (n=58)	DAPA	5 mg, qd; 6 months	Echocardiography	LAVI↓; LVMI↓; E/e'↓	(29)
Verma *et al*, 2019	NCT02998970	Patients with type 2 diabetes mellitus and coronary artery disease (n=49)	EMPA	10 mg, qd; 6 months	CMRI	LVM↓; LVEF↑; LVMI↓	(26)
Brown *et al*, 2020	NCT02956811	Left ventricular hypertrophy in individuals with type two diabetes (n=66)	DAPA	10 mg, qd; 12 months	CMRI	LVM↓	(30)
Santos-Gallego *et al*, 2021	NCT03485222	Non-diabetic patients with heart failure and reduced ejection fraction (n=48)	EMPA	10 mg, qd; 6 months	CMRI	LVM↓; LVEF↑; LVEDV↓; LVESV↓	(25)
Lee *et al*, 2021	NCT03485092	Left ventricular volumes in patients with type 2 diabetes, or prediabetes and heart failure with reduced ejection fraction (n=105)	DAPA	10 mg, qd; 36 weeks	CMRI	LVEF↑; LVMI↓; LVESVI↓; LVEDVI↓; LAVI↓	(22)
Omar *et al*, 2021	NCT03198585	Patients with heart failure with reduced ejection fraction (n=95)	EMPA	10 mg, qd; 12 weeks	Echocardiography	LVEF↑; LVESVI↓; LVEDVI↓; LAVI↓	(27)
Lan *et al*, 2021	Prospective observational study	Acute coronary syndrome in patients with type 2 diabetes (n=44)	EMPA	10 or 25 mg, qd; after 3-6 months	Echocardiography	LVMI↓; LAVI↓; E↓; E/e'↓	(31)
von Lewinski *et al*, 2022	NCT03087773	Patients with acute MI (n=800)	EMPA	10 mg, qd; 32 weeks	Echocardiography	LVEF↑; E /e'↓; LVEDV↓; LVESV↓; NT-proBNP↓	(32)
Ersbøll *et al*, 2022	The SIMPLE randomized clinical trial	Patients with type 2 diabetes at high cardiovascular risk (n=45)	EMPA	25 mg, qd; 13 weeks	Echocardiography	LVMI↓; E/e'↓	(33)

Table I. Continued.

Author(s), year	Clinical trial number/type	Patient characteristics	SGLT2i	Dose and action time	Diagnostic method	Outcomes	(Refs.)
Palmiero *et al*, 2023	A pilot prospective study. GLISCAR study	Patients with type 2 diabetes mellitus and reduced ejection fraction heart failure (n=31)	EMPA	10 mg, qd; 6 months	Echocardiography	LVEF↑; LV-GLS↑	(34)
Russo *et al*, 2023	Real World Study	Patients with type 2 diabetes mellitus (n=35)	EMPA/ DAPA	10 mg, qd; 6 months	Echocardiography	LVEF↑; LV-GLS↑	(35)

CMRI, cardiac magnetic resonance imaging; qd, quaque die; LAVI, left atrial volume index; LVMI, left ventricular mass index; E/e', ratio peak early diastolic mitral velocity to mitral annulus early diastolic velocity; LVM, left ventricular mass; LVEF, left ventricular ejection fraction; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; E, early diastolic filling velocity; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LV-GLS, LV global longitudinal strain; SGLT2is, sodium-glucose cotransporter type 2 inhibitors; EMPA, Empagliflozin; DAPA, Dapagliflozin.

demonstrated that SGLT2is exerts cardioprotective effects through the activation or inhibition of autophagy.

In mouse models of coronary artery ligation-induced diabetic and non-diabetic MI, EMPA-treated mice demonstrated a significant decrease in cardiomyocyte death due to excessive autophagy, which reduced autophagic flux by targeting the Na^+/H^+ exchanger 1 (NHE1) on cardiomyocytes (63). EMPA exerts myocardial protective effects through mitochondrial autophagy and the novel BECN1-Toll-like receptor (TLR)9-SIRT3 axis (84). Furthermore, EMPA exerts cardioprotective effects in non-diabetic mice with MI with acute hyperglycemia by suppressing beclin 1 (BCN1)-dependent autophagy rather than targeting NHE1 in cardiomyocytes (85). Previous studies have demonstrated that BCN1 promotes the crosstalk between apoptosis and autophagy (86). In another study, EMPA was reported to inhibit ER stress-induced autophagy by inhibiting the PERK/activating transcription factor 4/BCN1 signaling pathway, thereby alleviating myocardial I/R injury and cardiomyocyte apoptosis (87). Furthermore, overexpression of p62 and light chain 3II/I activates autophagy when EMPA is administered. It reduces cardiac lipid toxicity in Zucker diabetic fatty (ZDF) rats (88).

Likewise, DAPA represses cardiac remodeling and hypoxia-induced apoptosis in heart failure through the activation of autophagy via the AMPK/mTOR pathway (89). It also protects against myocardial I/R injury by limiting NLR family pyrin domain containing 3 (NLRP3) inflammatory vesicle activation and regulating autophagy (90). The dose of DAPA administered in this study was 40 mg/kg/day, which is 20X higher compared with the allometric-adapted dose used in human clinical trials. It cannot be ruled out that the final result is related to high doses. SGLT2is exert cardioprotective effects through the activation and inhibition of autophagy via the interference of varied pathological conditions and detection time. SGLT2is regulate autophagy through the AMPK pathway, ER stress and inflammasomes. These pathways also regulate the processes of cell apoptosis, inflammation and angiogenesis. However, the association between these pathological processes and autophagy or the precise mechanisms of SGLT2is are yet to be elucidated.

