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New Insights Into the Role of Sodium-Glucose Cotransporter 1 Inhibition in Cardiovascular Protection: A Literature Review

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Abstract

In recent years, numerous large-scale clinical trials have demonstrated that sodium-glucose cotransporter (SGLT) 2 inhibitors provide cardiovascular and renal protection regardless of diabetes status. Although SGLT1 is recognized as another primary isoform of SGLT, its precise role remains elusive. SGLT2 is highly expressed in the kidneys where it modulates glucose reabsorption, whereas SGLT1 is mainly expressed in the intestinal epithelium where it regulates dietary glucose uptake. Unlike SGLT2, which is minimally present in the heart, SGLT1 is abundantly expressed in the myocardium. SGLT1 may play a unique and supplementary role in glucose homeostasis. Thus, the targeting SGLT1 for inhibition could offer therapeutic benefits. During the early stages of cardiac injury, SGLT1 expression is considerably increased, ensuring an adequate energy supply to cardiac cells. However, preclinical research has indicated that prolonged SGLT1 overexpression may negatively affect the heart by triggering pathological mechanisms, such as cardiac inflammation, oxidative stress, fibrosis, apoptosis, and mitochondrial dysfunction. Thus, inhibiting SGLT1 could offer additional benefits beyond its effects on glucose absorption. Numerous clinical studies have demonstrated that SGLT1 inhibitors substantially benefit cardiovascular health by reducing the risks of cardiovascular mortality and hospitalization for heart failure (HF), regardless of the presence of diabetes or HF. Although the precise mechanisms underlying these beneficial effects are not fully understood, genetic models suggest that the malfunction of SGLT1 transporters adversely affects various tissues. This review explores both the positive and negative effects of SGLT1 inhibition on the heart. In addition, this review discusses potential mechanisms through which SGLT1 inhibition may confer cardiovascular protection on the basis of a thorough analysis of the fundamental research on SGLT1.

Key Words: Sodium-glucose cotransporter 1 inhibition; Cardiovascular disease; Heart failure; Glucose absorption; Cardioprotection.

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1. Introduction

Sodium-glucose cotransporters (SGLTs) enable the cellular uptake of glucose by using a sodium concentration gradient created by the Na^+/K^+-ATPase pump. Under normal physiological conditions, SGLT2 facilitates the reabsorption of 90% of glucose that is filtered by the kidneys. SGLT1 is crucial for the absorption of glucose in the small intestine and for the reabsorption of the remaining 10% of the glucose load filtered by the kidneys[1]. In recent years, multiple clinical trials involving patients with type 2 diabetes mellitus (T2DM)[2-8], non-T2DM-related heart failure (HF)[9-11], and chronic kidney disease (CKD)[12,13] have demonstrated the cardioprotective effects of SGLT2 inhibitors (Table 1). Thus, SGLT2 inhibitors have become a key therapeutic tool for HF and are now formally recommended as the first-line treatment for HF with reduced ejection fraction in the European Society of Cardiology (ESC) HF 2021 guidelines. In addition, the 2023 American Diabetes Association guidelines for diabetes care assign a Level of Evidence A for the use of SGLT2 inhibitors in patients with T2DM and established HF, regardless of the ejection fraction status. In 2019, the ESC and the European Association for the Study of Diabetes also recommended SGLT2 inhibitors as the first-line therapy

Table 1. Cardiovascular Protective Effects of SGLT2 Inhibitors in Cardiovascular, HF, and CKD Outcome Trials

Clinical trial	Intervention (enrollment)	Trial type	Main inclusion criteria	Median follow-up duration (y)	Primary outcomes [HR (95% CI); *P* value)
CV outcome trials					
EMPA-REG OUTCOME[2]	Empagliflozin (N = 7020)	Double-blind, placebo-controlled RCT	T2DM (%): 100 ASCVD; eGFR ≥ 30 mL/minute/1.73 m2 BMI ≤ 45 kg/m^2 HbA1c: 7.0% to 9.0% without GLD or 7.0% to 10.0% with stable GLD	3.3	Composite MACEs: 0.86 (0.74 to 0.99); $p = 0.04$ Cardiovascular death: 0.62 (0.49 to 0.77); $p < 0.001$ HHF: 0.65 (0.50 to 0.85); $p = 0.002$ All-cause mortality: 0.68 (0.57 to 0.82); $p < 0.001$ Nonfatal MI: 0.87 (0.70 to 1.09) Nonfatal stoke: 1.24 (0.92 to 1.67)
CANVAS[3]	Canagliflozin (N = 10 142)	Double-blind, placebo-controlled RCT	T2DM (%): 100 ASCVD or age ≥ 50 y with ≥2 risk factors for CVD	3.6	Composite MACEs: 0.86 (0.75 to 0.97); $p = 0.02$ Cardiovascular death: 0.87 (0.72 to 1.06) HHF: 0.67 (0.52 to 0.87) All-cause mortality: 0.87 (0.74 to 1.01) Nonfatal MI: 0.85 (0.69 to 1.05) Nonfatal stoke: 0.90 (0.71 to 1.15)
DECLARE-TIMI-58[4]	Dapagliflozin (N = 17 160)	Double-blind, placebo-controlled RCT	T2DM (%): 100 ASCVD or multiple risk factors for ASCVD eGFR ≥ 60 mL/minute/1.73 m^2	4.2	Composite MACEs: 0.83 (0.73 to 0.95); $p = 0.005$ Cardiovascular death: 0.98 (0.82 to 1.17) HHF: 0.73 (0.61 to 0.88) All-cause mortality: 0.93 (0.82 to 1.04) Nonfatal MI: 0.89 (0.77 to 1.01) Nonfatal stroke: 1.01 (0.84 to 1.21)
VERTIS-CV[6]	Ertugliflozin (N = 8246)	Double-blind, placebo-controlled RCT	T2DM (%): 100 CVD Age ≥ 40 y eGFR ≥ 30 mL/minute/1.73 m^2	3.5	Composite MACEs: 0.97 (0.85 to 1.11); $p = 0.001$ for noninferiority Cardiovascular death: 0.92 (0.77 to 1.11) HHF: 0.70 (0.54 to 0.90) All-cause mortality: 0.93 (0.80 to 1.08) Nonfatal MI: 1.04 (0.86 to 1.27) Nonfatal stoke: 1.00 (0.76 to 1.32)
HF outcome trials					
DAPA-HF[9]	Dapagliflozin (N = 4744)	Double-blind, placebo-controlled RCT	T2DM (%): 45 EF ≤ 40% NYHA class II, III, or IV NT-proBNP level ≥ 600 pg/mL eGFR ≥ 30 mL/minute/1.73 m^2	1.8	Composite of cardiovascular death or HF exacerbation: 0.74 (0.65 to 0.85); $p < 0.001$ Cardiovascular death: 0.82 (0.69 to 0.98) HHF: 0.70 (0.59 to 0.83) All-cause mortality: 0.83 (0.71 to 0.97)

