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LETTER TO THE EDITOR

Effects of sodium-dependent glucose transporter 2 inhibitors in patients with type 2 diabetes mellitus and asymptomatic heart failure

Mohamed H Laimoud, Ismail R Raslan

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Abstract

Sodium-dependent glucose transporter 2 inhibitors (SGLT2i) have been increasingly used with proven efficacy in patients with heart failure (HF), regardless of diabetes status. Grubić Rotkvić *et al* recently published an observational study on SGLT2i therapy in patients with type 2 diabetes mellitus and asymptomatic HF. They found that the use of SGLT2i led to reduced cardiac load and improved cardiovascular performance, reinforcing the evolving paradigm that SGLT2i are not merely glucose-lowering agents but are integral to the broader management of cardiovascular risk in patients with type 2 diabetes mellitus. The study by Grubić Rotkvić *et al* contributes to the growing body of literature supporting the early use of SGLT2i in patients with diabetic cardiomyopathy, offering a potential strategy to mitigate the progression of HF. Future larger studies should be conducted to confirm these findings, and explore the long-term cardiovascular benefits of SGLT2i, particularly in asymptomatic patients at risk of developing HF.

Key Words: Heart failure; Cardiovascular risk; Diabetes mellitus; Mortality; Sodium-dependent glucose transporter 2 inhibitors

Core Tip: Grubić Rotkvić *et al* published an observational study on the use of sodium-dependent glucose transporter 2 inhibitors (SGLT2i) in patients with type 2 diabetes mellitus and asymptomatic heart failure. Their findings included reduced cardiac load and improved cardiovascular performance related to the use of SGLT2i. This suggests that SGLT2i are not merely glucose-lowering drugs; they are integral to the broader cardiovascular management in patients with type 2 diabetes mellitus.

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TO THE EDITOR

The expanding interest in sodium-dependent glucose transporter 2 inhibitors (SGLT2i) as a cornerstone therapy in the management of heart failure (HF) has significantly impacted contemporary cardiology. A recent observational study by Grubić Rotkvić *et al*[1] provides crucial insights into the utility of SGLT2i in patients with type 2 diabetes mellitus (T2DM) who exhibit asymptomatic HF. Their study builds on previous data by focusing on the mechanisms underlying the cardioprotective effects of SGLT2i in this specific patient population.

IMPACT OF SGLT2I ON MYOCARDIAL FUNCTION

This prospective observational study evaluated a cohort of patients with T2DM receiving dual antidiabetic therapy, including metformin and either SGLT2i or dipeptidyl peptidase-4 inhibitors. The study divided treatment arms into two subgroups based on baseline parameters such as high-sensitivity C-reactive protein, myeloperoxidase, global longitudinal strain (GLS), N-terminal pro-brain natriuretic peptide, and systolic and diastolic blood pressures.

The results indicated that SGLT2i therapy led to a significant reduction in oxidative stress and inflammatory markers, particularly myeloperoxidase and high-sensitivity C-reactive protein, especially in patients with elevated baseline levels of these biomarkers. This aligns with evidence highlighting the anti-oxidative and anti-inflammatory properties of SGLT2i, contributing to their cardiovascular benefits[2,3]. Notably, there was a greater reduction in the studied variables in the patients with high baseline values, irrespective of the treatment group, after follow-up.