Ferroptosis. Ferroptosis is a form of programmed cell death different from cell apoptosis, cell necrosis and cell autophagy. It is mediated by iron-dependent lipid peroxides and characterized by reduced intracellular glutathione (GSH) expression, reduced GSH peroxidase 4 (GPX4) activity and the accumulation of ROS and lipid peroxides (91-93). Several studies have shown the role of ferroptosis in numerous cardiovascular diseases, such as cardiomyopathy, MI, myocardial I/R injury, atherosclerosis and heart failure (94-98). Furthermore, SGLT2is exert cardioprotective effects through the ferroptosis pathway. In model rats, CANA can treat heart failure with preserved ejection fraction (HFpEF) by reducing iron intake and iron overload, reducing lipid peroxidation, increasing GSH production and inhibiting oxidative stress to regulate ferroptosis (99).

Furthermore, advanced glycation end-products inhibit the expression of solute carrier family 7 member 11 and ferritin in diabetic cardiomyopathy and reduce GSH levels. This elevates lipid peroxidation levels and ferroptosis, which in turn triggers cardiac inflammation and cardiac remodeling, including

Table II. Effects of SGLT2is on cardiac structure and function in animal models.

Author(s), year	Animal model	SGLT2i	Dose and action time	Diagnostic method	Outcome	(Refs.)
Habibi *et al*, 2017	Diabetic models in female rodents	EMPA	10 mg/kg/day orally for 5 weeks	Echocardiography	E/e'↓;	(40)
Zhang *et al*, 2019	Pig model of heart failure with preserved ejection fraction	DAPA	Oral administration of 10 mg/day was started at the 9th week from the beginning of modeling for 9 weeks	Echocardiography	LVMI↓	(41)
Lee *et al*, 2019	Hypertensive heart failure rats	EMPA	20 weeks after modeling began, 12 mg/kg/day was administered for 12 weeks	Echocardiography	Ves↓; Ved↓; +dP /dt↑; -dP/dt↓	(42)
Santos-Gallego *et al*, 2019	Pig model of non-diabetic heart failure	EMPA	After modeling, 10 mg/kg/day was administered orally for 2 months	CMRI and echocardiography	LVEDV↓; LVESV↓; LVM↓; LVEF↑; GLS↑	(38)
Yurista *et al*, 2019	Rat model of MI induced by coronary artery ligation	EMPA	Oral doses of 30 mg/kg/day were started 2 days before surgery (early stage) or 2 weeks after surgery (late stage)	Echocardiography	LVEF↑; LVM↓	(39)
Lahnwong *et al*, 2020	Acute myocardial ischemia/ reperfusion injury rat model	DAPA	1 mg/kg was administered before ischemia, during ischemia and at the beginning of reperfusion	Echocardiography	LVEF↑	(43)
Kräker *et al*, 2020	A novel rodent model of heart failure induced by combined hypertension and diabetes	EMPA	10 mg/kg/day for 4 weeks after modeling	Echocardiography	LVEF↑; LVFS↑; GLS↑	(44)
Santos-Gallego *et al*, 2021	A 2-h balloon occlusion of the proximal left anterior descending branch induced diastolic dysfunction in non-diabetic heart failure model pigs	EMPA	10 days after MI, 7 mg/day for 2 months	CMRI and echocardiography	E/e′↓; EDPVR↓; LVEDP↓	(45)

Table II. Continued.

Author(s), year	Animal model	SGLT2i	Dose and action time	Diagnostic method	Outcome	(Refs.)
Lin *et al*, 2021	Myocardial dysfunction induced by mitral regurgitation in rats	DAPA	Two weeks after surgery, 10 mg/kg/day for 6 weeks	Echocardiography	Ves↓; Ved↓; LVIDd↓; LVEF↑; LVFS↑; +dP/dt↑	(46)
Zhang *et al*, 2021	Angiotensin II-induced cardiac fibrosis in rats	DAPA	Oral administration of 5 mg/kg/day for 4 weeks	Echocardiography	LVEF↓; LVFS↓; e'↑; E/e'↓; GLS↓	(178)

Ves, end-systolic volume; Ved, end-diastolic volume; +dP/dt, maximal velocity of pressure rise; -dP/dt, maximal velocity of pressure fall; LVIDd, left ventricular internal dimension at end-diastole; EDPVR, end-diastolic pressure volume relationship; LVEDP, left ventricular end-diastolic pressure; SGLT2is, sodium-glucose cotransporter type 2 inhibitors; CMRI, cardiac magnetic resonance imaging; GLS, global longitudinal strain; EMPA, Empagliflozin; DAPA, Dapagliflozin.

cardiomyocyte hypertrophy, pro-fibrotic response, fibrosis and ultimately cardiac dysfunction (100). Another study reported that CANA may reduce ferroptosis and improve myocardial oxidative stress in diabetic cardiomyopathy mice by regulating iron metabolism and the systemic cystine-glutamate antiporter (Xc^-)/GSH/GPX4 axis (101). However, the relationship and specific mechanism of CANA in regulating iron metabolism and the Xc^-/GSH/GPX4 axis require further evaluation. In addition, CANA has been reported to inhibit inflammation and ferroptosis through the activation of the AMPK pathway, thereby reducing lipotoxicity in cardiomyocytes (102).

Furthermore, EMPA prevents DNA oxidation and ferroptosis in trastuzumab-induced C57BL/6J mice, which attenuates cardiotoxicity (103). Likewise, DAPA suppresses the MAPK signaling pathway in a model of myocardial I/R injury, reducing ferroptosis and exerting protective benefits on the heart (104).

Inflammation. Inflammation is a leading factor affecting cardiac remodeling and the progression of heart failure (105,106). Toll-like receptors (TLRs), a family of transmembrane receptors, are recognized by danger-associated molecular patterns (DAMPs) in MI and activate nuclear factor-B (NF-κB), which in turn activates a cascade of inflammatory mediators, including cell adhesion molecules, chemokines, and inflammatory cytokines (107,108). Furthermore, the inflammasome, which are polymeric protein structures, form molecular platforms that are activated when cells are infected or stressed, stimulates the inflammatory response by activating several inflammatory cytokines, such as IL-1 and IL-18 (109). Thus, targeting specific cytokines, growth factors or inflammatory pathways could alleviate adverse cardiac remodeling.

