

# A Review of the Mechanism of Cardiac Benefit of Sodium-Glucose Cotransporter 2 Inhibitors

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**Abstract:** Sodium-glucose cotransporter 2 inhibitor (SGLT2i) is a new type of hypoglycemic drug, which can reduce the excitability of sympathetic nerve by regulating the metabolism of energy substrate, electrolyte, tissue fluid and circulating blood volume in the ganglion, interfering with inflammation and oxidative stress, offering protection to vascular endothelial cells, maintaining vasodilation function, regulating volume and pressure load and myocardial energy metabolism, as well as protecting cardiomyocytes and cardiac function.

**Keywords:** SGLT2i; Circulatory load; Cardiomyocyte; Myocardial energy

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## 1. Introduction

Hyperglycemia is a high-risk factor that poses a threat to human life and health. Under the hyperglycemic milieu, the metabolism of nutrients and energy supply in the body is disturbed, thereby resulting in disorder of blood lipid metabolism, impairment of mitochondrial function, imbalance of energy metabolism, acid-base imbalance, disorder of intracellular and extracellular electrolyte metabolism and so on. A series of pathological changes lead to oxidative stress, inflammatory reaction, continuous stimulation to damaged human blood vessels, nerves, heart and other tissues and organs, affect the physiological function of the body, and then induce adverse cardiovascular events, and even endanger the lives of patients. Hyperglycemia has become the leading cause of death in patients with diabetes. A large number of studies have confirmed that sodium-glucose cotransporter 2 inhibitor (SGLT2i) can reduce the incidence of adverse cardiovascular events in diabetic patients and protect cardiac and renal function. It is also suitable for non-diabetic cardiovascular patients<sup>[1]</sup>. This paper gives an overview of the cardiovascular benefit mechanism of SGLT2i.

## 2. Improving circulatory load

SGLT2i is a new type of hypoglycemic drug. The control of blood glucose does not depend on insulin and the function of human islet cells. Through competitive binding of sodium-glucose cotransporter 2, it inhibits glucose and sodium ion reabsorption, reduces blood glucose and volume load<sup>[2]</sup>, and reduces glycosylated hemoglobin. Patients have obvious cardiovascular benefits.

SGLT2i alleviates hyperemia by promoting urinary sodium excretion and osmotic diuresis, but does not affect arterial filling and perfusion. It is more likely to reduce interstitial fluid volume and reduce cardiac preload<sup>[3]</sup>. It can also reduce the infiltration of inflammatory cells in arterial plaques, increase the content

of nitric oxide (NO) in vascular endothelial cells, inhibit oxidative stress induced by high-risk factors such as blood lipids and blood sugar, prevent arteriosclerosis, protect vascular dilation, regulate cardiovascular circulatory load, reduce cardiac work, and protect cardiac function <sup>[4]</sup>. In addition, SGLT2i can reduce arterial blood pressure and regulate cardiac afterload by inhibiting the excitability of the sympathetic nervous system, but the specific mechanism is unknown <sup>[5]</sup>.

### 3. Protecting cardiomyocytes

In addition to hemodynamic factors, primary myocardial damage is the primary key cause of the occurrence and progression of cardiac insufficiency. SGLT2i has a good myocardial protective effect, which is related to the regulation of myocardial ion homeostasis and the improvement of myocardial blood supply. It is suggested that calcium/calmodulin-dependent kinase II (CaMKII) may be the intermediary of myocardial ischemia reperfusion injury <sup>[6]</sup>. SGLT2i can regulate Na<sup>+</sup>/Ca<sup>2+</sup> exchange, inhibit Na<sup>+</sup>/H<sup>+</sup> exchange protein and CaMKII, decrease the concentration of Na<sup>+</sup> and Ca<sup>2+</sup> in cytoplasm, increase the concentration of Ca<sup>2+</sup> in mitochondria and sarcoplasmic reticulum, enhance the contractile excitability of cardiomyocytes and the antioxidant ability of mitochondria, reduce cardiomyocyte apoptosis, and ensure normal myocardial contraction and relaxation <sup>[7]</sup>. Studies have confirmed that SGLT2i can reduce the infarct size of diabetic and non-diabetic myocardial infarction animal models <sup>[8]</sup>, improve myocardial fibrosis and ventricular remodeling induced by pressure load or myocardial infarction in rats, and protect cardiomyocytes <sup>[9, 10]</sup>. These suggest that SGLT2i can improve myocardial ischemic injury.

### 4. Improving myocardial energy metabolism

Under physiological conditions, there are two main sources of energy for the adult heart: mitochondrial oxidative phosphorylation (95%) and glycolysis (5%). About 40% of the ATP produced by mitochondria comes from the oxidation of fatty acids, and the rest comes from the oxidation of pyruvate (derived from glucose and lactic acid), ketone bodies and branched-chain amino acids <sup>[11]</sup>. Empagliflozin increased the ATP produced by the heart of diabetic mice by about 30% by increasing the oxidation rate of glucose and fatty acids <sup>[12]</sup>.

In heart failure, fatty acid oxidation rate decreased, ketone body oxidation increased, glucose uptake increased and oxidation decreased. In clinical studies on patients with decreased ejection fraction, it was found that the production capacities of fatty acids, ketone bodies, lactic acid and amino acids were about 71%, 16.4%, 5% and 6.4%, respectively <sup>[11]</sup>. SGLT2i can increase the level of plasma ketone body in patients with diabetes and heart failure, compete with fatty acids and glucose to enter cardiomyocyte mitochondria and be oxidized, ensure myocardial energy supply, reduce myocardial oxygen consumption <sup>[13]</sup>, reduce the production of reactive oxygen species, reduce mitochondrial damage, and reduce cardiomyocyte apoptosis. In addition, SGLT2i protects cardiac function by increasing the levels of hemoglobin and hematocrit, increasing cardiac oxygen supply and improving myocardial energy metabolism <sup>[14]</sup>.

### 5. Conclusion

In summary, SGLT2i benefits the heart by regulating circulatory load and myocardial energy supply as well as protecting the structure and function of cardiomyocytes and vascular endothelial cells; therefore, this medication is a powerful aid in the prevention and treatment of cardiovascular diseases. However, the unclear mechanism of action and side effects, such as urinary tract infection and fracture risk, limit its clinical application. Thus, in-depth analysis of the disease and its mechanism, improvement and optimization of pharmacodynamic and toxicological research, and minimization of the side effects of SGLT2i are sought after. This is to ensure that the application of SGLT2i will become more consistent with the concept of precision medicine advocated at present.

## Disclosure statement

The authors declare no conflict of interest.

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