EMPEROR-Preserved[11]	Empagliflozin (N = 5988)	Double-blind, placebo-controlled RCT	T2DM (%): 49.1 EF ≥ 40% NYHA class II, III, or IV	2.2	Composite of cardiovascular death or HF exacerbation: 0.79 (0.69 to 0.90); $p < 0.001$ Cardiovascular death: 0.91 (0.76 to 1.09) HHF: 0.71 (0.60 to 0.83) All-cause mortality: 1.00 (0.87 to 1.15)
EMPEROR-Reduced[10]	Empagliflozin (N = 3730)	Double-blind, placebo-controlled RCT	T2DM (%): 49.8 EF ≤ 40% NYHA class II, III, or IV	1.3	Composite of cardiovascular death or HF exacerbation: 0.75 (0.65 to 0.86); $p < 0.001$ Cardiovascular death: 0.92 (0.75 to 1.12) HHF: 0.69 (0.59 to 0.81) All-cause mortality: 0.91 (0.77 to 1.10)
SOLOIST-WHF[8]	Sotagliflozin (N = 1222, 20% with LVEF >50%)	Double-blind, placebo-controlled RCT	T2DM (%): 100 Age ≥18 y Recent HHF	0.75	Composite of cardiovascular death, HHF, or urgent visits for HF: 0.67 (0.52 to 0.85); $p < 0.001$) Cardiovascular death: 0.84 (0.58 to 1.22) HHF (total number, including urgent visits for HF): 0.64 (0.49 to 0.83) All-cause mortality: 0.82 (0.59 to 1.14)
SCORED[7]	Sotagliflozin (N = 10 584)	Double-blind, placebo-controlled RCT	T2DM (%): 100 eGFR: 25 to 60 mL/minute/1.73 m^2 CVD risks	1.3	Composite of cardiovascular death, HHF, or urgent visits for HF: 0.74 (0.63 to 0.88); $p < 0.001$ Cardiovascular death: 0.90 (0.73 to 1.12) HHF (total number, including urgent visits for HF): 0.67 (0.55 to 0.82) All-cause mortality: 0.99 (0.83 to 1.18)
CKD outcome trials					
CREDENCE[5]	Canagliflozin (N = 4401)	Double-blind, placebo-controlled RCT	T2DM (%): 100 Age ≥ 30 y eGFR ≥30 to <90 mL/minute/1.73 m^2 UACR > 300 to 5000 mg/g HbA1c: 6.5% to 12.0% Requirement for a stable dose of an ACE inhibitor or ARB	2.6	Composite of ESRD (dialysis, transplantation, or sustained eGFR at <15 mL/minute/1.73 m^2), sCr doubling, or renal or cardiovascular death: 0.70 (0.59 to 0.82); $p = 0.00001$ Composite of cardiovascular death or HHF: 0.69 (0.57 to0.83); $p < 0.001$ Cardiovascular death: 0.78 (0.61 to 1.00); $p = 0.05$ All-cause mortality: 0.83 (0.68 to 1.02)
DAPA-CKD[12]	Dapagliflozin (N = 4304)	Double-blind, placebo-controlled RCT	T2DM (%): 67.5 eGFR: 25 to 75 mL/minute/1.73 m^2 UACR: 200 to 5000 mg/g Required stable dose of ACE inhibitor or ARB	2.4	Composite of a sustained decrease in eGFR to ≥50% (confirmed after ≥28 days), ESRD (dialysis for ≥28 days, transplantation, or eGFR < 15 mL/minute/1.73 m^2 confirmed after ≥28 days), or renal or cardiovascular death: 0.61 (0.51 to 0.72); $p < 0.001$ Composite of cardiovascular death or HHF: 0.71 (0.55 to 0.92); $p = .009$ Cardiovascular death: 0.81 (0.58 to 1.12); p = NA All-cause mortality: 0.69 (0.53 to 0.88); $p = 0.004$
EMPA-KIDNEY[13]	Empagliflozin (N = 6609)	Double-blind, placebo-controlled RCT	T2DM (%): 44 eGFR ≥20 to <45 or ≥45 to <90 mL/minute/1.73 m^2 UACR ≥ 200 mg/g Use of ACE inhibitor or ARB	2.0	Composite of kidney disease (ESRD; a sustained decrease in eGFR to <10 mL/minute/1.73 m^2, a sustained decrease in eGFR to ≥40% from baseline, or renal death) progression or death from cardiovascular causes: 0.72 (0.64 to 0.82); $p < 0.001$ Composite of cardiovascular death or HHF: 0.84 (0.67 to 1.07); $p = 0.15$ Cardiovascular death: 0.84 (0.60 to 1.19) ESRD or death from cardiovascular causes: 0.73 (0.59 to 0.89) All-cause mortality: 0.87 (0.70 to 1.08); $p = 0.21$

Note. Adapted from "Sodium-Glucose Cotransporter-2 Inhibitors and Euglycemic Ketosis: Friends or Foes" by KB Tseng, 2024, J Intern Med Taiwan, 35(5), p. 318-320

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CVD, cardiovascular disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; EF, ejection fraction; ESRD, end-stage renal disease; GLD, glucose-lowering drug; HF, heart failure; HHF, hospitalization for heart failure; HbA1c, glycated hemoglobin; MACE, major adverse cardiovascular event; MI, myocardial infarction; NA, not applicable; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; RCT, randomized controlled trial; SGLT2, sodium-glucose cotransporter-2; T2DM, type 2 diabetes mellitus; UACR, urinary albumin-to-creatinine ratio.

for patients with T2DM at a high risk of atherosclerotic cardiovascular disease[14]. Thus, SGLT2 inhibitors are considered a valuable treatment option for reducing the risk of major adverse cardiovascular events, irrespective of the patient's diabetes status.

Recent findings from 2 clinical trials published in the New England Journal of Medicine, namely the SCORED trial involving patients with diabetes and CKD and the SOLOIST-WHF trial involving patients with diabetes and recently worsened HF, have reported the benefits of sotagliflozin, a dual SGLT1/SGLT2 inhibitor. Sotagliflozin was associated with a decreased risk of the composite endpoint of cardiovascular deaths and hospitalizations for HF in patients with T2DM combined with either CKD or recent worsening HF[7,8]. These results suggest that SGLT1 inhibition plays a distinct and complementary role to SGLT2 inhibition in glucose homeostasis, potentially offering additional cardioprotective benefits.

Many preclinical studies have demonstrated the crucial role of SGLT1 in the progression of heart disease. Inhibiting SGLT1 in the heart, which was previously believed to only suppress SGLT1 expression in cardiomyocytes, may enhance cardiac function and reduce the risk of arrhythmias. Reducing the activity of SGLT1 has been shown to improve both systolic and diastolic functions of the left ventricle in cases of diabetic cardiomyopathy, PRKAG2 cardiomyopathy, fluctuating diabetes, and chronic HF and in nondiabetic mice[15]. Furthermore, the suppression of SGLT1 expression is associated with decreased cardiac hypertrophy and fibrosis[16,17]. In addition, variations in the *SGLT1* gene that lead to a reduction in its activity are associated with a marked decrease in the incidence of HF, cardiovascular mortality, and diabetes[18]. However, some studies have indicated that mutations leading to defective SGLT1 transporters are associated with osmotic diarrhea, proximal tubular dysfunction, and nephrocalcinosis[19].

During the acute phase of ischemia-reperfusion injury, SGLT1 plays a compensatory protective role in the ischemic heart tissue by increasing glucose absorption[20,21]. However, specifically knocking out SGLT1 in cardiomyocytes or completely eliminating it does not affect the myocardium's baseline glucose uptake[15]. Thus, the clinical outcomes of SGLT1 inhibition remain difficult to predict.

This review provides a comprehensive overview of existing evidence on the beneficial and detrimental effects of SGLT1 inhibition on the heart. In addition, this review explores potential mechanisms through which SGLT1 inhibition offers cardiovascular protection on the basis of a thorough analysis of the fundamental research on SGLT1.

2. The expression and biologic roles of SGLT1 receptors

The SGLT1 protein, encoded by the *SLC5A* gene on chromosome 22q13.1, is composed of 664 amino acids and contains 14 transmembrane α-helical domains. This protein possesses a single glycosylation site situated between transmembrane helices 5 and 6 as well as two phosphorylation sites located between helices 6 and 7 and between helices 8 and 9, respectively[22]. SGLT1 functions as a high-affinity ($K_{0.5}$ of approximately 0.4 mM for glucose and 3.0 mM for sodium), low-capacity glucose transporter with a 2:1 stoichiometry for sodium and glucose[1]. This means that for each glucose molecule transported, two sodium ions are moved through SGLT1, enabling the cotransporter to facilitate glucose uptake into cells against its concentration gradient[23]. The expression of the SGLT1 protein is localized mainly to the apical brush border of the small intestine and the renal late proximal tubules as well as in the salivary glands, liver, lungs, skeletal muscle, heart, and pancreatic α-cells[22].

SGLT1 transport activity is regulated through various molecular mechanisms, including interactions with protein kinases. The SGLT1 protein con-

tains specific regulatory sites targeted by protein kinase A (PKA) and protein kinase C (PKC). PKA activation leads to an increase in the number of SGLT1 proteins present in the membrane of the small intestine[1]. In addition, PKA activators, such as 8-bromo-cyclic adenosine monophosphate, increase both the capacity and activity of SGLT in the plasma membrane[1]. PKA activity positively regulates both the expression and function of SGLT1, and these effects can be inhibited by the PKA inhibitor H-89[22]. By contrast, the effects of PKC on SGLT1 are more complex and exhibit species-specific differences[22]. PKC activation reduces SGLT1 transport capacity in rats and rabbits, whereas it increases transport capacity in humans[22]. These species differences contribute to the ongoing controversy regarding PKC-mediated regulation of SGLT1.

SGLT1 facilitates the transport of glucose and galactose across the brush-border membrane of the small intestine[24]. The expression of *SGLT1* is critical for efficient glucose absorption and is regulated by both short-term and long-term mechanisms that respond to the availability of luminal nutrients[25]. In patients with T2DM, increased mRNA and protein levels of SGLT1 in the intestinal brush border correlate with elevated intestinal glucose uptake[26]. The increased activity of SGLT1-mediated glucose absorption in the small intestine contributes to rapid postprandial hyperglycemia in diabetes[27].

In the kidney, *SGLT1* is expressed in the S3 segment of the proximal tubul.[28] In euglycemia, SGLT2 accounts for ≥90% of glucose reabsorption, whereas SGLT1 reabsorbs the remaining approximately 3% of filtered glucose.[29] However, in sustained hyperglycemia, the resorptive capacity of SGLT2 can become overwhelmed, increasing glucose delivery to the distal proximal tubule and enhancing SGLT1-mediated glucose reabsorption.[30] Understanding the compensatory role of SGLT1 in renal glucose handling is essential, particularly in diabetes.

