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COMMENT

Preventive effects of SGLT2 inhibitors on incident hypertension in patients with diabetes who do not have hypertension

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Patients with diabetes have a high prevalence of hypertension, the most potent risk factor for cardiovascular mortality [1]. The prevalence of hypertension in patients with diabetes is approximately three times higher than that in individuals without diabetes [2]. A recent review showed that ~50% of Japanese patients with diabetes have hypertension [3]. These findings indicate that hypertension is a common complication of diabetes. In addition, the coexistence of hypertension in patients with diabetes additively increases the likelihood of developing cardiovascular disease [1–3]. Therefore, preventing the development of hypertension through appropriate interventions is clinically important to reduce the risk of cardiovascular events in patients with diabetes who do not have hypertension.

Recently, sodium-glucose cotransporter-2 (SGLT2) inhibitors have emerged as antidiabetic agents with cardiorenal protective effects and are recommended as first-line treatment for high-risk patients with type 2 diabetes, including those with established cardiovascular disease, multiple cardiovascular risk factors, heart failure, and chronic kidney disease [4]. SGLT2 inhibitors have been shown to have blood pressure-lowering effects, which may contribute in part to the cardiorenal protective effects of SGLT2 inhibitors (Fig. 1). A meta-analysis showed that SGLT2 inhibitors reduced systolic and diastolic blood pressure levels by ~4.0 mmHg and 1.6 mmHg, respectively [5]. However, it is unknown whether SGLT2 inhibitors reduce the risk of developing hypertension in patients with diabetes who do not have hypertension. In the current issue of *Hypertension Research*, Suzuki et al. reported the results of a study conducted to determine whether SGLT2 inhibitors are associated with a lower risk of incident hypertension in patients with diabetes using the JMDC Claims Database, a large administrative claims database containing annual health checkup data and health insurance records [6]. The effects of SGLT2 inhibitors on incident hypertension were compared with those of dipeptidyl peptidase-4 (DPP-4) inhibitors, the most commonly used antidiabetic agents in Japan, in patients with diabetes without a prior diagnosis of hypertension. Propensity score matching analysis was used to create matched pairs of patients who were newly prescribed SGLT2 inhibitors ($n = 5708$) and those who were newly prescribed DPP-4 inhibitors ($n = 5708$), with a mean follow-up duration of 564 ± 493 days. The authors reported that the risk of incident hypertension was significantly lower in patients prescribed SGLT2 inhibitors than in those prescribed DPP-4 inhibitors. The results of the sensitivity analyses were consistent with the main findings. These findings suggest a potential advantage of SGLT2 inhibitors over DPP-4 inhibitors in reducing incident hypertension in patients with diabetes. The results of a previous meta-analysis showed that the blood pressure-lowering effects of SGLT2 inhibitors were more significant than those of DPP-4 inhibitors [7]. Therefore, SGLT2 inhibitors may be superior to DPP-4 inhibitors not only in lowering blood pressure but also in preventing incident hypertension in patients with diabetes.

What are the clinical implications of the preventive effects of SGLT2 inhibitors on incident hypertension beyond their blood pressure-lowering effects in patients with diabetes? In a sensitivity analysis in which incident hypertension was redefined as a diagnosis of hypertension with a prescription of antihypertensive medications, patients prescribed SGLT2 inhibitors had a significantly lower risk

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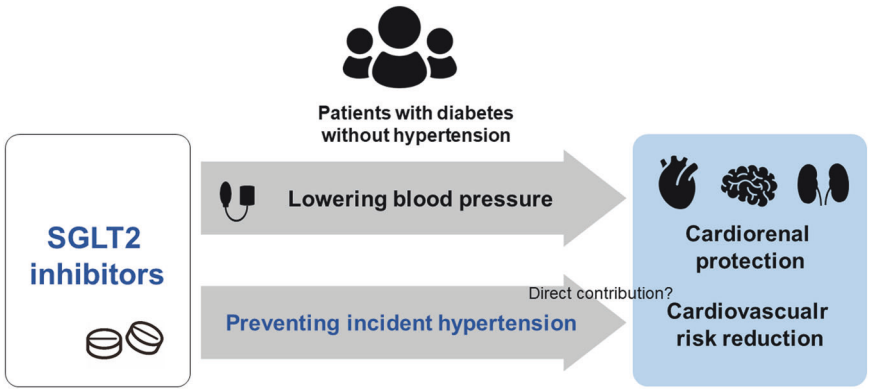

Fig. 1 Sodium-glucose cotransporter-2 (SGLT2) inhibitors may reduce cardiovascular risk through lowering blood pressure and preventing incident hypertension in patients with diabetes who do not have hypertension

of initiating antihypertensive drug treatment than patients prescribed DPP-4 inhibitors. The reduced risk of initiating antihypertensive drug treatment with SGLT2 inhibitors may have clinical significance beyond their blood pressure-lowering effects. Although antihypertensive drug treatment undoubtedly reduces cardiovascular risk, epidemiological studies have shown that cardiovascular risk is generally higher in patients treated with antihypertensive drugs than in untreated individuals with the same blood pressure levels, regardless of the blood pressure achieved [8–10]. These findings suggest that once antihypertensive drug treatment is initiated, it is difficult to fully reduce cardiovascular risk to that of untreated individuals with the same blood pressure levels with currently available antihypertensive drugs. Therefore, preventing the development of overt hypertension requiring antihypertensive drug treatment in untreated individuals is clinically important for reducing cardiovascular risk. The preventive effects of SGLT2 inhibitors on incident hypertension may have additional benefits beyond their blood pressure-lowering effects in reducing cardiovascular risk.

Further studies are expected to determine whether the preventive effects of SGLT2 inhibitors on incident hypertension directly contribute to cardiovascular risk reduction in patients with diabetes who do not have hypertension (Fig. 1). In addition, as mentioned by the authors, elderly individuals aged >75 years were not included in the study due to the characteristics of the JMDC Claims Database. Therefore, future studies are needed to determine whether the findings of this study are applicable to elderly individuals who often require caution when using SGLT2 inhibitors, such as those with sarcopenia or underweight individuals.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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