EXPANDING THE LITERATURE ON SGLT2I'S CARDIOPROTECTIVE MECHANISMS

Recent meta-analyses have underscored the multifaceted benefits of SGLT2i beyond glycemic control. SGLT2i have consistently demonstrated a significant reduction in HF hospitalisation and cardiovascular mortality across various populations, including patients with and without T2DM. These outcomes were particularly pronounced in patients with HF and reduced ejection fraction[4,5]. SGLT2i received a class IA recommendation for treatment of patients with HF and reduced ejection fraction, regardless of diabetes mellitus status, according to the American College of Cardiology and American Heart Association and guidelines[6,7]. The EMPULES trial is a multicentre international double-blind, clinical trial that randomised 530 patients with acute HF to receive empagliflozin or a placebo. The trial reported decreased mortality and HF-related hospitalisations during the 90-day follow-up, regardless of left ventricular ejection fraction and diabetes status[8]. The recent European Society of Cardiology recommended the use of SGLT2i as a class IA treatment for patients with HF and left ventricular ejection fraction (> 40%) to reduce HF-related hospitalisation and cardiovascular mortality[9]. Further, SGLT2i also demonstrated efficacy in patients with HF with preserved ejection fraction. The EMPEROR-Preserved trial and subsequent meta-analyses revealed a reduction in HF-related hospitalisations or cardiovascular death in these patients, thereby establishing SGLT2i as a versatile tool for managing HF across the ejection fraction spectrum[10,11].

MECHANISTIC INSIGHTS AND CLINICAL IMPLICATIONS

The protective cardiovascular effects of SGLT2i are attributed to several mechanisms, including osmotic diuresis, which leads to volume reduction, decreased blood pressure, and improved ventricular loading conditions. Additionally, SGLT2i reduce myocardial fibrosis, oxidative stress, and sympathetic nervous system activation, all of which are critical in HF pathophysiology[2]. Moreover, SGLT2i provide substantial renoprotective effects, particularly in patients with T2DM. They reduce the risk of adverse renal outcomes, likely by modulating intraglomerular pressure and reducing hyperfiltration[12]. This dual benefit for both the cardiovascular and renal systems makes SGLT2i appealing for managing

patients at high cardiovascular risk, regardless of established HF[13]. The European Society of Cardiology guidelines recommend SGLT2i as a class IA treatment for patients with HF and chronic kidney disease to decrease HF-related hospitalisations and cardiovascular mortality[9]. Despite the proven beneficial effects of SGLT2i in patients with HF and T2DM, caution is warranted for patients at risk of diabetic ketoacidosis, especially those with changes in insulin doses or dietary intake. A meta-analysis involving 60580 patients reported a doubled risk of diabetic ketoacidosis in patients with T2DM receiving SGLT2i, especially in those aged ≥ 60 years and those on SGLT2i for more than 52 weeks[14].

SIGNIFICANCE OF THE FINDINGS AND FUTURE DIRECTIONS

The study by Grubić Rotkvić *et al*[1] provides a nuanced understanding of the cardiometabolic benefits of SGLT2i, particularly in the early stages of HF. The observation that SGLT2i improve GLS and attenuates sympathetic nervous system activation without significantly lowering N-terminal pro-brain natriuretic peptide levels suggests that SGLT2i may exert their cardioprotective effects through mechanisms independent of natriuretic peptide modulation. The improvement in myocardial function, as evidenced by enhanced GLS and reduced oxidative stress, underscores the potential of SGLT2i in preventing the progression from asymptomatic to symptomatic HF in patients with diabetes[15,16].

However, the study also has limitations including the small sample size and short follow-up period, which may preclude definitive conclusions regarding the long-term benefits of SGLT2i use in this patient group. Moreover, the variability in effects among the different agents belonging to the SGLT2i and dipeptidyl peptidase-4 inhibitors classes warrants further large-scale studies to elucidate the differential effects of these drugs on cardiovascular outcomes.

CONCLUSIONS

The findings of the study by Grubić Rotkvić *et al*[1] reinforce the evolving paradigm that SGLT2i are not merely glucose-lowering agents but are integral to the broader management of cardiovascular risk in patients with T2DM. The study contributes to the growing literature supporting the early use of SGLT2i in diabetic cardiomyopathy, offering a potential strategy to mitigate the progression of HF. Future large studies should be conducted to confirm these findings and explore the long-term cardiovascular benefits of SGLT2i, particularly in asymptomatic patients at a risk of developing HF.

FOOTNOTES

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