Proinflammatory cytokines: TNF-α, IL-1 and IL-6. The activation of multiple pro-inflammatory cytokines, such as TNF-α, IL-1 and IL-6, mediates cardiac remodeling through their effects on cardiomyocytes, fibroblasts and immune cells (110). These cytokines can induce cardiomyocyte hypertrophy and apoptosis (111-113). Pro-inflammatory cytokines enhance the activity of matrix metalloproteinases and decrease the production of extracellular matrix (ECM) components in fibroblasts, which causes the ECM to degrade (114-116). Thus, pro-inflammatory cytokines serve a role in pathological cardiac remodeling. Furthermore, the pleiotropic anti-inflammatory factor IL-10 decreases the expression of TNF-α, IL-1 and IL-6 to reduce cardiac inflammation (117,118).

Furthermore, SGLT2is downregulates pro-inflammatory cytokines and improves cardiac function in cardiovascular diseases. DAPA decreased the levels of inflammatory cytokines IL-6 and TNF-α in HFpEF pigs administered deoxycorticosterone acetate and Ang II to construct an ejection fraction-preserving heart failure model (41). Likewise, EMPA decreased TNF-α and IL-6 levels in patients with HfpEF and ZDF obese rats, reduced inflammation and enhanced myocardial function (119). Furthermore, EMPA markedly decreased the level of TNF-α and reduced myocardial fibrosis in hypertensive heart failure rats (42). DAPA decreased the levels of the pro-inflammatory cytokines IL-1, IL-6 and TNF-α in viral myocarditis mice infected with Coxsackievirus B3. DAPA facilitated macrophage polarization through STAT3-related pathways to reduce myocarditis (120). Furthermore, DAPA

improves cardiac hypertrophy in streptozocin-induced type 2 diabetic rats by inhibiting the nuclear translocation of NF-κB and reducing the expression of calpain-1 in cardiomyocytes, decreasing IL-6 and TNF-α levels and upregulating IL-10 levels (58). In addition, DAPA regulates malondialdehyde, TNF-α and ROS levels by blocking the C-X3-C motif chemokine ligand 1/receptor 1 axis and NF-κB activity, thereby reducing lipopolysaccharide-induced inflammation and oxidative stress (121). However, this study was performed *in vitro* using H9C2 cells and requires validation in patients.

NLRP3 inflammasome. The NLRP3 inflammasome accelerates the process of fibrosis by stimulating the production of proinflammatory cytokines IL-1β and IL-18 (122). Several factors, including MI, stress, obesity, diabetes and metabolic syndrome, activate the NLRP3 inflammasome and promote inflammation (123-125). DAPA exerts anti-inflammatory effects on the development of diabetic cardiomyopathy in type 2 diabetic mice by decreasing the expression of NLRP3 inflammasome, IL-1β, IL-6 and TNF-α (126,127). Likewise, EMPA inhibits cardiac fibrosis and inflammation in non-diabetic mice treated with Doxorubicin via the NLRP3 and MyD88 signaling pathways and inhibition of NLRP3 and NF-κB inhibits the pro-inflammatory cytokine storms in Doxorubicin-treated cardiomyocytes (128). Furthermore, DAPA decreases p38-dependent TLR4 expression to prevent NLRP3 activation, which then enhances cardiac function in Doxorubicin-induced dilated cardiomyopathy (129). Finally, CANA reduces type 17 T-helper cell infiltration and protects cardiomyocytes from apoptosis by inhibiting the NLRP3 inflammasome pathway, which reduces myocarditis-induced cardiac inflammation (68).

Macrophages also serve a role in the inflammatory response during cardiac remodeling (130). SGLT2is reduce cardiac fibrosis by regulating macrophage M2 polarization in infarcted rat hearts via the STAT3 signaling pathway (131). Inflammatory and NF-κB signaling pathways are triggered in patients with arrhythmogenic cardiomyopathy (ACM) (132). DAPA reduces cardiac fibrosis and inflammation in ACM mice by reversing hypoxia-inducible factor (HIF)-2α signaling, inhibiting the NF-κB signaling pathway (133). Accumulating evidence indicates that the role of SGLT2is in controlling inflammation is associated with fat reduction, which is efficacious in epicardial adipose tissue (134). Although the aforementioned studies have reported that SGLT2is serve a myocardial-protective role through anti-inflammatory mechanisms, another study on EMPA reported conflicting results; EMPA did not show any effect on the NLRP3 inflammasome pathway or interleukin-1β levels (135). The present review concluded that the effectiveness of SGLT2is in inhibiting inflammation is indeterminate, and more comprehensive information is essential to draw further conclusions.

Oxidative stress and mitochondrial dysfunction. Oxidative stress is a redox imbalance caused by the excessive production of ROS and/or an impaired antioxidant response (136). The primary ROS sources in the heart are mitochondria, NADPH oxidase (NOX), xanthine oxidase (XO) and uncoupled nitric oxide synthase (NOS) (137). A large number of heart cells can be affected by NOX via redox signal transduction. NOX regulates redox-sensitive target proteins to limit the production of ROS (138). Under physiological circumstances, normal ROS signaling controls the growth and maturation of cardiomyocytes, the processing of cardiac calcium, excitatory systolic coupling and vascular tone (139). However, oxidative stress effectuated by a sharp rise in ROS causes cardiac hypertrophy, fibrosis, apoptosis and contractile failure under pathological circumstances (140). Furthermore, oxidative stress is considered a key factor in the development of pathological cardiac remodeling and heart failure, as this disrupts mitochondrial activity by inducing oxidative damage to mitochondrial DNA, RNA, lipids and proteins. Oxidative stress also impairs myocardial cell systolic function by inducing mitochondria-associated oxidative modifications of excitation-contraction-coupled core proteins (141). Several studies have shown that the cardiac benefits of SGLT2is are reduced oxidative stress *in vivo* and ameliorated mitochondrial dysfunction through multiple signaling pathways.

