EDITORIAL

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SGLT2 Inhibitors for Cardioprotection

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Sodium-glucose linked transporter 2 (SGLT2)inhibitors are integral in the management of type 2 diabetes mellitus (T2DM). SGLT2 inhibitors function by inhibiting SGLT2 in the renal proximal tubule. These inhibitors facilitate reduced glucose reabsorption, leading to glycosuria. Simultaneously, they decrease sodium reabsorption, resulting in natriuresis and diuresis, culminating in lowered blood glucose and blood pressure levels. These effects manifest independently of stimulating insulin release.[1] Additionally, SGLT2 inhibitors have demonstrated noteworthy cardiovascular benefits, extending beyond diabetes. These advantages include diminished risk of heart failure (HF)-related hospitalizations, cardiovascular mortality, and all-cause mortality. In this editorial, we attempted to examine the diverse effects of SGLT2 inhibitors that collectively contribute to cardiac protection.

SGLT2 inhibitors bring about a sustained reduction in systolic and diastolic blood pressure via diuresis and natriuresis, and a reduction in sympathetic tone.[1] They also exert antihypertensive effects through various mechanisms, including decreasing uric acid levels, shifting to ketogenic activity, and weight loss.[2] Recent research underscores uric acid's potential role in hypertension.[3] SGLT2 inhibitors can exert antihypertensive effects by decreasing uric acid levels.[2] Through these multifaceted actions, SGLT2 inhibitors emerge as efficacious agents for blood pressure management. A recent meta-analysis has underscored the safety and efficacy of SGLT2 inhibitors in regulating blood pressure and blood glucose, particularly when used as an adjunctive therapy for first-line antihypertensive treatment in individuals with T2DM and hypertension, who present a low risk of genital infections.[4]

SGLT2 inhibitors lead to lipolysis, gluconeogenesis, and ketogenesis. The increased glucose excretion prompts a metabolic shift from glucose to lipid utilization, which results in increased ketones in the liver. Additionally, SGLT2 inhibitors stimulate adipose tissue lipolysis, which further increases ketone body production.[5] Thus, the increased ketosis and lipolysis cause weight loss, aiding the management of essential hypertension and obesity.

Significantly, SGLT2 inhibitors substantially enhance endothelial function among patients with uncontrolled T2DM.[6] SGLT2 inhibitors decrease endothelial dysfunction by various mechanisms, including diminishing sympathetic activation and oxidative stress and reversing upregulation of endothelial cell senescence genes.[7] Empagliflozin (EMPA), in particular, improves vascular health by restoring and preserving the glycocalyx of endothelial cells of the abdominal aorta.[8]

SGLT2 inhibitors play a pivotal role in reducing cardiovascular mortality in people with diabetes mellitus. EMPA inhibits autolysis (autophagic cell death) in cardiomyocytes providing a cardioprotective effect. EMPA therapy yields significant reductions in infarct size and myocardial fibrosis in animal models of myocardial infarction, both in the presence and absence of diabetes mellitus. This results in enhanced cardiac function and survival rates. Notably, EMPA directly inhibits the activity of the Na^+/H^+ exchanger 1 (NHE1) in cardiomyocytes, thus curbing excessive autophagy, which is accelerated during ischemic and glucose-deprived conditions. NHE1 knockdown effectively mitigates EMPA-induced autolysis.

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Conversely, elevated NHE1 expression exacerbates starvation-induced cardiomyocyte death, a phenomenon counteracted by EMPA therapy. Subsequent in vitro and in vivo analyses using NHE1 and Beclin 1 knockout mice confirm that EMPA's cardioprotective effects are, at least in part, mediated by downregulating autophagic flux.[9] Thus, SGLT2 inhibitors present a novel and promising avenue for treating HF.

These cumulative findings have led to an increased global quest for the mechanisms underlying the therapeutic efficacy of this class of medicines. It has been shown that SGLT2 inhibitors can directly influence a number of cardiac systems that are known to play a role in the development of HF, including ion homeostasis, redox state, inflammation, and metabolism. Dysregulation of these systems underpins the HF phenotype, characterized by endothelial dysfunction, arrhythmogenesis, sudden cardiac mortality, diastolic dysfunction, fibrosis, and reduced cardiac performance. Many of these manifestations can be mitigated by SGLT2 inhibitors.[10]

The American Association of Clinical Endocrinology Clinical Practice Guideline recommends using SGLT2 inhibitors with established HF benefits to lower the risk of hospitalization for HF-related or cardiovascular death and to alleviate HF-related symptoms in people with T2DM and established HF (regardless of ejection fraction, background glucose-lowering, HF therapies, or glycated hemoglobin A_{1C}).[11]

Renin-angiotensin-aldosterone system (RAAS) blockers, angiotensin-converting-enzyme (ACE) inhibitors, or angiotensin receptor blockers (ARBs) are the first-choice group of drugs for the early treatment of hypertension diagnosed in patients with T2DM and albuminuria.[12] ACE inhibitors reduce the conversion of angiotensin I to angiotensin II and ARBs block the binding of angiotensin II to angiotensin II receptor type 1 receptors. Activation of the systemic RAAS results in end-organ dysfunction. In patients with diabetic kidney disease, both ACE inhibitors and ARBs have shown efficacy in reducing major cardiovascular events and end-stage kidney disease.[13]

SGLT2 inhibitors induce secondary contraction of the afferent glomerular arteriole by increasing sodium delivery to the macula densa. This process can help in counteracting local angiotensin II-mediated glomerular hypertension, improving the renal outcomes in patients with T2DM.[14] The combination of the natriuretic effect contributed by SGLT2 inhibitors and the vasodilatory effect contributed by ACE inhibitors/ARBs synergistically reduces cardiovascular events by reducing oxidative stress and inflammatory response.[15,16] This combination has also demonstrated improvements in insulin sensitivity.[17]

One meta-analysis highlighted the favorable outcomes of combination therapy of SGLT-2 inhibitors and ACEI/ARBs for managing hyperglycemia, body weight, and blood pressure in patients with T2DM. This combination therapy was found safe with additional acceptability.[18] Based on this evidence, ACEI/ARBs should be combined with SGLT2 inhibitors as their effects are synergistic in reducing various vascular complications.

Based on the robust scientific evidence outlined above, from a pharmacological perspective, due to their additional antihypertensive effect and synergistic interactions with ACE inhibitors/ARBs, SGLT2 inhibitors, backed by established cardiovascular benefits, should be initiated as the primary antidiabetic treatment in individuals at a heightened risk of atherosclerotic cardiovascular disease/HF. This specifically pertains to those with newly diagnosed T2DM in conjunction with essential hypertension. This recommendation is true when contraindications for SGLT2 inhibitors are absent. Notably, SGLT2 inhibitors can be prescribed without regard to the background glucose-lowering regimen, cardiovascular therapies, or A_{1C} levels, aligning with the latest American Association of Clinical Endocrinology guidelines.

Unlike metformin, which primarily addresses T2DM, its efficacy in managing essential hypertension remains comparatively less established. Conversely, SGLT2 inhibitors encompass both T2DM and essential hypertension due to their dual capacity to lower blood glucose and blood pressure. Moreover, their demonstrated synergistic effects with RAAS blockers further underscore their clinical utility.

In conclusion, the collective evidence underscores the substantial potential of SGLT2 inhibitors to serve as a paramount therapeutic option for individuals afflicted by T2DM concomitant with essential hypertension. As a first-line intervention, they present a compelling alternative to metformin,

with the prospect of preempting subsequent cardiac complications.

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