In addition to the intestines and kidneys, SGLT1 is expressed in the cell membranes of cardiomyocytes[31]. The role of SGLT1 in facilitating glucose transport into cardiomyocytes is essential. However, the long-term overexpression of *SGLT1* in the heart of mice led to pathological cardiac hypertrophy and left ventricular failure. By contrast, the knockdown of cardiac *SGLT1* could mitigate these adverse effects[32]. In addition, increased *SGLT1* mRNA expression was observed in the hearts of patients with T2DM and diabetic cardiomyopathy.[33] Additional studies should be conducted to evaluate the benefits and harms of *SGLT1* inhibition on cardiovascular disease (CVD).

3. Beneficial effects of SGLT1 inhibition on the heart in the cellular and animal experiments

Several studies have demonstrated that myocardial hypertrophy and ischemia are associated with the upregulation of SGLT1, whereas SGLT2 is not expressed[33,34]. Experimental models of myocardial injury have indicated that SGLT1 inhibition may confer cardioprotection[30,35]. In a study using human cardiac fibroblasts, SGLT1 inhibition prevented the development of diabetic cardiomyopathy, potentially through the downregulation of serum glucose levels or a direct effect on the cardiac tissue[36]. In addition, chronic pressure overload increased *SGLT1* gene expression, subsequently leading to the development of hypertrophic cardiomyopathy in mice[16]. This finding suggests that SGLT1 inhibition can attenuate cardiomyopathy. Moreover, the overexpression of *SGLT1* led to cardiac remodeling and increased interstitial fibrosis in mice, suggesting that the cardiac knockdown of *SGLT1* may promote both the development and progression of hypertrophic cardiomyopathy[32]. However, the precise mechanism through which SGLT1 induces cardiac hypertrophy and fibrosis remains unclear. In mice with ischemia-reperfusion injury, SGLT1 knock-

down protected against ischemic hearts[37]. Similarly, SGLT1 inhibition led to improvements in myocardial infarction (MI)-induced LV remodeling and HF in mice, suggesting that SGLT1 inhibitors could serve as a novel therapeutic approach in managing ischemia-induced cardiomyopathy[38].

4. Adverse effects of SGLT1 inhibition on the heart in the cellular and animal experiments

The expression of SGLT1 in the human heart facilitates glucose uptake[21], which may play a crucial role in myocardial fuel energetics during periods of nutritional stress. In diabetic or ischemic cardiomyopathy, SGLT1 activation can increase, possibly as an adaptive response to cardiac damage[33]. Furthermore, in the human myocardium, SGLT1 activation induced by insulin stimulation exerts positive inotropic effects, suggesting that SGLT1 has substantial functional effects when activated by stimulatory factors[39,40]. Compared with glucose transporters (GLUTs), which may become inefficient in the presence of low extracellular glucose levels, SGLTs function as active transporters that operate against the glucose concentration gradient. SGLTs couple glucose transport to the downhill Na^+ electrochemical gradient through the Na^+/K^+ ATPase, making them essential for cardiomyocyte survival in environments with low glucose levels, such as that observed in ischemia[1,41,42]. SGLT1 can protect against ischemia-reperfusion injury by enhancing the availability of glucose, thereby replenishing adenosine triphosphate (ATP) stores in ischemic cardiac tissues[21]. SGLT1 expression in the heart is upregulated 2- to 3-fold during myocardial ischemia, which appears to be an adaptive response to injury given its association with functional recovery in failing hearts after LV assist device insertion[33]. Thus, SGLT1 activation in the heart plays a crucial role in critical pathological conditions instead of baseline conditions. However, some studies have reported that chronic excessive activation of cardiac SGLT1 is associated with unfavorable effects[32,43]. Thus, the timing of SGLT1 activation is critical because it can have either protective or detrimental cardiac effects. Additional studies are needed to define the precise time course of SGLT1 activation and its effect on cardiac health.

Phlorizin, a selective SGLT1 inhibitor, exerts some nonspecific effects on mitochondrial energetics[44,45]. Phlorizin can induce mitochondrial swelling[44] and inhibit mitochondrial ATPase activity[45], leading to a decrease in mitochondrial ATP levels. This decrease in ATP levels may explain the reduction observed in the ATP content of hearts perfused with phlorizin, especially under normoxia where ATP synthesis is largely dependent on mitochondrial oxidative phosphorylation[21]. During the reperfusion period, a substantial reduction in ATP content was observed along with decreases in glucose uptake and lactate output, indicating a reduction in the glycolytic flux in this particular model of Langendorff heart perfusion. The lower glycolytic activity suggests impaired glucose delivery in phlorizin-perfused hearts during ischemia-reperfusion injury[21]. In rat models of acute MI, treatment with dual SGLT1/SGLT2 inhibitors exacerbated cardiac dysfunction[46]. Because SGLT2 receptors are not yet identified in the heart, this effect may be due to acute SGLT1 inhibition in the post-MI setting. Moreover, in the mouse models of ischemia-reperfusion injury, SGLT1 inhibition led to poor outcomes, including increased infarct size and cardiac dysfunction[21].

Overall, following acute myocardial ischemia, energy metabolism shifts toward carbohydrate instead of fatty acid consumption, which appears crucial for maintaining adequate ATP supply for cardiac contraction. SGLT1 receptors facilitate glucose uptake, providing the sole source of ATP through anaerobic glycolysis during myocardial ischemia. In this acute setting, SGLT1 inhibition may be detrimental. However, prolonged reliance

on glucose as the primary energy source for cardiac metabolism has been associated with cardiac dysfunction. Thus, the effect of SGLT1 inhibitors could be particularly crucial in this context[47].

5. Potentially detrimental effects of SGLT1 inhibition in clinical applications

Mutations in the *SGLT1* gene in the intestinal brush border result in glucose–galactose malabsorption, a rare disorder inherited in an autosomal recessive manner. These mutations result in an increased ratio of N-acetyl glucosaminidase to creatinine and retinol-binding protein to creatinine, leading to proximal tubule dysfunction[48]. In addition, renal tubular dysfunction, specifically distal tubular acidosis, is associated with the development of persistent metabolic acidosis, hypercalcemia, and nephrocalcinosis in patients with mutations in the *SGLT1* gene. However, most of these abnormalities can be effectively managed by adhering to a glucose- and galactose-free diet[48].

Given that *SGLT1* facilitates glucose absorption at the brush border of the small intestine, the inhibition of intestinal SGLT1 may be associated with osmotic diarrhea. Administration of sotagliflozin to patients with type 1 diabetes mellitus (T1DM) resulted in a higher incidence of diarrhea (4.1% in the sotagliflozin group vs 2.3% in the placebo group). However, these cases were generally mild to moderate and transient in nature[49]. Furthermore, in the Canagliflozin Cardiovascular Assessment Study (CANVAS) program, the canagliflozin group had a significantly higher incidence of osmotic diuresis than did the placebo group (34.5% vs 13.3%; $p < 0.001$) [3]. Similarly, adverse events related to volume depletion were more prevalent in the canagliflozin group than in the placebo group (26.0% vs 18.5%; $p = 0.009$) [3]. By contrast, the empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes (EMPA-REG OUTCOME) trial, which assessed empagliflozin, a selective SGLT2 inhibitor, did not observe an increased risk of volume depletion at doses of 10 and 25 mg per day [2]. In the CANVAS program, a higher incidence of diabetic ketoacidosis (DKA) was observed among patients administered canagliflozin compared with those receiving a placebo (0.6 vs 0.3 per 1000 patient-years, respectively; hazard ratio, 2.33; 95% CI, 0.76-7.17) [3]. A similar trend was observed following the administration of sotagliflozin in patients with T1DM who exhibited an increased susceptibility to DKA (risk of DKA was 3% in the sotagliflozin vs 0.6% in the placebo group) [49].

6. Clinical evidence of cardiovascular protection by SGLT1 inhibition

SGLT1 inhibition increases glucose delivery to the distal intestine, potentially altering the microbiome and enhancing the production of short-chain fatty acids. This increase could further promote glucagon-like peptide-1 (GLP-1) secretion and reduce glucose-dependent insulinotropic polypeptide (GIP) secretion[50]. The mechanisms through which SGLT1 inhibition mitigates the effects of MI and stroke may involve changes in GLP-1 levels. Elevated GLP-1 levels can reduce thrombus formation and increase atherosclerotic plaque stability[50,51]. In the SCORED trial, an increase in GLP-1 may partly explain the reduction in MI and stroke. However, this increase in GLP-1 induced by SGLT1 inhibition is lower than that induced by GLP-1 receptor agonists. Thus, SGLT1 inhibition may provide additional beneficial effects that are independent of an increase in GLP-1[51]. Mendelian randomization studies investigating the effects of missense variations in SGLT1 on metabolic disorders have indicated a correlation between SGLT1 inhibition and a decreased incidence of HF. This correlation may be attributed to the effect of SGLT1 inhibitors on the secretion of GLP-1 and GIP, both of which help regulate appetite and promote weight loss. Such effects are particu-

larly relevant for preventing HF, especially considering the increased risk of HF in individuals with T2DM and abdominal obesity compared with those with only one of these conditions[18].