EMPA improves mitochondrial function by inhibiting mitochondrial fission in type 2 diabetic hearts, as demonstrated by an increase in the expression of mitochondrial fusion-related proteins mitofusin-1 and optic atrophy 1 and the inhibition of DRP1 expression in type 2 diabetic db/db mice and H9C2 cardiomyocytes. In the present study, oxidative stress was reduced by increasing the expression of nuclear factor erythroid 2-related factor 2 (Nrf2) and its downstream genetic targets (59).

DAPA protects cardiomyocytes from hyperglycemia-induced damage by inhibiting NOX-mediated oxidative stress (142), whereas treatment with EMPA reduces LV hypertrophy and fibrosis after TAC and MI in non-diabetic mouse models and Sprague Dawley (SD) rats with coronary artery ligation-induced oxidative stress. Hypertrophy and fibrosis were improved by upregulating mitochondrial biogenesis, enhancing mitochondrial oxidative phosphorylation, reducing ROS production, attenuating apoptosis and increasing autophagy (39,143). EMPA treatment in diet-induced obese mice reduced cardiac fat accumulation and mitochondrial injury, improved myocardial hypertrophy and cardiac fibrosis and reduced cardiac dysfunction. This effect may be reduced by Sestrin2-mediated AMPK-mTOR signaling and Nrf2/heme oxygenase 1-mediated oxidative stress responses (144). In addition, EMPA inhibited high-fructose diet-induced cardiac dysfunction in type 2 diabetic SD rats by attenuating mitochondria-driven oxidative stress (145). DAPA reduces oxidative stress, mitochondrial dysfunction, fibrosis, hypertrophy and inflammation in Doxorubicin-stimulated rats via inhibition of PI3K/AKT/Nrf2 signaling (61). This study used only male and no female animals, while females may be more sensitive to Doxorubicin and mimic the clinical state.

Energy metabolism. Modifications in myocardial energy metabolism contribute to the development of pathological cardiac remodeling (146). It is often manifested by a switch of the heart back to the fetal genetic program and a shift in preference of metabolic substrate from fatty acids to glucose (147,148). Cardiac remodeling is associated with reduced lipid oxidation capacity and increased glucose dependence (149). Although the conversion of myocardial metabolic substrates from fatty acids to glucose lowers oxygen consumption, it can be detrimental to cardiac performance

and aggravate heart failure because of insufficient energy production (150,151). Furthermore, preserving fatty acid oxidation during stress overload prevents the effects of glucose on cardiac remodeling (152,153). Thus, promoting the use of fatty acids and other metabolic substrates to regulate energy metabolism may be a promising therapeutic strategy for heart failure and to improve cardiac remodeling (154).

EMPA reduces excessive glycolysis in TAC-induced cardiac overload mice by binding to glucose transporter (GLUT) proteins, such as GLUT1 and GLUT4, which increases the expression of CD36, restores fatty acid uptake and improves mitochondrial oxidative phosphorylation. The reduced glucose uptake may also lead to an impaired pentose phosphate pathway, which in turn activates AMP-activated protein kinases and blocks mTOR complex 1 (mTORC1) to reduce cardiac hypertrophy (57).

Contrastingly, EMPA has been shown to improve diabetic cardiac remodeling in diabetic cardiomyopathic rats by reducing fatty acid and increasing glucose metabolism (155), although this may be related to increased fatty acids in diabetic heart disease, which leads to lipid toxicity and insulin resistance (146,156), hence the contrasting results reported. EMPA significantly elevated cardiac metabolism and cardiac ATP production in coronary artery-ligated non-diabetic male SD rats by increasing ketone body bioavailability and myocardial oxidation of glucose and fatty acids (39). However, this study did not provide direct evidence that EMPA-treated hearts were associated with increased ketone body oxidation, nor did it quantify the relationship between ketone body oxidation and increased myocardial ATP levels.

Similarly, EMPA altered the myocardial fuel metabolic substrates from glucose to ketone bodies, free fatty acids and branched-chain amino acids in non-diabetic pigs induced by 2 h of proximal balloon occlusion of the left anterior descending branch. This improved myocardial energy, enhanced LV systolic function and improved unfavorable LV remodeling (38).

Angiogenesis. Angiogenesis is the physiological and pathological process of forming new microvessels from pre-existing capillaries in response to hypoxia. Angiogenesis involves endothelial cell proliferation, migration, differentiation, tube formation and regulation of angiogenic factors (157-159). The development of cardiac remodeling is significantly influenced by microvascular density (157,160). Several studies have demonstrated that promoting angiogenesis increases the density of microvessels and arteriolar, thus reducing cardiac remodeling (161-165).

