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LETTER TO THE EDITOR

SGLT2 inhibitors in the prevention of diabetic cardiomyopathy: Targeting the silent threat

Panayotis K Vlachakis, Panagiotis Theofilis, Dimitris Tousoulis

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Abstract

Heart failure (HF) is a major global health challenge, particularly among individuals with type 2 diabetes mellitus (T2DM), who are at significantly higher risk of developing HF. Diabetic cardiomyopathy, a unique form of heart disease, often progresses silently until advanced stages. Recent research has focused on sodium-dependent glucose transporter 2 inhibitors (SGLT2i), originally developed for hyperglycemia, which have shown potential in reducing cardiovascular risks, including HF hospitalizations, irrespective of diabetic status. In this editorial we comment on the article by Grubić Rotkvić *et al* published in the recent issue of the *World Journal of Cardiology*. The investigators examined the effects of SGLT2i on myocardial function in T2DM patients with asymptomatic HF, finding significant improvements in stroke volume index and reductions in systemic vascular resistance, suggesting enhanced cardiac output. Additionally, SGLT2i demonstrated anti-inflammatory and antioxidant effects, as well as blood pressure reduction, though the study's limitations—such as small sample size and observational design—necessitate larger randomized trials to confirm these findings. The study underscores the potential of early intervention with SGLT2i in preventing HF progression in T2DM patients.

Key Words: Sodium-dependent glucose transporter 2 inhibitor; Diabetes mellitus; Heart failure; Pathophysiology; Inflammation; Oxidative stress

Core Tip: Sodium-dependent glucose transporter 2 inhibitors show promise in improving cardiac function and reducing cardiovascular risks in patients with type 2 diabetes mellitus and asymptomatic heart failure (HF). Early intervention with these drugs could be key in preventing the progression of diabetic cardiomyopathy, making them an important consideration in managing high-risk diabetic patients before symptoms of HF emerge.

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TO THE EDITOR

Heart failure (HF) continues to be one of the most formidable challenges in modern medicine and is a leading cause of morbidity and mortality worldwide, with a 5-year mortality rate comparable to that of malignancies[1]. The burden is particularly heavy among individuals with type 2 diabetes mellitus (T2DM), who face a significantly elevated risk—two to five times higher—of developing HF compared to those without diabetes[2]. In the intersection of these two chronic conditions lies diabetic cardiomyopathy, a unique form of heart disease that develops independently of other diabetic complications, and often remains asymptomatic until it progresses to a more severe stage[3].

The growing recognition of this silent threat has spurred research into potential therapeutic interventions, with Sodium-dependent glucose transporter 2 inhibitors (SGLT2i) emerging as a promising class of drugs. Originally developed for diabetes treatment, SGLT2i have shown unexpected efficacy in reducing cardiovascular risks, including the burden of HF, regardless of the type or stage of HF and the diabetic status of the patient, as shown by groundbreaking trials such as EMPAREG-OUTCOME, DAPA-HF, EMPEROR-Reduced, EMPULSE and EMPEROR-Preserved[4,5].

A recent observational study by Grubić Rotkvić *et al*[6] delves into the effects of SGLT2 inhibitors on myocardial function in patients with T2DM and asymptomatic HF[6]. The study focuses on HF stages A and B, where early intervention could potentially alter the trajectory of the disease before symptoms manifest. Patients in this study were treated with either SGLT2i or dipeptidyl peptidase-4 inhibitors (DPP-4i), with a comprehensive follow-up over six months to assess various biomarkers and echocardiographic parameters. The findings of this study, although nuanced, shed light on the potential benefits of SGLT2i in a subset of diabetic patients who are often under the radar.

Slow left ventricle relaxation, especially at elevated heart rates, is a prominent feature of HF with preserved ejection fraction and, together with myocardial stiffening and impaired ventricular-arterial coupling, contributes to reduced stroke volume and abnormal systolic function during stress, even when systolic function appears normal at rest[7]. In contrast with the findings from a recent meta-analysis, which did not demonstrate a significant mean change in stroke volume with SGLTi therapy, the study by Grubić Rotkvić *et al*[6] showed that SGLT2i therapy was associated with a significant increase in stroke volume index, suggesting an improvement in cardiac output—an effect that may be linked to a reduction in systemic vascular resistance[8].