The results of the SCORED[7] and SOLOIST-WHF[8] trials indicate that combining SGLT1 inhibition with SGLT2 inhibition in patients with T2DM may affect cardiac and cardiorenal outcomes, potentially offering benefits comparable to those observed with SGLT2 inhibitors alone[52]. In addition, this combined approach reduced the incidence of both nonfatal and total fatal MI by 32% (hazard ratio, 0.68 [95% confidence interval, 0.52-0.89]; p = 0.004)[7]. The specific mechanisms underlying this reduction in fatal and nonfatal MI observed in the SCORED trial remain to be determined, but they may be largely related to the effects of SGLT1 inhibition on GLP-1 levels and changes in the intestinal microbiome[53]. However, additional prospective and comparative studies are necessary to investigate the benefits of additional SGLT1 inhibition on top of SGLT2 inhibition in patients without T2DM.

Taken together, the current evidence suggests that SGLT1 inhibition effectively provides cardiovascular protection. Thus, SGLT1 inhibitors can be used for the treatment of CVD. However, further evaluation in clinical trials is still necessary. More SGLT1 inhibitors or dual SGLT1/SGLT2 inhibitors will be developed in the near future and their cardiovascular benefits will be investigated.

7. Potential mechanisms through which SGLT1 inhibition confers cardiovascular protection

The benefits of SGLT2 inhibitors extend beyond glycemic control, as demonstrated in recent large-scale clinical trials examining cardiovascular and renal outcomes[2-13]. Similarly, an increasing number of studies have indicated that SGLT1 inhibition offers cardiovascular protection. This section discusses the cardiovascular benefits of SGLT1 inhibitors and explores their potential molecular mechanisms (Figure 1).

7.1 Attenuating oxidative stress in cardiomyocytes

Exposure to high glucose levels stimulates the production of nicotinamide adenine dinucleotide phosphate oxidases (Nox) through Ras-related C3 botulinum toxin substrate 1 (Rac1) activation and p47phox translocation to the plasma membrane, leading to reactive oxygen species (ROS) production and eventually cell death[43]. In addition, glucose fluctuations can exacerbate cardiac SGLT1 expression and lead to increased oxidative stress, inflammation, fibrosis, and mitochondrial damage in cardiomyocytes, ultimately resulting in cardiac diastolic dysfunction and hypertrophy[54,55]. Excessive oxidative stress and persistent ROS production play crucial roles in the pathogenesis of heart diseases, such as cardiomyopathy and atrial fibrillation, through the facilitation of inflammation and fibrosis[56,57]. Furthermore, SGLT1 plays a critical role in myocardial injury induced by glucose fluctuations through oxidative stress and mitochondrial dysfunction[55]. Moreover, myocardial SGLT1 expression is positively associated with the production of superoxide ($O:_2^-$) and the expression of genes related to fibrosis, inflammation, and cell wall stretching[58].

In animal studies on diabetes, fluctuating blood glucose levels were associated with increased cardiac SGLT1 expression, oxidative stress, and mitochondrial dysfunction[55]. In addition, knockdown of SGLT1 could stabilize mitochondrial function and reduce oxidative stress caused by these glucose fluctuations[55,59].

Nox is a primary source of ROS in cardiomyocytes[60], and adenosine monophosphate-activated protein kinase (AMPK) can inhibit ROS production by blocking Nox2 activation[61]. In addition, the activation of AMPK inhibits the activation of Rac1 and the membrane translocation of p47phox

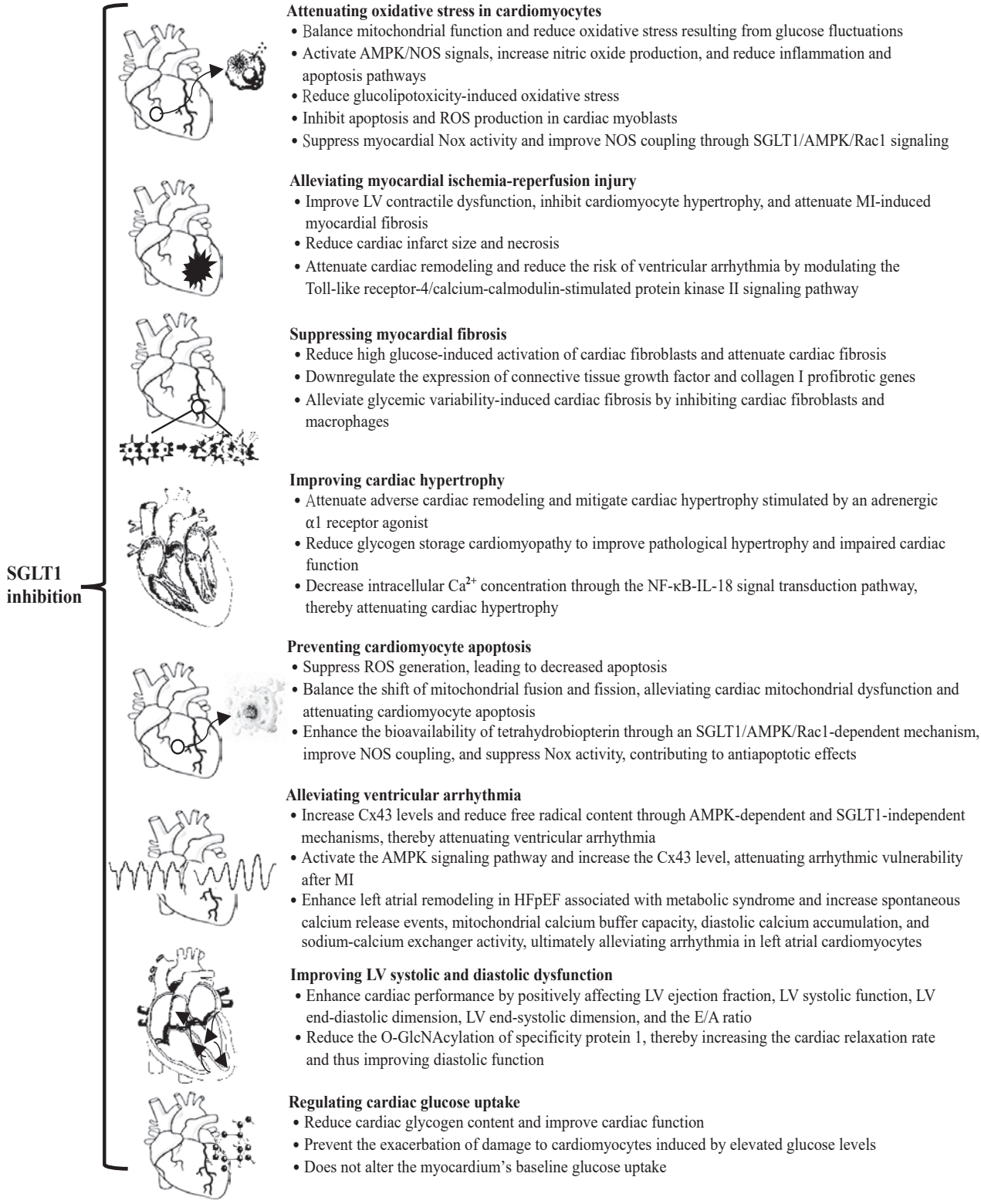

Figure 1. Potential mechanisms of SGLT1 inhibition in cardiovascular protection.
Abbreviations: AMPK, denosine 5'-monophosphate-activated protein kinase; Cx43, connexin43; HFpEF, heart failure with preserved ejection fraction; IL-18, interleukin-18; LV, left ventricular; MI, myocardial infarction; NF-κB, nuclear factor kappa B; NOS, nitric oxide synthase; Nox, nicotinamide adenine dinucleotide phosphate oxidases; O-GlcNAc, O-Linked β-N-Acetylglucosamine; ROS, reactive oxygen species; SGLT1, sodium glucose cotransporter 1.

and Rac1, thereby suppressing Nox activity and $O:_2^-$ generation. This action also reduces inflammation and increases the bioavailability of tetrahydrobiopterin, a crucial factor necessary for the coupling of nitric oxide synthase (NOS)[15]. Canagliflozin, a dual SGLT1/2 inhibitor, can activate AMPK/NOS signals, increase nitric oxide production, and reduce inflammation and apoptosis pathways[58]. Inhibition of SGLT1 by dapagliflozin and canagliflozin reduced glucolipotoxicity-induced oxidative stress in cardiomyocytes[62]. By blocking SGLT1, dapagliflozin and canagliflozin suppressed apoptosis in cardiac myoblasts and attenuated ROS production[54]. Furthermore, canagliflozin inhibited myocardial Nox activity and improved NOS coupling through the SGLT1/AMPK/Rac1 signaling pathway, resulting in global anti-inflammatory effects on the human myocardium[58]. However, empagliflozin, which specifically inhibits SGLT2, does not affect NOS coupling or Nox activity[58]. Thus, inhibiting SGLT1 may be an effective therapeutic strategy to attenuate and prevent cardiomyocyte injury.