Previous studies have shown that EMPA promotes myocardial microcirculatory perfusion and cardiac function by reducing AMPK-mediated mitochondrial fission and oxidative stress and stabilizing F-actin (166). Studies in a mouse model of diabetes-related hindlimb ischemia found that DAPA promotes vascular endothelial cell proliferation and migration through the prolyl hydroxylase domain protein 2/HIF-1α axis, the secretion of multiple angiogenic factors, the formation of neovascularization and increases in blood perfusion (167). EMPA improves systolic dysfunction during LV pressure overload in mice by activating the AKT/endothelial NOS (eNOS)/NO pathway to prevent endothelial apoptosis and maintain capillarization (168). In the event of myocardial I/R injury in non-diabetic mice, EMPA inhibits the DNA-dependent protein kinase catalytic subunit/fission 1 protein/mitochondrial fission pathway, protecting the microvascular system (169). However, the microvascular function *in vivo* is difficult to evaluate. In this study, only electron microscopy was used to observe the structural changes of microvessels in mice treated with EMPA, which is insufficient. However, coronary blood flow reserve can also be used. Another study demonstrated that DAPA reduces cardiac endothelial dysfunction and microvascular injury by inhibition of the XO/sarco(endo) plasmic reticulum calcium ATPase 2/calmodulin-dependent kinase II/coffilin pathway in I/R injury mice (170). EMPA also improves endothelial cell dysfunction induced by a mutant aldehyde dehydrogenase 2 unable to metabolize acetaldehyde by inhibiting NHE1 and activating the AKT kinase and eNOS pathways (171). EMPA attenuates cardiac microvascular I/R injury through the activation of the AMP-activated protein kinase α1 (AMPKα1)/UNC-52-like kinase 1/FUN14 domain containing 1/mitophagy pathway (172).

5. Molecular mechanisms of SGLT2is in pathological cardiac remodeling

TGF-β1/Smad2/3 pathway. The development of cardiac fibrosis is regulated by members of the TGF-β family, particularly TGF-β1, which activates Smad-dependent or non-Smad-mediated signaling pathways (173). TGF-β1 is a key cytokine mediating the conversion of cardiac fibroblasts into myofibroblasts that is regulated by numerous substances (174). Previous studies have shown that EMPA significantly decreases TGF-β1/Smad2 levels and upregulates the expression of the negative feedback regulator Smad7 to alleviate cardiac oxidative stress and fibrosis in diabetic mice (175). Furthermore, the antifibrotic activity of Smad7 on TGF-β and epidermal growth factor receptor 2 reduces myofibroblast activation and the production of structural and matrix proteins (176). Early administration of EMPA during MI reduces myocardial fibrosis and inhibits the TGF-1/Smad3 fibrotic pathway (177). This study explored the effects of EMPA on early cardiac physiology and fibrosis after myocardial infarction. Only samples taken after 4 weeks of administration were examined, and earlier samples were not evaluated, so the results may differ. DAPA reduces TGF-β1 levels and increases the expression of the negative feedback regulator Smad7 in Ang II-induced cardiac remodeling (178).

Reportedly, the activation of AMPKα inhibits the TGF-β/Smad pathway (179,180). DAPA protects against diabetic cardiomyopathy and myocardial fibrosis by inhibiting endothelial-interstitial transformation and fibroblast activation in the AMPKα/TGF-β/Smad signaling pathway (181). Furthermore, DAPA reduces myocardial fibrosis by inhibiting TGF-β1/Smad signaling pathways in normoglycemic chronic heart failure rabbits (182).

MAPK pathway. MAPK is a class of highly conserved serine/threonine protein kinases regulated by a cascade of tertiary phosphorylation activation (183,184). MAPK is divided into four subgroups: Extracellular signal-regulated kinase 1/2 (ERK1/2), c-Jun N-terminal kinase (JNK), p38 MAPK and

