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Unveiling the cardioprotective mechanisms of SGLT2 inhibitors beyond glycemic control

Zhang KX *et al*. Cardioprotective mechanisms of SGLT2 inhibitors

Ke-Xin Zhang, Cheng-Xia Kan, Fang Han, Jing-Wen Zhang, Xiao-Dong Sun

Abstract

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have emerged as a pivotal intervention in diabetes management, offering significant cardiovascular benefits. Empagliflozin, in particular, has demonstrated cardioprotective effects beyond its glucose-lowering action, reducing heart failure hospitalizations and improving cardiac function. Intriguingly, the cardioprotective mechanisms appear to be independent of glucose-lowering, possibly mediated through several mechanisms involving shifts in cardiac metabolism, anti-fibrotic, anti-inflammatory and anti-oxidative pathways. This editorial encapsulates the multifaceted cardiovascular advantages of SGLT2 inhibitors, highlighting the need for further research to unravel their full therapeutic potential in cardiac care.

Key Words: Diabetes; Sodium-glucose cotransporter-2; Cardiovascular diseases; Empagliflozin

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Core Tip: Sodium-glucose cotransporter-2 inhibitors like empagliflozin offer cardioprotective benefits that extend beyond blood glucose control, improving heart function and reducing failure-related hospitalizations. Ongoing research is crucial to uncover the underlying mechanisms, potentially revolutionizing heart failure treatment across various patient profiles.

INTRODUCTION

The global rise in diabetes represents a significant public health challenge and is closely associated with an increased risk of cardiovascular diseases (CVD)[1]. The lack of specific treatments to halt its progression has left a significant gap in therapeutic strategies. Consequently, there is an urgent need for novel approaches to prevent and manage cardiac complications resulting from diabetes. Sodium-glucose cotransporter-2 (SGLT2) inhibitors (*e.g.*, empagliflozin), primarily known for their glucose-lowering capability, have emerged as an unexpected ally against CVD in patients with diabetes. SGLT2 inhibitors may have beneficial effects on heart failure, including cases with dilated cardiomyopathy, by improving cardiac function and reducing hospitalization rates for heart failure[2]. However, the obscure cardioprotective mechanisms of these inhibitors have sparked considerable scientific interest. The study by Li *et al*[3] provides an intriguing insight into the molecular dynamics through which empagliflozin may exert its therapeutic effects on the diabetic heart.

Clinical trials have demonstrated that SGLT2 inhibitors significantly reduce the risk of hospitalization for heart failure and cardiovascular death. Notably, the DAPA-HF and EMPEROR-Reduced trials highlighted the positive effects of SGLT2 inhibition in patients with heart failure with reduced ejection fraction, including those with and without diabetes[4-10]. A comprehensive meta-analysis further reinforced these findings, indicating that SGLT2 inhibitors decrease the risk of cardiovascular death or first hospitalization for heart failure across a broad spectrum of left ventricular ejection fractions[2,4]. Additionally, a meta-analysis involving over 21000 participants revealed

consistent reductions in the risk of composite cardiovascular death or hospitalization for heart failure, as well as all-cause mortality[11]. Evidence from clinical studies also indicates that SGLT2 inhibitors can improve diastolic function, particularly in heart failure with preserved ejection fraction, a condition commonly seen in diabetic heart disease[12].

Similarly, animal studies have provided additional evidence to support the cardioprotective role of SGLT2 inhibitors. A meta-analysis of preclinical animal models found that SGLT2 inhibitors can reduce myocardial infarct size in animal models independent of diabetes, indicating a potential for broad cardioprotective applications beyond glucose-lowering effects[13]. Our studies also demonstrated that empagliflozin could alleviate obesity-related cardiac dysfunction and attenuate ischemia/reperfusion injury[14,15]. These studies provide evidence that SGLT2 inhibitors could benefit a wide population of heart failure patients, not just those with reduced ejection fraction.

Based on the experimental data provided by Li *et al*[3], the treatment with empagliflozin shows therapeutic promise in mitigating diabetic cardiomyopathy in db/db mice. The treatment improves cardiac function, reduces myocardial apoptosis, and beneficially modulates signaling pathways associated with cardiac health, such as increased phosphorylation of adenosine monophosphate-activated protein kinase (AMPK)/peroxisome proliferator-activated receptor gamma coactivator-1alpha (PGC-1α) proteins and decreased phosphorylation of myosin phosphatase target subunit 1. Furthermore, *in vitro* experiments support these findings, demonstrating that empagliflozin protects cardiomyocytes from high-glucose-induced mitochondrial damage, oxidative stress, and apoptosis, effects that are partly reversed by the addition of compound C, an AMPK inhibitor. The results are corroborated by the use of Rho kinase inhibitors and PGC-1α overexpression, which further validates the role of these pathways in cardiac protection. Interestingly, no SGLT2 protein expression was detected in cardiomyocytes, suggesting that the cardioprotective effects of empagliflozin may be independent of its glucose-lowering action and possibly mediated by AMPK/PGC-1α pathways. This indicates a potential non-glycemic

beneficial effect of SGLT2 inhibitors on cardiac function in the context of diabetes, meriting further investigation. This study highlights novel mechanisms regarding effectiveness of SGLT2 inhibitors in treating diabetic cardiomyopathy.

