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Editorial

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Off-target Effects of Sodium-glucose Cotransporter 2 (SGLT-2) Inhibitor in Cardiovascular Disease

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The newest class of diabetes medicines, the sodium-glucose cotransporter-2 (SGLT-2) inhibitors, are transforming medical therapy for diabetes patients with cardiovascular disease (CVD). Several cardiovascular outcome trials (CVOTs) have shown that SGLT-2 inhibitors produce effects beyond glucose lowering and have demonstrated beneficial cardiovascular and renal effects that have been observed across a broad range of patients with type 2 diabetes mellitus (T2DM).[1] Recently, Food and Drug Administration expanded the indications for SGLT-2 inhibitors for T2DM patients who have either established CVD or are at risk of developing CVD. Furthermore, new clinical trials have been launched to expand the use of their SGLT-2 inhibitors in patients with chronic heart failure. Interestingly, the Dapagliflozin and Prevention of Adverse-Outcomes in Heart Faiure (DAPA-HF) Trial showed clinical benefit in heart failure with and without T2DM, which support the idea that SGLT-2 inhibitor may be beneficial to patients beyond diabetes.[2]

In spite of being explicitly designed to inhibit SGLT-2 in the kidney, they have lately been investigated for their off-target cardiovascular actions. However, it is not yet elucidated whether the cardiovascular beneficial effects of SGLT-2 inhibitors are due to kidney-related systemic alterations or due to direct cardiovascular effects, or both. To examine whether SGLT-2 inhibitors operate directly on cardiac specific pathophysiological mechanisms without interference of other mediating factors, including plasma circulating glucose and insulin, isolated cardiac cell and organ studies are required.[3] Recently, Lim et al.[4] reported that long-term diet for 4 weeks with canagliflozin had smaller infarct sizes in isolated Langendorff-perfused hearts from diabetic and nondiabetic rats. However, interestingly, direct treatment of isolated nondiabetic rat hearts with canagliflozin had no impact on infarct size. They proposed that the infarct-sparing effect of long-term treatment with canagliflozin results from either a glucose-independent effect or up-regulation of cardiac prosurvival pathways.

While SGLT-2 has not been detected at all in the heart, increasing evidence demonstrate the existence of SGLT-2 in non-cardiac endothelial cells. Several studies have reported that SGLT-2 inhibitors directly alter endothelial cells and smooth muscle cells by reducing SGLT-2-mediated glucose uptake, ameliorating vasorelaxation, increasing adenosine monophosphate-activated protein kinase (AMPK) activity and preventing mitochondrial dysfunction in hyperglycemic and inflamed vascular cells.[3] In this issue of *Korean Circulation*

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Journal, Lee et al.[5] elaborately demonstrated that dapagliflozin (1 mg/kg/day) had an anti-atherosclerotic effect by reducing percent area stenosis by optical coherence tomography imaging and atheroma burden by immunohistochemistry staining in non-diabetic rabbit abdominal aorta injury model. They focused on the anti-inflammatory response of dapagliflozin, assessed by macrophage infiltration and polarization (i.e., inducible nitric oxide synthase/arginase-1 ratio) and tumor necrosis factor (TNF)-α expression in the injured aorta tissue, which was associated with the attenuated expression of Toll-like receptor 4/nuclear factor-kappa B signaling pathway. In fact, recent reports have shown the suppression of atherosclerosis or endothelial dysfunction in response to SGLT-2 inhibitor administration. Han et al.[6] investigated the effect of empagliflozin on the progression of atherosclerosis in ApoE$^{-/-}$ mice fed a western diet. Empagliflozin groups showed smaller atherosclerotic plaque areas in the aortic arch/valve, and lower insulin resistance and inflammation markers (TNF-α, interleukin [IL]-6, monocyte chemoattractant protein-1, etc.) compared with glimepiride group. Other researcher also reported that SGLT-2 inhibitor administration reduced reactive oxygen species generation, which might decrease the expression of inflammatory molecules (IL-1β, IL-18, NLRP3 inflammasome) in the abdominal aorta of streptozotocin-induced diabetic mice.[7]

Although the anti-atherosclerotic effect of SGLT-2 inhibitors can play a role to prevent CVD events in T2DM patients, the observed reductions of cardiovascular outcomes in CVOTs were much earlier and powerful than would be expected by an anti-atherosclerotic effect. These findings have led to speculation about the potential underlying mechanisms involved in direct cardiac protection, even though SGLT-2 does not express in cardiomyocytes (CMs). Suggested mechanisms include the inhibition of L-type Ca^{2+} channel and/or Na^+/H^+ exchanger 1 (NHE-1), which can reduce cytosolic (Ca^{2+}) and (Na^+) and increased mitochondrial (Ca^{2+}) in CMs.[8] These findings may reflect improved mitochondrial capacity to synthesize ATP and target oxidants, which would be beneficial to restore the energetic state of CMs that is known to be decreased in heart failure. In molecular binding studies, SGLT-2 inhibitors exhibit high binding affinities with the extracellular Na^+-binding site of the NHE-1, which indicate that the SGLT-2 inhibitors exert an off-target effect on the NHE-1.[3] Recently, Juni et al.[9] reported that cardiac microvascular endothelial cells (CMECs) confer a direct positive effect on contraction and relaxation of CMs, an effect that requires nitric oxide, is diminished after CMEC stimulation with TNF-α, and is restored by empagliflozin. In addition, cardiac fibroblasts are valuable targets for therapeutic applications due to their role in cardiac remodeling after MI. Pre-incubation with dapagliflozin (0.3–0.5 μM) showed attenuation of lipopolysaccharide-induced upregulation of inflammasome complex such as NLRP3, ASC, and caspase-1 mRNA levels in cardiac fibroblasts, which was mediated through increased AMPK activation without the involvement of SGLT.[10] These mechanisms are not separate entities but are all intrinsically interrelated, and together may induce contractile, vascular and mitochondrial dysfunction, and cell death in the heart, which may evolve into left ventricular concentric or eccentric hypertrophy and heart failure.

Bridging the gap from treating diabetes by lowering blood sugar to simultaneously reducing the risk of CVDs with a single medicine is a great leap forward for diabetes treatment with significant implications for endocrinologists and cardiologists. In this respect, SGLT-2 inhibitors are regarded as a promising option, when we are faced with the challenge of choosing the optimal drug for treating T2DM patients.

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