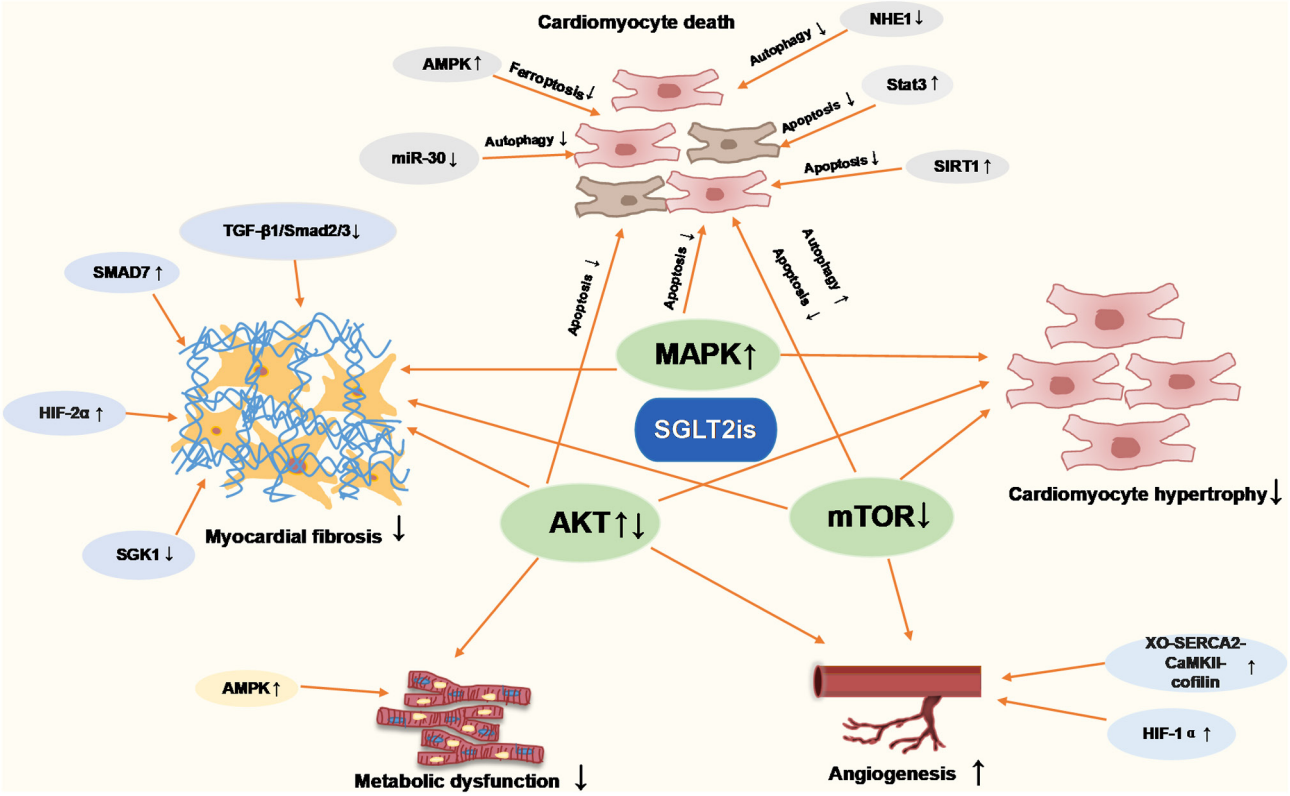

Figure 2. Role of SGLT2is in inhibiting pathological cardiac remodeling. SGLT2is, sodium-glucose cotransporter type 2 inhibitors; AMPK, AMP-activated protein kinase; NHE1, Na^+/H^+ exchanger 1; SIRT1, sirtuin-1; XO, xanthine oxidase; SERCA2, sarco(endo)plasmic reticulum calcium-ATPase 2; CaMKII, calmodulin-dependent kinase II; HIF1-α, hypoxia-inducible factor 1-α; SGK1, serum and glucocorticoid-induced protein kinase 1.

ERK5 (185,186). Under pathological conditions, the MAPK signaling pathway is activated by numerous extracellular stimulation signals and is essential for cell proliferation, differentiation, apoptosis and stress response (184,187). These findings suggested that the MAPK signaling pathway regulates cardiac remodeling due to multiple pathologies (188-191).

Furthermore, TAC activated ERK1/2, p38 and JNK in mice and treatment with DAPA inhibited the expression of JNK and p38 to reduce cardiac remodeling (56). Likewise, DAPA attenuated palmitic acid-induced cell hypertrophy and apoptosis and improved cardiac dysfunction and remodeling in high-fat diet-induced obese mice. This protective effect both *in vivo* and *in vitro* is mediated by the NHE1/MAPK signaling pathway (192), and whether DAPA exerts cardio-protective effects through NHE1 requires further evaluation. Furthermore, this suggests that the protective effect of EMPA on the heart may be mediated through stimulation of the ERK1/2 signaling pathway in I/R injury (69).

mTOR and Akt. mTOR, a class of atypical serine/threonine protein kinases, is a member of the phosphatidylinositol 3-kinase (PI3K)-related protein kinase family. The interaction of mTOR with different proteins forms two macromolecular complexes with different structures and functions, mTORC1 and mTORC2 (193). mTOR also integrates multiple extracellular signals, such as nutrient levels, energy and growth factors, and serves a role in cell growth, proliferation, survival, protein synthesis, autophagy and metabolism (194,195). Several studies have shown its crucial role in the physiological and pathological processes of the heart (196-201). Furthermore, the Akt and AMPK pathways are regulators of mTORC1, with AMPK negatively regulating the mTOR signaling pathway (202).

Another study reported that Ertugliflozin reduces LV fibrosis in mice with cardiac hypertrophy by activating the AMPK/mTOR pathway and inhibiting its downstream targets p70S6K and 4E-BP1 (203). This target mediates translation to promote mTORC1 synthesis and causes mTORC1-induced myocardial hypertrophy (204). Likewise, EMPA modulates autophagy in cardiomyocytes to ameliorate sunitinib-induced cardiac dysfunction, an effect mediated by the activation of sunitinib-inhibited AMPK and reducing Sunitinib-activated mTOR levels (37). AMPK/mTOR is one of the main pathways regulating autophagy, which can be regulated by direct phosphorylation of UNC-51-like kinases 1 (205). Furthermore, EMPA improves obesity-related cardiac dysfunction by increasing the AMPK level and endothelial nitric oxide synthase phosphorylation, and inhibiting Akt and mTOR phosphorylation (144). Previous research has demonstrated that the heart can be protected by inhibiting the PI3K/AKT/mTOR pathway (206). CANA alleviates cardiomyocyte lipotoxicity in diabetic cardiomyopathy mouse models by blocking the mTOR/HIF-1 pathway (207). Likewise, CANA is an SGLT1i/SGLT2is and its impact on the mTOR signaling pathway should be excluded from SGLT1 interference.

Other molecular signaling pathways. Serum and glucocorticoid-induced protein kinase 1 (SGK1) are the main mediators of cardiac remodeling through the activation of epithelial sodium channel (ENaC) proteins responsible for promoting fibrosis and upregulating

