Potential Mechanisms of Sodium-Glucose Co-Transporter 2 Inhibitors

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Sodium-glucose co-transporter 2 (SGLT2) inhibitors, originally used for diabetes mellitus, are gaining more popularity for other indications, owing to their positive cardiovascular and renal effects. SGLT2 inhibitors reduce heart failure (HF) hospitalization and improve cardiovascular outcomes in patients with type 2 diabetes. SGLT2 inhibitors exhibit pleotropic effects on the cardiovascular system. It is clear that these beneficial effects are not related to the anti-glycemic properties. Cardiovascular benefits of SGLT2 inhibitors are mediated by several pathways. Enhanced diuresis and vascular dilation result in afterload reduction and coronary blood flow augmentation. Ketogenesis mediated by adipose tissue and hepatocytes promote ketogenesis, which serves as an energy source for the failing heart. In addition, SGLT2 inhibitors contribute to decreasing inflammation and improving systolic and diastolic functions by reducing fibrosis and inhibiting remodeling pathways.

heart failure sodium-glucose co-transporter diabetes

1. General Effects

Early afterload reduction and enhanced diuresis with the concomitant decrease in filling pressures probably play a role in the rapid reduction in HF hospitalizations that have been observed in the major clinical trials. In addition, SGLT2 inhibitors also cause a modest weigh reduction that may help in reducing blood pressure and improving glycemic control. The reduction in blood pressure is suggested to be secondary to improving endothelial function and decreasing arterial stiffness and sympathetic activity (discussed below) and unrelated to volume depletion or natriuresis [1][2]. Since osmotic diuresis associated with SGLT2 inhibitors is dependent on glucose level, this effect does not explain the benefits in non-diabetic patients with HF [1]. NT-proBNP is an important prognostic marker in HF, which reflects the volume status and the overall wall stress. However, in the DEFINE-HF trial, there was no decrease in NT-proBNP concentration despite the improvement in HF status [3]. This finding raises questions about the role of natriuresis associated with SGLT2 inhibition in improving HF outcomes [1]. Likewise, weight reduction is observed mainly in diabetic patients, and therefore, does not provide an explanation for cardiovascular benefits in non-diabetic patients.

2. Effects on Sympathetic Pathways

HF is associated with the activation of several neurohormonal pathways, including the sympathetic system, renin–angiotensin–aldosterone system, and the natriuretic peptides pathways. Despite a modest decline in blood

pressure and intravascular volume depletion associated with SGLT2 inhibitors, there is no concomitant increase in heart rate. This finding may indicate a possible effect on the sympathetic system [4][5]. In experimental rat models with metabolic syndrome, luseogliflozin (a selective SGLT2 inhibitor) improved the circadian rhythm of the sympathetic nervous system [6]. In another model of hypertensive mice, chemical denervation caused a reduction in blood pressure, blood glucose, and renal SGLT2 protein expression [7]. Furthermore, the inhibition of SGLT2 in these models reduced the level of tyrosine hydroxylase and norepinephrine. Evidence for improving cardiac nerve activity with empagliflozin was demonstrated in diabetic patients with AMI in the EMBODY trial [8]. These findings may give insight to the role of SGLT2 inhibitors in preventing lethal arrhythmia in the acute phase of AMI.

3. Cardio-Renal Pathways

SGLT2 inhibitors exhibit natriuretic effects by acting on SGLT and Sodium/Hydrogen exchanger 3 (NHE3) receptors in the proximal tubule, resulting in an increase in the fractional excretion of sodium [9]. Afferent arteriolar vasoconstriction caused by SGLT2 inhibitors leads to a decrease in renal blood and an increase in erythropoietin (EPO) synthesis, which in turn promotes adenosine triphosphate (ATP) production and utilization in the cardiac tissue, and may help reduce inflammation [10]. In one study, empagliflozin administration induced erythropoiesis and iron utilization mediated by increased EPO secretion [11]. Nevertheless, it should be noted that the administration of darbepoetin alfa in patients with HF leads to an increase in hematocrit but without improvement in outcomes [12]. Another potential mediator in the cardiovascular–renal arena is serum uric acid. Uric acid is elevated in patients with diabetes and considered a part of the metabolic syndrome. Hyperuricemia in diabetic patients is associated with increased risk of hypertension, cardiovascular events, and progression of diabetic kidney disease. SGLT2 inhibitors reduce uric acid concentration by enhancing its urinary excretion facilitated by glucose transporter 9 [13].