7.2 Alleviating myocardial ischemia-reperfusion injury

Ischemia-reperfusion injury is considered a critical factor in the pathology of CVD, leading to substantial damage to cardiomyocytes and subsequently increasing the risk of HF[63]. The overexpression of cardiac SGLT1 in mice led to pathologic hypertrophy and interstitial fibrosis[32]. Moreover, SGLT1 protein level was found to be considerably high in patients with hypertrophic, ischemic, and diabetic cardiomyopathy[33,34]. The use of KGA-2727, a selective SGLT1 inhibitor, improved LV contractile dysfunction, inhibited cardiomyocyte hypertrophy, and attenuated myocardial fibrosis induced by MI. Moreover, the cardioprotective effects of KGA-2727 were observed without changes in blood sugar levels in mice, suggesting that its benefits are independent of SGLT1 inhibition in the kidney and small intestine[38]. During myocardial ischemia, AMPK regulates SGLT1 expression through the extracellular signal-related kinase pathway. SGLT1 interacts with the epidermal growth factor receptor, which, in turn, increases the activity of protein kinase C and Nox, leading to enhanced oxidative stress and resultant ischemic injury[37]. However, recent experimental evidence indicates that the cardiomyocyte-specific knockdown of SGLT1 reduces infarct size, necrosis, and oxidative stress[37]. In addition, sotagliflozin was observed to attenuate cardiac remodeling and significantly reduce vulnerability to ventricular arrhythmia in mice post MI through the modulation of the Toll-like receptor-4/calcium-calmodulin-stimulated protein kinase II signaling pathway[64]. These findings suggest that SGLT1 inhibition could be a novel therapeutic strategy to alleviate cardiac ischemia-reperfusion injury. However, the findings of the aforementioned studies are inconsistent. In mice with ischemia-reperfusion injury, the use of phlorizin to inhibit SGLT1 led to impaired cardiac functional recovery and increased myocardial injury[21]. These adverse effects might be attributed to high doses of phlorizin exerting a substantial effect on cardiac glucose transport, independent of SGLT1 inhibition. Considerable caution is warranted when using this inhibitor to investigate the role of SGLT1 in the heart[65].

7.3 Suppressing cardiac fibrosis

Cardiac fibroblasts play a key pathophysiological role in cardiac remodeling and are crucial cellular effectors in the development of cardiac fibrosis[66]. These cells transition from an inactive to an active type, leading to increased proliferation, migration, and excessive extracellular matrix (ECM) production, ultimately contributing to cardiac fibrosis[66]. The ECM is normally regulated by a balance between matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases; however, an imbalance can trigger cardiac fibrosis[36,67,68]. High

glucose levels activate cardiac fibroblasts, enhancing their growth and migration; increasing the expression of various proteins and enzymes, such as SGLT1, MMP-2, transforming growth factor-β1, and collagens; and activating the p38 MAPK and extracellular-signal-regulated kinase 1 and 2 pathways[17,36]. The overexpression of SGLT1 amplifies the effects of high glucose levels, contributing to interstitial fibrosis and cardiac remodeling[17,32]. By contrast, SGLT1 knockdown reduces the high glucose-induced activation of cardiac fibroblasts and attenuates cardiac fibrosis[17]. Specifically, silencing SGLT1 reduces cardiac fibrosis by downregulating connective tissue growth factor and collagen I profibrotic genes in pressure overload-induced mouse cardiomyopathy[16]. In addition, SGLT1 inhibition can mitigate glycemic variability-induced cardiac fibrosis by inhibiting the activation of both cardiac fibroblasts and macrophages[69].

7.4 Improving cardiac hypertrophy

Cardiac hypertrophy is an adaptive response to various heart diseases, such as chronic hypertension. However, sustained hypertrophy can lead to cardiac fibrosis and HF, substantially increasing the risk of cardiac morbidity and mortality[70]. Chronic pressure overload induced cardiac hypertrophy in mice through increased expression of SGLT1 and interleukin-18 genes[16]. SGLT1 knockout attenuated adverse cardiac remodeling induced by transverse aortic constriction and mitigated cardiac hypertrophy stimulated by an adrenergic α1 receptor agonist in neonatal mouse hearts[16]. SGLT1 overexpression can cause pathologic cardiac hypertrophy and LV failure, but these deleterious effects can be reversed if the overexpression is suppressed, as demonstrated in a murine model of PRKAG2 cardiomyopathy[32]. Epidermal growth factor (EGF), which is implicated in cell proliferation and differentiation, is associated with cardiac hypertrophy. EGF can upregulate glucose absorption through increased SGLT1 expression[71]. SGLT1 overexpression in the hypertrophic myocardium increases the phosphorylation of the intracellular secondary messengers AMPK, ERK-1/2 and mammalian target of rapamycin[34]. Moreover, chronic overexpression of SGLT1 contributes to glycogen storage cardiomyopathy, leading to pathological hypertrophy and impaired cardiac function. The genetic and pharmacological inhibition of SGLT1 could prevent this harmful cardiomyopathy phenotype[32,72]. Nuclear factor kappa B (NF-κB) plays a crucial role in the development of hypertrophic myocardium, and chronic pressure overload induced by transverse aortic constriction activates NF-κB, which, in turn, contributes to the overexpression of SGLT1. Overexpression of SGLT1 may increase intracellular Ca^{2+} concentration through the NF-κB-IL-18 signaling pathway, thereby inducing cardiac hypertrophy[15]. Collectively, these findings indicate that under cellular stress, SGLT1 exerts prohypertrophic and detrimental effects on cardiomyocytes. Thus, targeting SGLT1 in cardiomyocytes may represent a novel pharmacological strategy for treating patients with cardiac diseases, such as hypertrophic cardiomyopathy.

7.5 Preventing cardiac apoptosis

Cardiomyocyte apoptosis is a critical process in diabetic cardiomyopathy.[73] Cardiomyocyte apoptosis increased by 85-fold in patients with diabetes than in those without diabetes. This finding indicates a high sensitivity of cardiomyocytes to diabetes-induced apoptosis[74]. Thus, targeting apoptotic signaling pathways may be a viable strategy to hinder the progression of diabetic cardiomyopathy. Studies have reported a considerable upregulation of SGLT1 in patients with diabetic cardiomyopathy. SGLT1 inhibition attenuated apoptosis and suppressed the development of diabetic cardiomyopathy through the JNK and p38 MAPK pathways[75]. Furthermore, the downregulation of SGLT1 markedly

reduced the protein and mRNA expression of apoptosis-related markers, such as caspase-3 and Bax, while increasing the levels of the antiapoptotic gene *bcl2* in diabetic cardiomyopathy rats[75]. In addition, the inhibition of SGLT1 by dapagliflozin and canagliflozin reduced ROS generation and apoptosis in cultured cardiomyocytes[62]. Knockdown of *SGLT1* balanced the processes of mitochondrial fusion and fission in the hearts of diabetic mice, thereby alleviating cardiac mitochondrial dysfunction and attenuating cardiomyocyte apoptosis[55]. The high affinity of canagliflozin for SGLT1 enhanced the bioavailability of tetrahydrobiopterin through an SGLT1/AMPK/Rac1-dependent mechanism. This mechanism, in turn, improved NOS coupling and suppressed Nox activity, leading to antiapoptotic effects in the human myocardium[58]. These findings indicate a crucial SGLT1-mediated mechanism that underlies the cardioprotective effects of canagliflozin.

7.6 Alleviating ventricular arrhythmia

Connexin43 (Cx43) plays a crucial role in the heart's electrical conduction system, and its function is sensitive to the redox status within cells. Decreased ventricular Cx43 levels are associated with ventricular arrhythmias[76]. Therapeutic strategies that increase Cx43 levels, such as gene transfer, could reduce susceptibility to arrhythmias post MI[77]. Activation of the AMPK signaling pathway by dapagliflozin not only reduces ROS levels but also affects myocardial SGLT1 activity[78]. Moreover, treatment of the heart with dapagliflozin substantially increased the Cx43 level and reduced free radical content through AMPK-dependent and SGLT1-independent mechanisms, thereby attenuating ventricular arrhythmia in normoglycemic infarcted rats[78]. Silencing AMPK may exacerbate cardiac gap junction remodeling after MI through a Cx43 pathway[79]. Inhibiting SGLT1 to activate the AMPK signaling pathway and increase the Cx43 level reduced arrhythmic vulnerability after MI[15]. Bode and colleagues demonstrated that sotagliflozin enhances left atrial remodeling in HF with preserved ejection fraction associated with metabolic syndrome. In addition, sotagliflozin could enhance spontaneous calcium release events, mitochondrial calcium buffering capacity, diastolic calcium accumulation, and sodium-calcium exchanger activity. Furthermore, sotagliflozin exerted antiarrhythmic effects on left atrial cardiomyocytes[80].

