SODIUM–GLUCOSE COTRANSPORTER 2 INHIBITORS (SGLT2 INHIBITORS): CARDIOPROTECTIVE MECHANISMS AND CLINICAL EFFICACY IN HEART FAILURE

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Abstract. Heart failure (HF) is becoming an increasingly serious healthcare challenge due to population aging and the rising prevalence of comorbid conditions. Although major advances in treatment have improved patient outcomes, HF continues to impose a substantial clinical and economic burden, highlighting the need for novel therapeutic strategies [1]. Sodium–glucose cotransporter 2 inhibitors (SGLT2 inhibitors) have recently emerged as a promising treatment option, demonstrating beneficial effects across the entire spectrum of HF, regardless of left ventricular ejection fraction (LVEF). This review explores the diverse mechanisms underlying the cardioprotective properties of SGLT2 inhibitors, including their ability to regulate energy metabolism, reduce oxidative stress, suppress inflammation, and promote autophagy. In addition, SGLT2 inhibitors shift myocardial energy utilization away from carbohydrates toward more energy-efficient substrates such as fatty acids and ketone bodies, thereby improving mitochondrial function and decreasing insulin resistance.

Keywords: heart failure, SGLT2 inhibitors, cardioprotective properties, pleiotropic effects, chronic kidney disease, inflammation, oxidative stress, autophagy

Introduction. Over the past several decades, the prevalence of heart failure (HF) has steadily risen, largely driven by population aging and the growing burden of associated comorbidities. Current estimates suggest that the lifetime risk of developing HF ranges from 20% to 30%. Management strategies for HF are primarily determined by left ventricular ejection fraction (LVEF). Among recent therapeutic advances, sodium–glucose cotransporter 2 inhibitors (SGLT2 inhibitors) have emerged as a particularly important class of drugs, as they have demonstrated clinical benefits across the full spectrum of HF, irrespective of LVEF [1]. A substantial number of clinical trials have evaluated the efficacy of SGLT2 inhibitors in patients with HF, both with and without diabetes mellitus, who were already receiving guideline-directed HF therapy. These studies consistently reported improved cardiovascular and renal outcomes. Beyond HF, SGLT2 inhibitors have also shown protective effects in patients with chronic kidney disease (CKD). Their primary mechanism involves blocking

glucose and sodium reabsorption in the proximal renal tubule, thereby enhancing tubuloglomerular feedback, lowering intraglomerular pressure, and slowing the decline in glomerular filtration rate (GFR) [2,3].

Thus, these agents exert mild diuretic and natriuretic effects, which contribute to reduced preload and lower left ventricular filling pressures. Experimental and clinical evidence further suggests anti-inflammatory properties, attenuation of sympathetic nervous system activity, and increases in hemoglobin concentration. Collectively, these findings indicate that the therapeutic effects of SGLT2 inhibitors extend well beyond glycemic control. Nevertheless, the full range of their pleiotropic mechanisms has not yet been completely elucidated. This review aims to summarize the current understanding of the multifaceted actions of SGLT2 inhibitors and their beneficial role in patients with HF [4].

Energy for myocardium

In the healthy myocardium, energy production relies predominantly on long-chain fatty acids, which account for approximately 60% of total energy generation. Carbohydrates also play a major role, with glucose contributing around 30% and lactate about 10%. Ketone bodies and amino acids provide only a small proportion of the heart's energy requirements under normal physiological conditions. Since cardiac tissue has a limited capacity to store metabolic substrates, a constant supply of these energy sources from the bloodstream is essential to maintain continuous myocardial activity. Among the available substrates, glucose is considered the most oxygen-efficient source of energy, demonstrating a phosphate-to-oxygen (P/O) ratio of approximately 2.58. In comparison, fatty acids have a lower efficiency, with a P/O ratio close to 2.33, whereas ketone bodies show an intermediate value of nearly 2.5, making them the second most efficient fuel for myocardial metabolism [5].

The relative contribution of cardiac energy substrates changes continuously in response to both physiological and pathological conditions. Normal states such as physical exercise or dietary modifications can alter myocardial metabolism, while diseases including diabetes mellitus, hypoxia, myocardial ischemia, arrhythmias, and heart failure (HF) may induce more profound metabolic disturbances. The heart's ability to rapidly adapt its fuel preference according to metabolic demands is referred to as metabolic flexibility.