4. Modulation of Energy Sources and Inflammatory Process

Glycosuria induced by SGLT2 inhibitors combined with the decrease in insulin and the increase in glucagon levels mimic starvation and cause lipolysis and fatty acid oxygenation, leading, finally, to ketogenesis [14]. Ketone bodies levels increase in conditions with oxidative stress, such as exercise, starvation, sepsis, and HF [15]. Under physiological conditions, the metabolism of healthy hearts depends on free fatty acids and glucose, whereas in the failing heart, a shift towards increased ketone utilization occurs [16][17]. In the failing heart, ketone bodies serve as an important source of energy as they require less oxygen per molecule of the ATP generated, and may also provide protective anti-inflammatory and antioxidant properties by inhibiting the nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain-containing 3 (NLRP3) inflammasome [18][19][20]. The modulation of mitochondrial autophagy is another pathway that may explain SGLT2 inhibitors' positive cardiac effects. Autophagy is a catabolic process aimed at cleaning intracellular debris through lysosomes, and it contributes to cell hemostasis; however, this pathway is impaired in diabetic patients [21]. SGLT2 inhibitors, by mimicking nutrition deprivation, can stimulate autophagy mediated by Siritin-1 and adenosine 5′ monophosphate-activated protein kinas, thus adding another cardioprotective effect [22].

5. Microvascular Function

In an insulin resistance mouse model, empagliflozin increased the coronary flow reserve, indicating a possible positive effect on vascular function [23]. In diabetic patients, treatment with empagliflozin was associated with weight loss and reduction in several cardiac biomarkers; however, there was no improvement in coronary flow velocity reserve assesses by echo Doppler [24]. In another small trial, dapagliflozin administration improved myocardial blood flow and myocardial flow reserve measured by ^{13}N-ammonia PET/CT in diabetic patients with stable coronary artery disease [25]. Differences in the results may reflect different methods in assessing coronary flow or the absence of class effect.

6. Effect on Lipid Profile

By mimicking starvation conditions, the inhibition of SGLT2 induces lipolysis in the adipose tissue and causes an increase in non-esterified fatty acids, which in turn promotes cholesterol biosynthesis in the liver and finally causes the downregulation of low-density lipoprotein cholesterol (LDL-C) [26][27]. This pathway may explain the tendency towards increase in circulating LDL-C, following SGLT2 inhibitors treatment [28]. Among the different SGLT2 inhibitor drugs, canagliflozin was associated with the worst effect on the lipid profile [28]. Along with the increase in LDL-C levels, a modest increase in high-density lipoprotein (HDL-C) has been reported with the use of SGLT2 inhibitors [26][27][28]. It should be noted, however, that the cardiovascular benefits of SGLT2 inhibitors are maintained regardless of the LDL-C or HDL-C levels [29].

7. Effect on Remodeling and Fibrosis

Several echocardiographic and animal-model studies have demonstrated the anti-remodeling effects of SGLT2 inhibitors. In non-diabetic rats, empagliflozin results in reduced collagen deposition and the inhibition of a fibrosis pathway when administered early after the induction of AMI [30]. In mouse models of pressure overload (induced by transverse aortic restriction), dapagliflozin reduced fibrosis and improved cardiac systolic function [31]. The anti-fibrotic effects of SGLT2 inhibitors may be mediated by inhibiting angiotensin II pathways, which finally leads to changes in the size, shape, geometry, and function of cardiac muscles [32][33][34][35]. In the EMPA-HEART trial, empagliflozin resulted in reduced LV mass index in diabetic patients with preserved LV function and coronary artery disease [36]. Likewise, in the SUGAR-DM-HF trial, empagliflozin led to reduction in LV end-systolic and end-diastolic volumes in diabetic and prediabetic patients with HFREF [37]. In a recent meta-analysis of randomized controlled trials of cardiac remodeling, as measured by cardiac magnetic resonance imaging, SGLT2 inhibitors' treatment showed a decrease in LV mass [38]. Global longitudinal strain measured by speckle tracking was also shown to be positively affected by SGLT2 inhibition among patients with diabetes [39]. A significant improvement in diastolic parameters was also observed in patients with HFPEF [40]. This finding may in part explain the benefit observed in the clinical trials of SGLT2 inhibitors in HFPEF [41][42].

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