7.7 Improving LV systolic and diastolic dysfunction

LV dysfunction is characterized by impaired systolic and diastolic measures, leading to HF with either reduced or preserved ejection fraction[81]. Previous preclinical studies have demonstrated a correlation between SGLT1 expression and LV systolic and diastolic functions in various conditions, including dilated cardiomyopathy, diabetes, PRKAG2 cardiomyopathy, and congestive HF, and in nondiabetic mice[15]. In patients with end-stage HF, SGLT1 expression was positively correlated with LV end-diastolic diameter and negatively correlated with LV systolic function[82]. Several studies have indicated that the deficiency, suppression, or genetic knockout of SGLT1 can mitigate cardiac hypertrophy induced by transverse aortic constriction or aortocaval fistula surgery, thereby maintaining optimal LV function in the presence of pressure overload-induced congestive HF[15]. In addition, mizagliflozin, an inhibitor of sodium-glucose SGLT1, enhanced cardiac performance by positively affecting various parameters, such as LV ejection fraction, LV systolic function, LV end-diastolic dimension, LV end-systolic dimension, and the E/A ratio in diabetic rats, in a concentration-dependent manner[75].

O-Linked β-N-Acetylglucosamine (O-GlcNAc) is a crucial posttranslational modification that plays a vital role in regulating cellular processes, particularly cardiac and vascular functions[82]. O-GlcNAcyla-

tion involves the attachment of N-acetylglucosamine to serine or threonine residues on proteins located in the cytosol, nucleus, and mitochondria. O-GlcNAcylation plays a key role in modulating cellular signaling and is associated with various physiological and pathological processes[83]. Precise adjustments to the enzymes regulating cardiac O-GlcNAcylation can substantially influence the structure and function of the diabetic heart[84]. Moreover, elevated levels of protein O-GlcNAcylation in the heart were linked with various pathological conditions, including diabetes, ischemia, and hypertrophic HF[85]. By contrast, a decrease in the O-GlcNAcylation of specificity protein 1 was associated with an increase in the cardiac relaxation rate, leading to improved diastolic function[85]. A study demonstrated that inhibiting the O-GlcNAcylation of specificity protein 1 reduced SGLT1 expression in renal proximal tubule cells[86]. Another study indicated that the systemic knockdown of O-GlcNAcylation downregulated the expression of SGLT1 in the intestine and kidneys. This finding demonstrated that O-GlcNAcylation regulates SGLT1 gene expression[87]. Given the limited research, further investigation into the potential relationship between O-GlcNAcylation of specificity protein 1, SGLT1 expression, and SGLT1 inhibitors in the context of cardiac systolic and diastolic dysfunction is warranted.

7.8 Regulating cardiac glucose uptake

The heart depends on a continuous supply of various metabolic substrates for its functioning. Although fatty acids are the main substrates used by the heart, there is a marked shift toward glucose metabolism under certain conditions, such as in response to insulin, during ischemia, or in hypertrophic hearts. In mice, cardiac SGLT1 enhances ATP reserves in the ischemic heart tissue during the initial phase of ischemia-reperfusion injury by increasing glucose utilization. This mechanism considerably enhances cardiac energy metabolism, even in the presence of insulin resistance[20,21]. In an experimental mouse model of diet-induced obesity, phlorizin impeded insulin-stimulated glucose uptake in cardiomyocytes in a dosage-dependent manner during the initial phase of ischemia-reperfusion injury. This disruption led to a marked reduction in ATP levels within the heart tissue, ultimately impairing heart function recovery and exacerbating myocardial damage[20]. However, cardiac SGLT1 does not contribute to overall glucose uptake, likely due to the presence of the SLC5A1 transcript variant. The inhibitory effect of phlorizin on cardiac glucose uptake is independent of SGLT1 and can be explained by the inhibition of GLUTs[21].

The knockdown of *SGLT1* reduced cardiac glycogen content and improved cardiac function in a model of PRKAG2 cardiomyopathy[32]. However, neither a general knockout of *SGLT1* nor a specific knockout in cardiomyocytes altered the myocardium's baseline glucose uptake[15]. During the reperfusion period, elevated glucose levels exacerbated MI in the nondiabetic heart; however, this exacerbation was mitigated in the diabetic rat heart through the downregulation of SGLT1 expression[88]. By inhibiting SGLT1 in the nondiabetic heart, the damage induced by elevated glucose levels can be prevented. This finding indicates the potential of SGLT1 as a therapeutic target for improving outcomes in acute MI associated with hyperglycemia[88].

Given the limitations of current research, future studies should investigate the relationship between SGLT1 inhibition and cardiac glucose uptake in the context of cardiac energy metabolism.

8. Conclusion

Large clinical trials have demonstrated that SGLT2 inhibitors not only reduce overall risk factors for heart and kidney diseases, including the progression of albuminuria, but also lower the risks of hospitalization for HF and CKD progression across all stages of the cardiorenal continuum,

regardless of diabetes status. In contrast to SGLT2, SGLT1 is substantially expressed in the human heart and may directly affect cardiac function. SGLT1 inhibition has been demonstrated to have considerable potential as a means of treating CVD, irrespective of diabetes status. Blocking SGLT1 can protect the cardiovascular system by reducing oxidative stress, inflammation, ventricular arrhythmia, myocardial hypertrophy, fibrosis, and apoptosis. Moreover, inhibiting SGLT1 can alleviate ischemia-reperfusion injury, enhance cardiac performance, and reduce HF risk. Thus, regulating the activity of SGLT1 is a promising strategy to mitigate adverse cardiac effects, but further clinical trials are needed to validate these benefits. Inhibiting SGLT1 may be detrimental in acute conditions, such as myocardial ischemia, where glucose absorption is crucial for energy production. Moreover, SGLT1 expression substantially increases during myocardial ischemia, indicating an adaptive response that aids functional recovery in failing hearts. Thus, SGLT1 inhibition presents a dual challenge, potentially benefiting or harming heart function and integrity depending on the context. Further research is essential to investigate the protective and detrimental effects of SGLT1 inhibition on the heart. Currently, data on dual SGLT1/SGLT2 inhibitors are limited, and more safety and efficacy data from clinical trials are necessary to confirm their effectiveness in preventing cardiovascular complications associated with diabetes and to develop specific inhibitors targeting SGLT1.

References

1. Wright EM, Loo DD, Hirayama BA. Biology of human sodium glucose transporters. Physiol Rev 2011;91(2):733-94.
2. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373(22):2117-28.
3. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377(7):644-57.
4. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380(4):347-57.
5. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380(24):2295-306.
6. Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. N Engl J Med 2020;383(15):1425-35.
7. Bhatt DL, Szarek M, Pitt B, et al. Sotagliflozin in patients with diabetes and chronic kidney disease. N Engl J Med 2021;384(2):129-39.
8. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. N Engl J Med 2021;384(2):117-28.
9. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381(21):1995-2008.
10. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med 2020;383(15):1413-24.
11. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med 2021;385(16);1451-61.
12. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020;383(15):1436-46.
13. The EMPA-KIDNEY Collaborative Group; Herrington WG, Staplin N, et al. Empagliflozin in patients with chronic kidney disease. N Engl J Med 2023;388(2):117-27.
14. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J 2020;41(45):255-323.
15. Li Y, Xu G. Sodium glucose cotransporter 1 (SGLT1) inhibitors in cardiovascular protection: Mechanism progresses and challenges. Pharmacol Res 2022;176:106049.
16. Matsushita N, Ishida N, Ibi M, et al. Chronic pressure overload induces cardiac hypertrophy and fibrosis via increases in SGLT1 and IL-18 gene expression in mice. Int Heart J 2018;59(5):1123-33.
17. Lin H, Guan L, Meng L, Uzui H, Guo H. SGLT1 knockdown attenuates cardiac fibroblast activation in diabetic cardiac fibrosis. Front Pharmacol 2021;12:700366.
18. Seidelmann SB, Feofanova E, Yu B, et al. Genetic variants in SGLT1, glucose tolerance, and cardiometabolic risk. J Am Coll Cardiol 2018;72(15): 1763-73.
19. Tsimihodimos V, Filippas-Ntekouan S, Elisaf M. SGLT1 inhibition: Pros and cons. Eur J Pharmacol 2018;838:153-6.
20. Yoshii A, Nagoshi T, Kashiwagi Y, et al. Cardiac ischemia-reperfusion injury under insulin-resistant conditions: SGLT1 but not SGLT2 plays a compensatory protective role in diet-induced obesity. Cardiovasc Diabetol 2019;18(1):1-14.
21. Kashiwagi Y, Nagoshi T, Yoshino T, et al. Expression of SGLT1 in human hearts and impairment of cardiac glucose uptake by phlorizin during ischemia-reperfusion injury in mice. PLoS One 2015;10(6):e0130605.
22. Sano R, Shinozaki Y, Ohta T. Sodium–glucose cotransporters: Functional properties and pharmaceutical potential. J