The mechanisms underlying the cardioprotective action of SGLT2i remain debated and are still under investigation, given that SGLT2i is not expressed in the human myocardium[9]. Among the putative mechanisms are anti-inflammatory and antioxidant pathways. Specifically, we have previously shown that, according to a meta-analysis of 30 studies on rodents, administration of SGLT2i is associated with a reduction in inflammatory markers (interleukin-6, tumor necrosis factor-alpha, C-reactive protein, monocyte chemoattractant protein-1)[10]. Such findings have been reported also in human studies, as evidenced in a meta-analysis by Buttice *et al*[1] A potential mechanism involves the restoration of autophagy, where SGLT2i activate the sirtuin 1/adenosine monophosphate-activated protein kinase pathway while inhibiting the autophagy-inhibiting Akt/mammalian target of rapamycin complex 1 pathway, reducing inflammation and oxidative stress[1,1]. The authors did not report significant differences based on treatment allocation, possibly owing to DPP4i-related anti-inflammatory effects[1]. The investigators further found that treatment of such patients with antidiabetic agents produced an improvement in circulating myeloperoxidase, suggesting their antioxidant effect. Indeed, SGLT2i are known to possess antioxidant properties, as highlighted in numerous preclinical and clinical studies[1].

An important observation of this study is the changes in blood pressure (BP). According to the results, there were significant reductions with both drug classes in patients with systolic and diastolic BP above the cutoffs. While SGLT2i are not predominantly known for the BP-lowering effects, accumulated evidence suggests a secondary effect in BP regulation, possibly through inhibition of the sympathetic nervous system and the renin-angiotensin-aldosterone system [1]. As shown by Iqbal *et al*[17] in a meta-analysis of 10 randomized controlled trials, SGLT2i reduced 24-hour ambulatory systolic BP and diastolic BP by approximately 5 mmHg and 3 mmHg, respectively[1]. The BP-lowering effects of DPP4i are perhaps lesser known. However, it should be stated that according to a systematic review and meta-analysis of 15 trials conducted by Zhang *et al*[18], DPP4i produced greater systolic and diastolic BP reductions compared to placebo (3 mmHg and 1 mmHg, respectively)[1]. However, when compared to SGLT2i, their effects on BP were of lesser magnitude [1], a difference that was not seen in the study of Grubić Rotkvić *et al*[6] A possible explanation for such discrepancy is the limited sample size which might not have allowed for a reliable head-to-head comparison[6].

The study by Grubić Rotkvić *et al*[6] provides valuable insights but is limited by several factors that affect the generalizability and robustness of the findings. The small sample size reduces the statistical power of the study, making it difficult

to draw definitive conclusions, while the short follow-up period may not allow for the observation of long-term effects. Furthermore, its observational design is prone to bias and confounding, as it does not control for potential differences between patient groups that could influence outcomes. The reliance on surrogate markers, such as stroke volume index and high sensitivity C-reactive protein, though informative, may not fully capture the broader clinical impact of SGLT2i, particularly in relation to hard endpoints like hospitalization or mortality. Additionally, the absence of randomization increases the risk of selection bias, which further limits the ability to establish causality. To confirm these findings and better understand the cardioprotective effects of SGLT2i, larger, randomized controlled trials with longer follow-up are essential, particularly in patients with asymptomatic HF. These trials should aim to clarify the underlying mechanisms and assess clinically meaningful outcomes.

In conclusion, the study by Grubić Rotkvić *et al*[6] contributes to the growing body of evidence supporting the use of SGLT2i in diabetic patients with early-stage, asymptomatic HF. These findings highlight the potential for SGLT2 inhibitors to alter the trajectory of diabetic cardiomyopathy by offering both metabolic and cardioprotective benefits. This high-risk group of patients must be kept on our "radar", as early intervention with SGLT2i could prevent or delay HF progression, reduce hospitalization rates, and improve long-term cardiovascular outcomes. As our understanding of their mechanisms evolves, SGLT2i are poised to play a pivotal role in the prevention and management of HF in T2DM patients, making them a critical consideration in clinical decision-making. Larger trials and long-term follow-up studies will further inform optimal patient selection and timing of intervention.

FOOTNOTES

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