Under pathological conditions, this adaptive capacity becomes impaired, resulting in less efficient ATP generation. When these metabolic alterations are transient, they are generally well tolerated and have minimal impact on myocardial contractility. However, in the failing heart, both metabolic flexibility and mitochondrial performance are significantly compromised, creating a state of chronic energy deficiency. Studies have shown that mitochondrial dysfunction and reduced oxidative capacity in HF may decrease ATP production by nearly 40% compared with healthy myocardium. In this

setting, cardiac metabolism shifts away from fatty acid oxidation toward greater reliance on glucose utilization and glycolysis. Increased expression of glucose transporter 1 (GLUT1) has been linked to enhanced glucose uptake by cardiomyocytes. At the same time, impaired coupling between glycolysis and glucose oxidation, together with reduced catabolism of branched-chain amino acids (BCAAs), leads to accumulation of glycolytic intermediates and BCAAs within myocardial cells. This metabolic imbalance activates the mammalian target of rapamycin (mTOR) signaling pathway, which has been associated with insulin resistance and adverse cardiac remodeling. Furthermore, the failing myocardium appears to increase its utilization of ketone bodies as an alternative energy source in an attempt to compensate for impaired energy production [5,6].

In addition, SGLT2 inhibitors have been shown to alleviate insulin resistance and improve insulin sensitivity in peripheral tissues. These metabolic benefits are believed to arise through several complementary mechanisms, including attenuation of glucotoxicity, reduction of inflammatory activity, and improvement in oxidative balance. As a result, circulating insulin levels decrease, despite the absence of SGLT2 expression in pancreatic α- and β-cells, indicating that these effects occur independently of direct pancreatic regulation. This mechanism may play an important role in the beneficial effects of SGLT2 inhibitors in heart failure. Elevated insulin concentrations have been linked to adverse left ventricular remodeling through activation of mitogen-activated protein kinase signaling pathways and other growth-promoting processes. Furthermore, hyperinsulinemia is associated with increased sympathetic nervous system activity, which may contribute to worsening diastolic dysfunction and impaired cardiac performance [7,8,9]

Modulation of oxidative stress

SGLT2 inhibitors have shown considerable potential to directly enhance cardiac function by mitigating reactive oxygen species (ROS)-mediated pathological pathways. Experimental studies using animal models have demonstrated that empagliflozin can interrupt mechanisms responsible for mitochondrial injury by increasing the expression of the anti-apoptotic protein Bcl-2 while simultaneously suppressing the pro-apoptotic protein BAX. Through this regulatory effect, mitochondrial outer membrane permeabilization and cytochrome c release are inhibited, thereby reducing cardiomyocyte apoptosis. Furthermore, empagliflozin appears to promote mitochondrial biogenesis via activation of the PGC-1α/NRF-1 signaling pathway. This contributes to an increase in mitochondrial content and improved mitochondrial function, ultimately leading to lower intracellular ROS generation and enhanced cellular energetic balance [10].

Inflammation

The inflammatory response observed in heart failure (HF) is largely driven by

activation of the innate immune system. Key components of this process include stimulation of pattern-recognition receptors (PRRs), production of anti-cardiac antibodies, migration of proinflammatory monocytes from the spleen, and elevated circulating levels of free kappa and lambda light chains [11]. Among PRRs, Toll-like receptor 4 (TLR-4), which is highly expressed in human cardiac tissue, plays a central role in myocardial inflammation. Increased levels of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) activate signaling pathways mediated by TLR-4. This subsequently promotes activation of the NLRP3 inflammasome and enhances the expression of proinflammatory mediators, including interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and nuclear factor kappa B (NF-κB). Although short-term activation of TLR-4 may exert protective effects in acute cardiac stress, persistent stimulation in heart failure with reduced ejection fraction (HFrEF) appears to contribute to chronic inflammation, inflammatory cell recruitment, and progressive cardiac remodeling. Patients with advanced or end-stage heart failure (HF) frequently exhibit circulating anti-cardiac antibodies directed against several myocardial targets, including β1-adrenergic receptors, mitochondrial proteins, troponin I, sarcolemmal Na^+/K^+-ATPase, and myosin [12]. These autoimmune responses are believed to contribute to ongoing myocardial injury and progressive deterioration of cardiac function.

Chronic inflammatory states are also associated with elevated levels of free kappa and lambda light chains, which have been shown in experimental models to promote cardiomyocyte apoptosis and stimulate cardiac fibroblast proliferation [13,14]. In parallel, proinflammatory monocytes originating from the spleen migrate into cardiac tissue, where they facilitate myofibroblast formation and interstitial collagen accumulation, thereby contributing to myocardial fibrosis and structural remodeling. Importantly, the inflammatory response in HF is not limited to the myocardium itself but also affects the coronary vascular endothelium, further aggravating cardiovascular dysfunction.