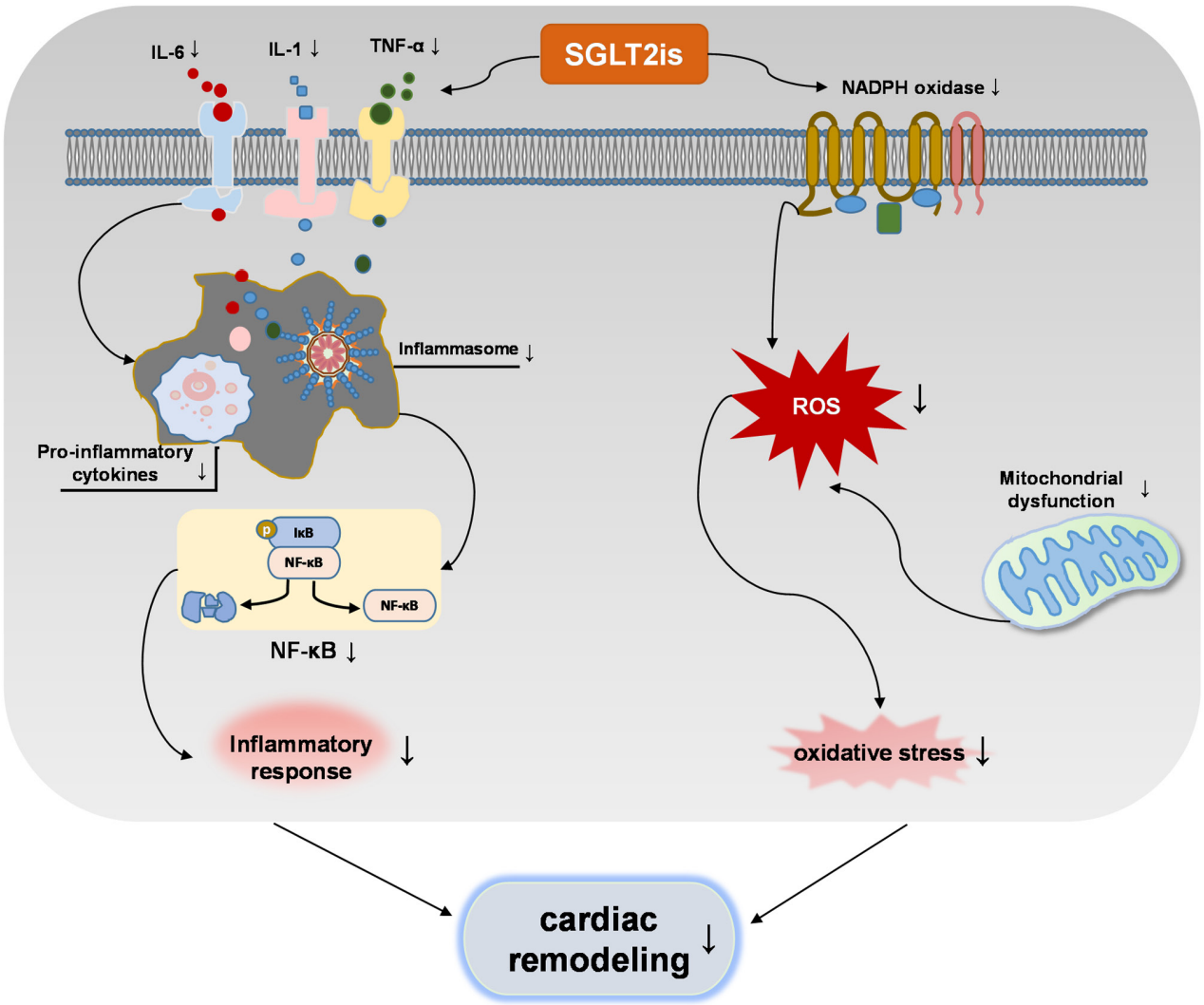

Figure 3. Indirect effect of SGLT2is on pathological cardiac remodeling by inhibiting the crosstalk between inflammation and oxidative stress. SGLT2is, sodium-glucose cotransporter type 2 inhibitors; ROS, reactive oxygen species; IκB, inhibitor of NF-κB.

NHE1 activity (208,209). DAPA attenuates LVDD and myocardial fibrosis by modulating SGK1 signaling and ENaC protein (210). Due to the use of pigs in this study, the sample size was small and the results had statistical limitations. The JAK/STAT signaling pathway is a promoter of fibroblast activation and ischemic-induced cardiac dysfunction (211,212). CANA attenuates fibrosis by reducing JAK/STAT signaling, activating AMPK and through antioxidant signaling (213). Characteristics of diabetic cardiomyopathy include decreased cyclic guanosine monophosphate (cGMP) levels and altered soluble guanylate cyclase enzyme (sGC)-cGMP- dependent protein kinase (PKG) signaling, which regulate systolic and diastolic dysfunction under diabetic conditions (214,215). Furthermore, EMPA improves cardiac function by preventing oxidative stress-induced injury via the sGC/cGMP/PKG pathway (216).

6. Conclusion

The present review provided a comprehensive summary of the molecular mechanisms through which SGLT2is attenuate pathological cardiac remodeling in animal and *in vitro* cellular models. The molecular pathways of SGLT2is in cardiac remodeling in terms of cardiac hypertrophy, cardiac fibrosis, inflammation, apoptosis, autophagy, ferroptosis, oxidative stress and energy metabolism, were summarized in Fig. 2. Thus, which supports the potential use of SGLT2i as a therapeutic which can inhibit numerous mechanisms of cardiac remodeling, such as MI, I/R and diabetic cardiomyopathy. SGLT2is are directly or indirectly involved in regulating molecular pathways of cardiac remodeling. Of note, the interaction between inflammation and oxidative stress increases the production of ROS and pro-inflammatory mediators, and SGLT2is inhibit this interaction to regulate cardiac remodeling (Fig. 3). Based on this summary, it is speculated that SGLT2is exert inhibitory effects on cardiac remodeling (Fig. 4).

To date, the effect of SGLT2is on cardiac remodeling has been evaluated by several approaches, but studies on how it functions in the heart require further evaluation. In addition, the epigenetic mechanisms of SGLT2is in cardiac remodeling have not been reported. In recent years, the impact of epigenetics on disease development has received significant attention and studies on cardiac diseases suggest that the epigenetic mechanisms of SGLT2is require further assessment in future studies.

Regarding diabetic and non-diabetic pathological cardiac remodeling, few studies have simultaneously compared