Diabetes Investig 2020;11(4):770-82.
23. Wood IS, Trayhurn P. Glucose transporters (GLUT and SGLT): Expanded families of sugar transport proteins. Br J Nutr 2003; 89(1):3-9.
24. Röder PV, Geillinger KE, Zietek TS, Thorens B, Koepsell H, Daniel H. The role of SGLT1 and GLUT2 in intestinal glucose transport and sensing. PLoS ONE 2014;9(2):e89977.
25. Dyer J, Hosie KB, Shirazi-Beechey SP. Nutrient regulation of human intestinal sugar transporter (SGLT1) expression. Gut 1997;41(1):56-9.
26. Dyer J, Wood IS, Palejwala A, Ellis A, Shirazi-Beechey SP. Expression of monosaccharide transporters in intestine of diabetic humans. Am J Physiol Gastrointest Liver Physiol 2002;282(2):G241-8.
27. Dobbins RL, Greenway FL, Chen L, et al. Selective sodium-dependent glucose transporter 1 inhibitors block glucose absorption and impair glucose-dependent insulinotropic peptide release. Am J Physiol Gastrointest Liver Physiol 2015;308(11):G946-54.
28. Vrhovac I, Balen Eror D, Klessen D, et al. Localizations of Na (+)-D-glucose cotransporters SGLT1 and SGLT2 in human kidney and of SGLT1 in human small intestine, liver, lung, and heart. Pflugers Archiv 2015;467(9):1881-98.
29. Rieg T, Masuda T, Gerasimova M, et al. Increase in SGLT1-mediated transport explains renal glucose reabsorption during genetic and pharmacological SGLT2 inhibition in euglycemia. Am J Physiol Renal Physiol 2014;306(2):F188-93.
30. Song P, Onishi A, Koepsell H, Vallon V. Sodium glucose cotransporter SGLT1 as a therapeutic target in diabetes mellitus. Expert Opin Ther Targets 2016;20(9):1109-25.
31. Zhou L, Cryan EV, D'Andrea MR, Belkowski S, Conway BR, Demarest KT. Humancardiomyocytes express high level of Na+/glucose cotransporter 1 (SGLT1). J Cell Biochem 2003;90(2):339-46.
32. Ramratnam M, Sharma RK, D'Auria S, et al. Transgenic knockdown of cardiac sodium/glucose cotransporter 1 (SGLT1) attenuates PRKAG2 cardiomyopathy, whereas transgenic overexpression of cardiac SGLT1 causes pathologic hypertrophy and dysfunction in mice. J Am Heart Assoc 2014;3(4):e000899.
33. Banerjee SK, McGaffin KR, Pastor-Soler NM, Ahmad F.. SGLT1 is a novel cardiac glucose transporter that is perturbed in disease states. Cardiovasc Res 2009;84(1): 111-8.
34. Di Franco A, Cantini G, Tani A, et al. Sodium-dependent glucose transporters (SGLT) in human ischemic heart: A new potential pharmacological target. Int J Cardiol 2017;243:8690.
35. Cai Q, Li B, Yu F, et al. Investigation of the Protective Effects of Phlorizin on Diabetic Cardiomyopathy in db/db Mice by Quantitative Proteomics. J Diabetes Res 2013;2013:263845.
36. Meng L, Uzui H, Guo H, Tada H. Role of SGLT1 in high glucose level-induced MMP-2 expression in human cardiac fibroblasts. Mol Med Rep 2018;17(5):6887-92.
37. Li Z, Agrawal V, Ramratnam V, et al. Cardiac sodium-glucose co-transporter 1 (SGLT1) is a novel mediator of ischemia/reperfusion Injury. Cardiovasc Res 2019;115(11):1646-58.
38. Sawa Y, Saito M, Ishida N, et al. Pretreatment with KGA-2727, a selective SGLT1 inhibitor, is protective against myocardial infarction-induced ventricular remodeling and heart failure in mice. J Pharmacol Sci 2020;142(1):16-25.
39. von Lewinski D, Rainer PP, Gasser R, et al. Glucose-transporter-mediated positive inotropic effects in human myocardium of diabetic and nondiabetic patients. Metabolism 2010;59(7):1020-8.
40. von Lewinski D, Gasser R, Rainer PP, et al. Functional effects of glucose transporters in human ventricular myocardium. Eur J Heart Fail 2010;12(2):106-13.
41. Yu AS, Hirayama BA, Timbol G, et al. Regional distribution of SGLT activity in rat brain in vivo. Am J Physiol Cell Physiol 2013;304(3):C240-7.
42. Tahrani AA, Barnett AH, Bailey CJ. SGLT inhibitors in management of diabetes. Lancet Diabetes Endocrinol 2013;1(2):140-51.
43. Balteau M, Tajeddine N, de Meester C,, et al. NADPH oxidase activation by hyperglycaemia in cardiomyocytes is independent of glucose metabolism but requires SGLT1. Cardiovasc Res 2011;92(2):237-46.
44. Burgos MH, Aoki A, Sacerdote FL. Ultrastructure of Isolated Kidney Mitochondria Treated with Phlorizin and Atp. J Cell Biol 1964;23(2):207-15.
45. Tellez de Inon MT. Inhibition of mitochondrial ATPase by phlorizin. Acta Physiol Lat Am 1968;18(3):268-71.
46. Connelly KA, Zhang Y, Desjardins JF, Thai K, Gilbert RE. Dual inhibition of sodium-glucose linked cotransporters 1 and 2 exacerbates cardiac dysfunction following experimental myocardial infarction. Cardiovasc Diabetol 2018;17(1):99.
47. García-Ropero Á, Vargas-Delgado AP, Santos-Gallego CG, Badimon JJ. Inhibition of sodium glucose cotransporters improves cardiac performance. Int J Mol Sci 2019;20(13):3289.
48. Soylu OB, Ecevit C, Altinoz S, et al. Nephrocalcinosis in glucose-galactose malabsorption: Nephrocalcinosis and proximal tubular dysfunction in a young infant with a novel mutation of SGLT1. Eur J Pediatr 2008;167(12):1395-8.
49. Garg SK, Henry RR, Banks P, et al. Effects of sotagliflozin added to insulin in patients with type 1 diabetes. N Engl J Med 2017;377(24):2337-48.
50. Cefalo CMA, Cinti F, Moffa S, et al. Sotagliflozin, the first dual SGLT inhibitor: Current outlook and perspectives. Cardiovasc Diabetol 2019;18(1):20.
51. Pitt B, Bhatt DL. Does SGLT1 inhibition add benefit to SGLT2 inhibition in type 2 diabetes? Circulation 2021;144(1):4-6.
52. McGuire DK, Shih WJ, Cosentino F, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: A meta-analysis. JAMA Cardiol 2021;6(2):148-58.
53. Pitt B, Bhatt DL, Metra M. Does SGLT1 inhibition add to the benefits of SGLT2 inhibition in the prevention and treatment of heart failure? Eur Heart J 2022;43(45):4754-7.
54. Zhao M, Li N, Zhou H. SGLT1: A potential drug target for cardiovascular disease. Drug Des Devel Ther 2023;17:2011-23.
55. Wu W, Chai Q, Zhang Z. Glucose fluctuation accelerates cardiac injury of diabetic mice via sodium-dependent

