Dipeptidyl Peptidase-4 Inhibitor Versus Sodium-Glucose Cotransporter-2 Inhibitor in the Management of Type 2 Diabetes

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Currently, dipeptidyl peptidase-4 inhibitors (DPP4i) and sodium-glucose cotransporter-2 inhibitors (SGLT2i) are frequently used to treat type 2 diabetes. In this issue (Journal of Endocrinology and Metabolism, 2019), Matsuba et al compared the effects of treatment with sitagliptin (DPP4i) for 24 weeks in the ASSET-K study [1-7] with those with ipragliflozin (SGLT2i) for 24 weeks in the ASSIGN-K study [8-10] and found different effects of these two drugs on clinical parameters [11]. At the baseline, the patients treated by SGLT2i were younger and showed higher body mass index (BMI) and blood pressure as compared with patients treated with DPP4i, indicating that the patients treated by SGLT2i were more likely to have metabolic syndrome than patients treated with DPP4i. A significantly higher incidence of hypertension and dyslipidemia in patients treated by SGLT2i as compared with patients treated with DPP4i supported this hypothesis. HbA1c values were similar in both groups at the baseline.

The difference between two groups in effects on HbA1c was not significant at 12 or 24 weeks [11]. BMI showed a significantly larger decrease with SGLT2i treatment than DPP4i treatment throughout most of the study period [11]. The mean blood pressure also showed a significantly larger decrease with SGLT2i treatment than DPP4i treatment [11]. The decrease of the estimated glomerular filtration rate (eGFR) after 24 weeks was significantly larger in patients treated with DPP4i than those receiving SGLT2i [11].

I previously reported possible anti-atherosclerotic effects beyond glucose lowering [12] (Fig. 1). SGLT2i reduces renal glucose reabsorption and decreases plasma glucose, in an insulin-independent manner, which induces reduction of body weight. Reduction of body weight, improvement of insulin sensitivity and osmotic diuresis decrease blood pressure. Our previous studies also demonstrated that SGLT2i significantly reduced body weight and blood pressure [13, 14].

The EMPA-REG OUTCOME trial showed that empagliflozin significantly reduced incident or worsening of nephropathy, progression to macroalbuminuria, doubling of serum cre-

atinine level accompanied by eGFR of ≤ 45 mL/min/1.73 m^2 and initiation of renal replacement therapy [15]. The CANVAS program also demonstrated that canagliflozin reduced progression to macroalbuminuria, and 40% reduction in eGFR, renal replacement therapy, or renal death [16]. Very recently, CREDENCE trial showed that canagliflozin significantly reduced the relative risk of renal failure in patients with type 2 diabetes and albuminuric chronic kidney disease [17]. The relative risk of the renal-specific composite of end-stage kidney disease, a doubling of the creatinine level, or death from renal causes was lower by 34%, and the relative risk of end-stage kidney disease was lower by 32% in patients treated with canagliflozin. Recent accumulated high level of evidences showed a significant renal protective effect of SGLT2i.

Various underlying mechanisms may contribute to renal protection by SGLT2i [18-20] (Fig. 1). Sano et al mentioned that SGLT2i reduces the overload of the proximal tubules and improves tubulointerstitial hypoxia, inducing the recovery of erythropoietin production by fibroblasts [21]. They concluded that increased hematocrit during SGLT2i therapy indicates the recovery of tubulointerstitial function in diabetic kidney [21]. We think that elevated erythropoietin may be a possible mechanism for the renal protective effect of SGLT2i. Chronic treatment with recombinant human erythropoietin exerted renal protective effects beyond hematopoiesis in streptozotocin-induced diabetic rat [22]. Erythropoietin protected mouse podocytes from damage by advanced glycation end-products [23]. Furthermore, erythropoietin ameliorated podocyte injury in advanced diabetic nephropathy in the db/db mouse [24].

Suppression of reabsorption of glucose via proximal tubule by SGLT2i may improve tubulo-glomerular feedback [20], which may reduce intraglomerular pressure and glomerular hyperfiltration. Reduction of blood pressure, serum urate levels and utilization of ketone bodies by failing kidney may also contribute to renal protection by SGLT2i [19].

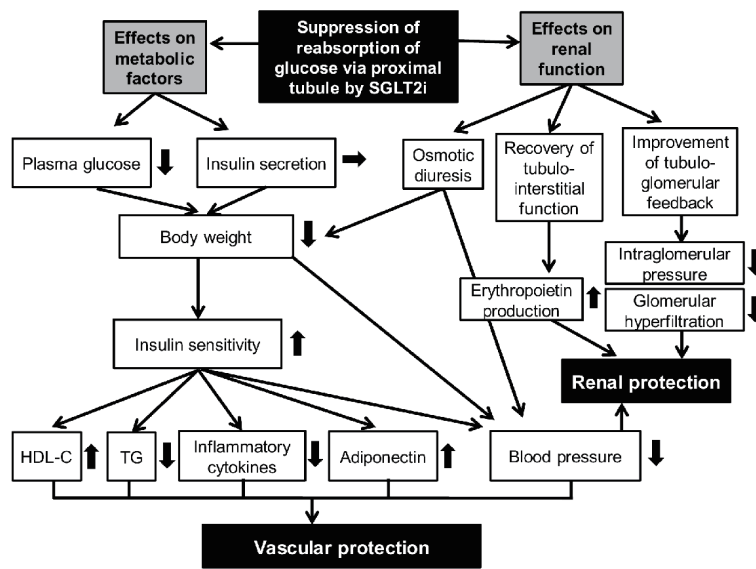## Acknowledgments

Financial Disclosure

Figure 1. Putative mechanisms for vascular and renal protection by SGLT2i. SGLT2i: sodium-glucose cotransporter-2 inhibitors.

Conflict of Interest

The author declares that he has no conflict of interest concerning this article.

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