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COMMENT

Blood pressure lowering effects of sodium-glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA)

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Keywords Blood pressure · Sodium-glucose cotransporter 2 inhibitors · Glucagon-like peptide-1 receptor agonists · Type 2 diabetes

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Two classes of antidiabetic agents, sodium-glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA), have recently emerged as hypoglycemic agents with superior cardiorenal protective effects. This has resulted in these two types of drugs being actively recommended as first-line agents in patients with diabetes with established atherosclerotic cardiovascular disease (ASCVD) [1]. Interestingly, SGLT2i and GLP-1RA have entirely different mechanisms of action. SGLT2 inhibitors are glucose-lowering agents that increase urinary glucose excretion by modulating selective inhibition of SGLT2 in the proximal renal tubule [2]. Ipragliflozin, one of the SGLT2 inhibitors, was the first such agent to obtain regulatory approval in Japan on January 17, 2014. There is evidence that ipragliflozin has favorable metabolic effects that include improved glycemic control and decreased blood pressure (BP), body weight (BW), and visceral adipose tissue, changes that indicate a potential cardiovascular protective effect [3]. The authors of that study suggested that the mechanisms underlying the cardiovascular and renal benefits of SGLT2 inhibition, including BP reduction, may play a significant role in these beneficial effects. Throughout the 24-month study period, mean systolic BP was lower in the ipragliflozin group than in the placebo group, with the changes in systolic BP correlating significantly with the decrease in body mass index in the ipragliflozin group. This led the authors to suggest that the reduction in systolic BP and loss of BW might be the mechanisms for the BP-lowering effect of SGLT2 inhibitors. A meta-analysis also showed that weight loss, but not a reduced HbA1c level, was significantly and independently associated with BP reductions in GLP-1RA and SGLT2 inhibitor treatment [4]. Meanwhile, several mechanisms for the antihypertensive effect associated with GLP-1RA have been reported. For example, a study showed that recombinant GLP-1RA improved endothelial function in patients with type 2 diabetes [5], while another study showed that exenatide increases the plasma concentrations of a number of vasodilators and suppresses the renin-angiotensin system [6]. In addition, GLP-1RA typically causes weight loss through appetite suppression [7].

The EMPA-REG OUTCOME trial showed that empagliflozin markedly reduced the risk of CV mortality compared to that observed with placebo [8]. However, the mechanisms by which SGLT2 inhibitors exert these benefits beyond glucose-lowering are not fully understood. Several mechanisms to account for the antihypertensive effects associated with SGLT2 inhibitors have been reported and are thought to be mediated partly through enhanced urinary sodium excretion, while glucose-induced osmotic diuresis may cause excessive urine output, thereby contributing to weight loss and a reduction in blood pressure [9].

Of the various diabetes medications, both GLP-1RA and SGLT2 inhibitors have been shown to improve cardiovascular outcomes in ASVCD patients with type 2 diabetes. However, the exact mechanisms responsible for the BP-lowering effects and loss of BW associated with these two agents have not been fully understood. As described in this manuscript, the relationship between SGLT2 inhibitors and systolic BP is clear, with this reduction in BP potentially improving cardiovascular outcomes. Lower blood pressure and BW loss correlate independently with SGLT2 inhibitor treatment, with the effect of both GLP-1RA and SGLT2

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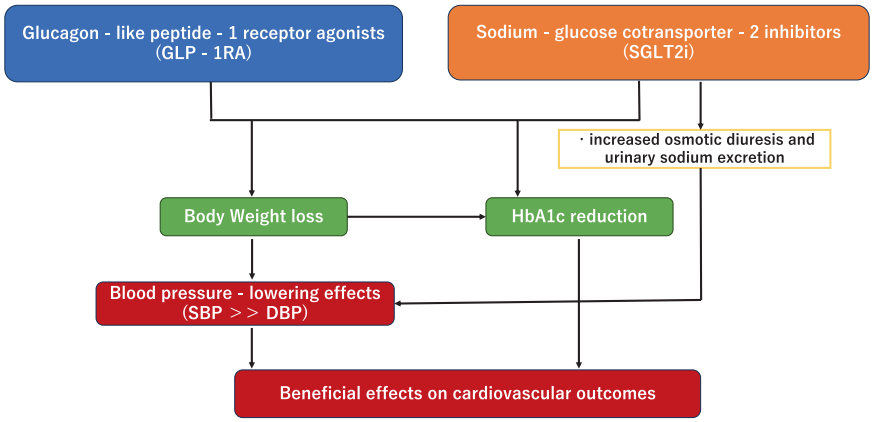

Fig. 1 GLP-1RA leads to a loss of body weight, which has a downstream effect by reducing systolic blood pressure and improving cardiovascular outcomes. On the other hand, SGLT2i induces increased osmotic diuresis and urinary sodium excretion, thereby contributing to a reduction in HbA1c levels and systolic blood pressure. The combined actions of a loss of body weight loss and a reduction in HbA1c levels associated with both drug classes decrease systolic blood pressure, culminating in beneficial effects on cardiovascular outcomes

inhibitors being significantly greater on systolic BP than on diastolic BP [4].

In conclusion, it is essential to strategically use both GLP-1RA and SGLT2i for cardiovascular prevention in ASCVD patients with type 2 diabetes by targeting HbA1c levels and achieving blood pressure control (Fig. 1).

Compliance with ethical standards

Conflict of interest ST has received honoraria from Daiichi Sankyo, AstraZeneca, Bayer, Boehringer Ingelheim Japan, TSUMURA, and Novo Nordisk Pharma.

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