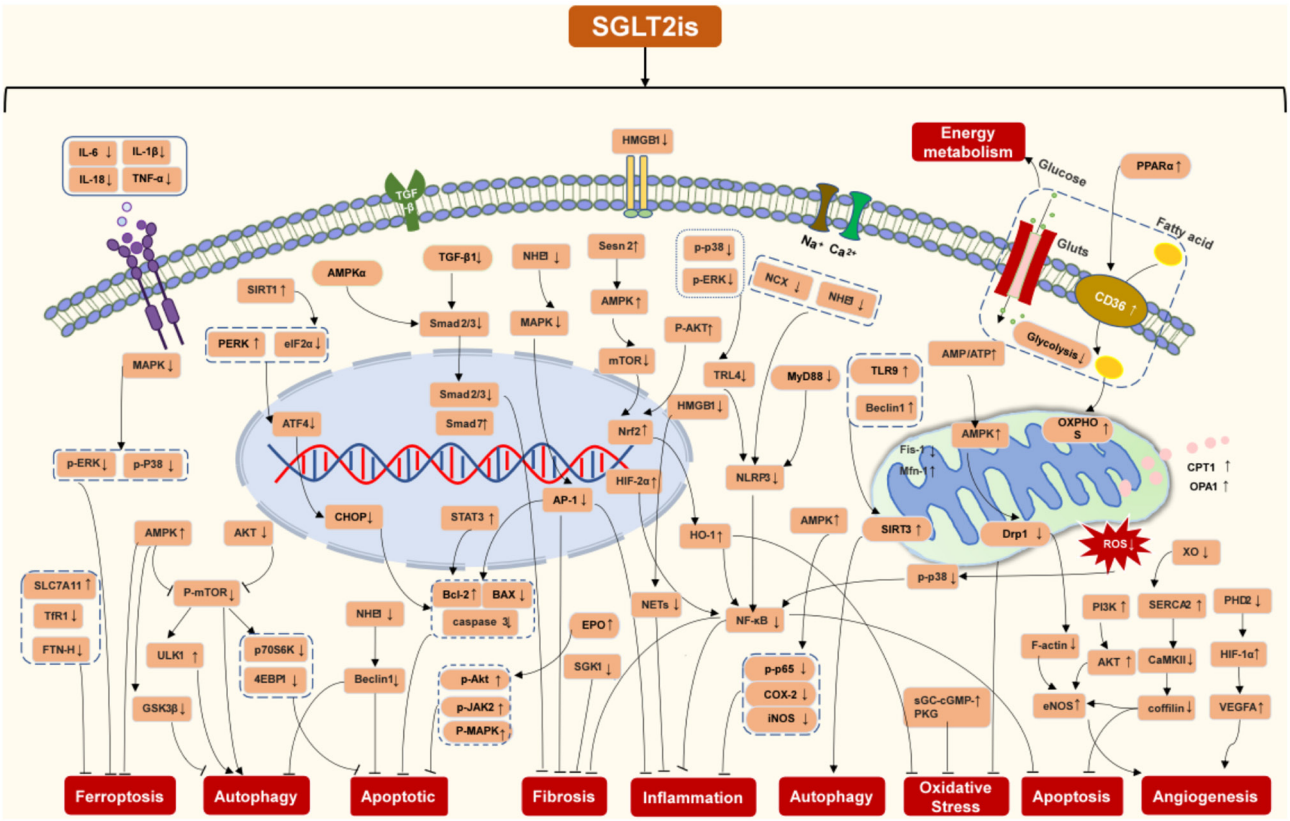

Figure 4. Schematic of the regulatory mechanisms of SGLT2is in pathological cardiac remodeling. SGLT2is, sodium-glucose cotransporter type 2 inhibitors; HMGB1, high mobility group box 1; TNF-α, tumor necrosis factor-α; ROS, reactive oxygen species; AMPK, AMP-activated protein; Nrf2, nuclear factor erythroid 2-related factor 2; NF-κB, nuclear factor-B; ERK, extracellular signal-regulated kinase; PI3K, phosphatidylinositol 3-kinase; CD36, cluster of differentiation 36; SGK1, serum and glucocorticoid-induced protein kinase 1; NHE1, Na^+/H^+ exchanger 1; SIRT1, sirtuin-1; XO, xanthine oxidase; SERCA2, sarco(endo)plasmic reticulum calcium-ATPase 2; CaMKII, calmodulin-dependent kinase II; HIF1-α, hypoxia-inducible factor 1-α; sGC, soluble guanylate cyclase enzyme; cGMP, cyclic guanosine monophosphate; PKG, cGMP-dependent protein kinase; eIF2, eukaryotic initiation factor 2; PERK, protein kinase RNA-like ER kinase; CHOP, C/EBP homologous protein; ATF4, activating transcription factor 4; ULK1, UNC-52-like kinase 1; GSK3β, glycogen synthase kinase 3β; p70S6K, 70 kDa ribosomal protein S6 kinase; 4EBP1, 4E-binding protein 1; SLC7A11, solute carrier family 7a member 11; PPARα, peroxisome proliferator-activated receptor α; NCX, sodium-calcium exchangers; TFR1, transferrin receptor 1; FTN-H, ferritin heavy-chain; AP-1, activator protein-1; EPO, erythropoietin; NETs, neutrophil extracellular traps; HO-1, heme oxygenase-1; TRL4, toll-like receptor 4; MyD88, myeloid differentiation primary response 88; NLRP3, NLR family pyrin domain containing 3; COX-2, cyclooxygenase-2; iNOS, inducible nitric oxide synthase; OXPHOS, oxidative phosphorylation; Drp1, dynamin-related protein 1; eNOS, endothelial nitric oxide synthase; Fis-1, fission 1; MFN-1, mitofusin 1; CPT1, carnitine O-palmitoyltransferase 1; Opa1, optic atrophy 1; PHD2, prolyl hydroxylase 2; VEGFA, vascular endothelial growth factor A.

whether both occur through the same mechanism. SGLT2is have been clinically approved for use in non-diabetic heart failure, while in diabetic heart disease, their role may be influenced by SGLT2 targets. Thus, exploring the mechanism of action of SGLT2is in non-diabetic cardiac remodeling may provide a basis for clinical application in the heart.

The present review emphasizes that SGLT2is are not only effective in controlling blood sugar in diabetes but can also mitigate heart damage, suggesting their dual use in managing both conditions.

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Availability of data and materials

Not applicable.

Authors' contributions

BC, YF and JG conceived, designed and planned the study. All authors collected and read the literature. BC and JG were responsible for the literature review and preparing the first draft of the manuscript. HY, XW and JG revised the manuscript. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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