glucose cotransporter 1 (SGLT1). Arch Biochem Biophys 2021;709:108968.
56. Liu Q, Wang S, Cai L. Diabetic cardiomyopathy and its mechanisms: Role of oxidative stress and damage. J Diabetes Investig 2014;5(6):623-34.
57. Reilly SN, Jayaram R, Nahar K, et al. Atrial sources of reactive oxygen species vary with the duration and substrate of atrial fibrillation: Implications for the antiarrhythmic effect of statins. Circulation 2011;124(10):1107-17.
58. Kondo H, Akoumianakis I, Badi I, et al. Effects of canagliflozin on human myocardial redox signalling: Clinical implications. Eur Heart J 2021;42(48):4947-60.
59. Chai Q, Miao J, Liu M, Zhang Z, Meng Z, Wu W. Knockdown of SGLT1 prevents the apoptosis of cardiomyocytes induced by glucose fluctuation via relieving oxidative stress and mitochondrial dysfunction. Biochem Cell Biol 2021;99(3):356-63.
60. Konior A, Schramm A, Czesnikiewicz-Guzik M, Guzik TJ. NADPH oxidases in vascular pathology. Antioxid Redox Signal 2014;20(17):2794-814.
61. Balteau M, Van Steenbergen A, Timmermans AD, et al. AMPK activation by glucagon-like peptide-1 prevents NADPH oxidase activation induced by hyperglycemia in adult cardiomyocytes. Am J Physiol Heart Circ Physiol 2014;307(8):H1120-33.
62. Dasari D, Bhat A, Mangali S, et al. Canagliflozin and dapagliflozin attenuate glucolipotoxicity-induced oxidative stress and apoptosis in cardiomyocytes via inhibition of sodium-glucose cotransporter-1. ACS Pharmacol Transl Sci 2022;5(4):216-25.
63. Gunata M, Parlakpinar H. A review of myocardial ischaemia/reperfusion injury: Pathophysiology, experimental models, biomarkers, genetics and pharmacological treatment. Cell Biochem Funct 2021;39(2):190-217.
64. Gong Y, Kong B, Shuai W, Chen T, Zhang J, Huang H. Effect of sotagliflozin on ventricular arrhythmias in mice with myocardial infraction. Eur J Pharmacol 2022;936:175357.
65. Ferté L, Marino A, Battault S, et al. New insight in understanding the contribution of SGLT1 in cardiac glucose uptake: Evidence for a truncated form in mice and humans. Am J Physiol Heart Circ Physiol 2021;320(2):H838-53.
66. Frangogiannis NG. Cardiac fibrosis. Cardiovasc Res 2021;117(6):1450-88.
67. Shi YF, Chi JF, Tang WL, et al. Effects of rosuvastatin on the production and activation of matrix metalloproteinase-2 and migration of cultured rat vascular smooth muscle cells induced by homocysteine. J Zhejiang Univ Sci B 2013;14(8):696-704.
68. Meng L, Liu L, Zhou C, et al. Polyphenols and polypeptides in Chinese rice wine inhibit homocysteine-induced proliferation and migration of vascular smooth muscle cells. J Cardiovasc Pharmacol 2016;67(6):482-90.
69. Wu W, Chai Q, Zhang Z. Inhibition of SGLT1 Alleviates the Glycemic Variability-Induced Cardiac Fibrosis via Inhibition of Activation of Macrophage and Cardiac Fibroblasts. Mol Cell Biol 2022;42(2):e0028221.
70. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med 1990;322(22):1561-6.
71. Wang CW, Chang WL, Huang YC, et al. An essential role of cAMP response element-binding protein in epidermal growth factor-mediated induction of sodium/glucose cotransporter 1 gene expression and intestinal glucose uptake. Int J Biochem Cell Biol 2015;64:239-51.
72. Banerjee SK, Wang DW, Alzamora R, et al. SGLT1, a novel cardiac glucose transporter, mediates increased glucose uptake in PRKAG2 cardiomyopathy. J Mol Cell Cardiol 2010;49(4): 683-92.
73. Li Z, Zhang T, Dai H, et al. Involvement of endoplasmic reticulum stress in myocardial apoptosis of streptozocin-induced diabetic rats. J Clin Biochem Nutr 2007;41(1):58-67.
74. Ouyang C, You J, Xie Z. The interplay between autophagy and apoptosis in the diabetic heart. J Mol Cell Cardiol 2014;71:71-80.
75. Lin N, Lin H, Yang Q, et al. SGLT1 inhibition attenuates apoptosis in diabetic cardiomyopathy via the JNK and p38 pathway. Front Pharmacol 2021;11:598353.
76. Sovari AA, Rutledge CA, Jeong EM, et al. Mitochondria oxidative stress, connexin43 remodeling, and sudden arrhythmic death. Circ Arrhythm Electrophysiol 2013;6(3):623-31.
77. Greener ID, Sasano T, Wan X, et al. Connexin43 gene transfer reduces ventricular tachycardia susceptibility after myocardial infarction. J Am Coll Cardiol 2012;60(12):1103-10.
78. Lee CC, Chen WT, Chen SY, Lee TM. Dapagliflozin attenuates arrhythmic vulnerabilities by regulating connexin43 expression via the AMPK pathway in postinfarcted rat hearts. Biochem Pharmacol 2021;192:114674.
79. Dufeys C, Daskalopoulos EP, Castanares-Zapatero D, et al. AMPKα1 deletion in myofibroblasts exacerbates post-myocardial infarction fibrosis by a connexin 43 mechanism. Basic Res Cardiol 2021;116(1):1-20.
80. Bode D, Semmler L, Wakula P, et al. Dual SGLT-1 and SGLT-2 inhibition improves left atrial dysfunction in HFpEF. Cardiovasc Diabetol 2021;20(1):7.
81. Levene J, Voigt A, Thoma F, Mulukutla S, et al. Patient Outcomes by Ventricular Systolic and Diastolic Function. J Am Heart Assoc 2024;13(4):e033211.
82. Zachara NE. The roles of O-linked β-N-acetylglucosamine in cardiovascular physiology and disease. Am J Physiol. Heart Circ Physiol 2012;302(10):H1905-18.
83. Issad T, Al-Mukh H, Bouaboud A, Pagesy P. Protein O-GlcNAcylation and the regulation of energy homeostasis: lessons from knock-out mouse models. J Biomed Sci 2022;29(1):64.
84. Prakoso D, Lim SY, Erickson JR, et al. Fine-tuning the cardiac OGlcNAcylation regulatory enzymes governs the functional and structural phenotype of the diabetic heart. Cardiovasc Res 2021;118(1):212-25.
85. Belke DD. Swim-exercised mice show a decreased level of protein OGlcNAcylation and expression of O-GlcNAc transferase in heart. J Appl Physiol(1985) 2011;111(1):157-62.
86. Suh HN, Lee YJ, Kim MO, Ryu JM, Han HJ. Glucosamine-induced Sp1 OGlcNAcylation ameliorates hypoxia-induced

SGLT dysfunction in primary cultured renal proximal tubule cells. J Cell Physiol 2014;229(10):1557-68.
87. Nishimura K, Fujita Y, Ida S, et al. Glycaemia and body weight are regulated by sodium-glucose cotransporter 1 (SGLT1) expression via O-GlcNAcylation in the intestine. Mol Metab 2022;59:101458.
88. Almalki A, Arjun S, Harding I, et al. Hyperglycemic exacerbation of myocardial infarction through SGLT1-a glucose paradox. MedRxiv 2023; 2023-03.

鈉 - 葡萄糖協同轉運蛋白 1 的抑制在心血管保護角色之新見解：文獻回顧

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摘要

近年來，許多大規模的臨床試驗已經證明，無論是否有糖尿病，鈉 - 葡萄糖協同轉運蛋白 2 抑制劑都能提供顯著的心血管疾病和腎臟之保護作用。雖然鈉 - 葡萄糖協同轉運蛋白 1 是鈉 - 葡萄糖協同轉運蛋白的另一個主要異形體，但其所扮演的角色至今仍然不明確。鈉 - 葡萄糖協同轉運蛋白 2 高度分布於腎臟中，能調節大部份葡萄糖再吸收，而鈉 - 葡萄糖協同轉運蛋白 1 主要分布在腸道上皮細胞中，調節膳食中葡萄糖之吸收。不同於心臟中幾乎不存在有鈉 - 葡萄糖協同轉運蛋白 2，鈉 - 葡萄糖協同轉運蛋白 1 則高度分布於心肌之中。鈉 - 葡萄糖協同轉運蛋白 1 在葡萄糖轉換中扮演獨特和輔助性的潛在角色。因此，抑制鈉 - 葡萄糖協同轉運蛋白 1 可能提供治療許多疾病之潛力。在心臟受傷的早期階段，鈉 - 葡萄糖協同轉運蛋白 1 的運作會大幅增加，以確保心肌細胞有持續足夠的能量供應。然而，臨床前的研究指出，長期鈉 - 葡萄糖協同轉運蛋白 1 過度活動可能會誘發許多負面病理機轉（如心臟炎症、氧化壓力、纖維化、細胞凋亡和線粒體功能障礙），這些效應對心臟是有傷害的。因此，除了影響葡萄糖的吸收之外，抑制鈉 - 葡萄糖協同轉運蛋白 1 似乎可以提供許多心臟保護的額外好處。許多臨床研究已經證明，無論是否存在糖尿病或心臟衰竭，鈉 - 葡萄糖協同轉運蛋白 1 抑制劑可以透過降低心血管死亡風險和心臟衰竭住院風險，顯著有益於心血管保護。儘管鈉 - 葡萄糖協同轉運蛋白 1 抑制劑有許多有益於心血管的好處，但其詳細的作用機轉尚未完全明確。基因模型顯示鈉 - 葡萄糖協同轉運蛋白 1 的功能失調對各種器官組織會產生負向的影響。本文綜論主要在探討鈉 - 葡萄糖協同轉運蛋白 1 之抑制對心臟的正面和負面影響。另外，藉由對鈉 - 葡萄糖協同轉運蛋白 1 之基礎研究的深入分析，本文同時探討鈉 - 葡萄糖協同轉運蛋白 1 之抑制可能透過那些潛在機制來提供心血管保護。