SGLT2 inhibitors, beyond their role in glucose excretion, confer cardiac protection through several mechanisms[16,17] (Figure 1). Primarily, they act as mild diuretics, which reduce cardiac preload and afterload by promoting natriuresis and osmotic diuresis, thereby lessening the cardiac load[18]. They also beneficially shift cardiac metabolism away from fatty acid oxidation, which is less oxygen-efficient, towards glucose utilization and potentially towards ketone body utilization, thus improving the heart's energy efficiency[19]. These drugs may also protect against cardiac fibrosis by several means: they reduce hyperglycemia-related advanced glycation end-products, downregulate transforming growth factor-beta, and inhibit the cardiac sodium-hydrogen exchanger, which together help to prevent hypertrophy and fibrosis[20,21].

Moreover, SGLT2 inhibitors contribute to reducing arrhythmia risks and modulate ion homeostasis within the heart, suggesting their role in improving myocardial cell function and calcium handling[22]. Their cardioprotective effects extend to anti-inflammatory and antioxidant actions, as they curb nuclear factor-kappaB activity and enhance the production of antioxidant system (*e.g.*, Sestrin2, nuclear factor-erythroid 2 related factor 2, heme oxygenase-1)[14,23]. This helps in decreasing oxidative stress, another factor that contributes to heart failure. In addition, these drugs improve endothelial function and arterial compliance, partly through increased nitric oxide production, and affect the secretion of adipokines, which are involved in the pathophysiology of heart failure[24-26]. This endothelial protection is confirmed by studies showing that empagliflozin suppresses endothelial apoptosis and maintains capillarization through the protein kinase B/endothelial nitric oxide synthase/nitric oxide pathway, thereby enhancing heart performance[27]. Cai *et al*[28] further demonstrated that empagliflozin mitigates endothelial oxidative stress and hampers mitochondrial apoptosis *via* the AMPK/Unc-51 Like autophagy activating kinase 1/FUN14 Domain Containing 1/mitophagy axis, thereby improving cardiac

microvascular structure and endothelial function. SGLT2 inhibitors also induce protective autophagy, reduce apoptosis in cardiac cells, and are being studied for their potential effects on specific molecular pathways such as Sestrin2-AMPK, which are associated with the management of heart failure[14,23,29]. Overall, the multifaceted approach of SGLT2 inhibitors underscores their potential as a therapeutic strategy for cardiovascular health, with ongoing research continuing to unravel their complex mechanisms and benefits.

Nevertheless, the exact mechanisms by which SGLT2 inhibitors exert their cardioprotective effects are still under investigation, and it is likely that multiple mechanisms work in concert. Perhaps the most striking revelation was empagliflozin's effectiveness in the absence of SGLT2 expression in cardiomyocytes. This finding propels the drug beyond its antidiabetic terrain, spotlighting its potential as a targeted therapy for CVD. The cardioprotective effects observed in patients with heart failure, including those with CVD, have led to an expansion of the indications for SGLT2 inhibitors beyond diabetes to include treatment of heart failure with reduced ejection fraction, with ongoing research potentially further broadening their therapeutic applications. Despite these promising findings, further research is necessary to fully elucidate the extent to which these mechanisms contribute to the cardiovascular benefits of SGLT2 inhibitors understanding will enhance the clinical application of these agents and potentially lead to more targeted treatments for patients with diabetic heart disease and heart failure.

CONCLUSION

In conclusion, SGLT2 inhibitors have become an essential therapeutic advancement in the management of diabetes due to their low risk of hypoglycemia and notable cardiovascular benefits. Beyond their glucose-lowering effects, SGLT2 inhibitors are recognized for their efficacy in treating heart failure through various non-glycemic mechanisms. These include hemodynamic changes, anti-inflammatory, anti-fibrotic, antioxidant, and metabolic effects, which together contribute to the cardiovascular

advantages observed with SGLT2 inhibitors use. Further research is ongoing to fully understand the mechanisms through which they exert their cardioprotective effects.

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