SGLT2 inhibitors appear to exert significant anti-inflammatory and antifibrotic effects that may contribute to their cardioprotective properties. In experimental mouse models, dapagliflozin was shown to suppress activation of the NLRP3 inflammasome and reduce myocardial fibrosis [15]. Clinical studies in humans have similarly demonstrated that SGLT2 inhibitors lower circulating levels of several inflammatory mediators, including TNF-α, IL-1, IL-6, intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and components associated with AMPK-dependent signaling pathways [16,17,18]. Additional evidence from studies using human umbilical vein endothelial cells exposed to dapagliflozin revealed decreased lipopolysaccharide-induced expression of TLR-4 and reduced NF-κB p65 phosphorylation [17]. Moreover, dapagliflozin appears to promote macrophage

polarization away from the proinflammatory M1 phenotype toward the anti-inflammatory M2 phenotype. These findings suggest that SGLT2 inhibitors may exert direct immunomodulatory actions independent of glucose lowering, partly through modulation of NF-κB signaling and suppression of TLR-4-mediated inflammatory pathways [17]. Further support for the anti-inflammatory potential of this drug class was provided by the CANOSSA trial, which demonstrated that canagliflozin therapy was associated with sustained reductions in high-sensitivity C-reactive protein (hs-CRP) levels at 3, 6, and 12 months compared with baseline values.

The SGLT2 inhibitors and autophagy

Cardiomyocytes possess only a limited capacity for regeneration and replacement following injury. Under conditions of cellular damage, autophagy serves as an adaptive mechanism through which dysfunctional cellular components are degraded and recycled, providing an alternative source of ATP necessary for cell survival. When activated at low to moderate levels of stress, autophagic flux generally exerts cardioprotective effects. Various forms of myocardial stress, including hypoxia, ischemia, and cardiotoxic injury, are known to stimulate autophagy. In these settings, autophagic activity helps maintain cellular homeostasis and supports myocardial adaptation to adverse conditions. Nevertheless, although autophagy initially functions as a protective response, excessive or dysregulated activation may become detrimental and contribute to cardiomyocyte death. Thus, autophagy appears to have a dual role in the myocardium, acting as both a survival mechanism and, under certain circumstances, a pathway leading to cellular injury and loss.

Cell death associated with excessive autophagy is referred to as autosis, a process that reflects maladaptive overactivation of autophagic pathways. This phenomenon has been observed in ischemia–reperfusion injury and may be attenuated by limiting autophagic flux. In contrast, certain cardiotoxic agents, such as doxorubicin, initially induce autophagy as a protective response aimed at preserving cellular integrity. However, under severe or prolonged stress conditions, this adaptive mechanism becomes insufficient, ultimately resulting in cardiomyocyte death [19]. In humans, mutations in the lysosome-associated membrane protein 2 (LAMP2) gene are associated with a form of cardiomyopathy known as Danon disease. Moreover, animal studies have demonstrated that disruption of autophagy-related proteins, particularly Atg5, leads to mitochondrial structural collapse, sarcomere disorganization, and progressive systolic dysfunction [20]. Emerging evidence suggests that SGLT2 inhibitors enhance autophagic flux in both myocardial and renal tissues. In addition, these agents facilitate the clearance of damaged mitochondria and support the restoration of mitochondrial quality and function [21]. Through their pleiotropic actions, SGLT2 inhibitors help preserve cardiomyocyte viability, reduce apoptosis, and maintain tissue architecture by limiting inflammation and fibrotic remodeling. These

effects are largely mediated by increased activation of AMP-activated protein kinase (AMPK) alongside suppression of the mechanistic target of rapamycin (mTOR) signaling pathway in stressed tissues.

Conclusion

SGLT2 inhibitors represent a major therapeutic advancement in the management of heart failure, owing to their broad spectrum of actions that extend well beyond glycaemic control. These agents enhance myocardial energetic efficiency, attenuate oxidative stress, and modulate key inflammatory signaling pathways, collectively contributing to cardioprotection and improved cardiac performance. In addition, SGLT2 inhibitors promote autophagic processes, facilitating the clearance of damaged intracellular components and supporting the preservation of cardiomyocyte integrity. Despite substantial progress in understanding their mechanisms of action, the full spectrum of the pleiotropic effects of SGLT2 inhibitors remains incompletely defined. Further research is warranted to elucidate these pathways in greater detail and to optimize their clinical application in heart failure and related cardiometabolic conditions.

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