An Age of Sodium-Glucose Cotransporter-2 Inhibitor Priority: Are We Ready?

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Over the past decade, the use of dipeptidyl peptidase-4 (DPP-4) inhibitors in Korea has steadily increased, replacing sulfonylurea as the most commonly used add-on drug for metformin because of its low risk of hypoglycemia and its relatively better glucose-lowering effect among Asians [1,2]. However, DPP-4 inhibitors have not shown beneficial cardiovascular effects beyond safety in randomized controlled clinical trials among type 2 diabetes mellitus (T2DM) patients [3,4]. In contrast, followed by the striking results of the EMPA-REG OUTCOME study (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) [5], a series of clinical trials demonstrated the protective effects of sodium-glucose cotransporter-2 (SGLT2) inhibitors on cardiovascular and renal complications [6-8]. Thus, most updated treatment guidelines recommend SGLT2 inhibitors to be considered as the preferred choice for T2DM patients with atherosclerotic cardiovascular disease, heart failure, nephropathy, or multiple risk factors [9,10]; SGLT2 inhibitors are accordingly being used in an increasing number of Korean T2DM patients. Today, there is even a practical guide to help doctors who are not experts in T2DM treatment to prescribe SGLT2 inhibitors to protect against cardiovascular and kidney complications in T2DM patients with high cardiovascular risk [11]. Indeed, it is the age of SGLT2 inhibitors in T2DM drugs.

In Diabetes & Metabolism Journal, Hong et al. [12] investigated short-term effects of SGLT2 inhibitors in the real-world setting of one general hospital in Korea. Although the analysis was performed only in a 3-month retrospective design, they confirmed good glucose-lowering efficacy of SGLT2 inhibitors as an add-on drug (–0.94% of glycosylated hemoglobin [HbA1c] change) under various anti-diabetic drug combinations including quadruple therapy, consistent with a previous study [13]. In addition, when changed from other anti-diabetic drugs to SGLT2 inhibitors (switch therapy), an overall –0.42% HbA1c lowering effect was observed. This is slightly better than the results of previous meta-analysis in which SGLT2 inhibitors appeared minimally more potent than DPP-4 inhibitors [14]. Real-world evidence as used in this study has weaknesses and uses. Considering the selection bias, it is desirable to target many subjects in various clinical conditions from various institutions. The decision to select or change a certain medication might have been easier in situations in which clinicians expected the treatment to have more positive effects. For example, SGLT2 inhibitors would have been preferable in obese patients with renal or cardiovascular risk. Moreover, the consequences of switching therapy in this study might have included specific clinical situations, resulting in drug switches (e.g., side effects on existing drugs). Nevertheless, the results of switching therapy to SGLT2 inhibitors are interesting because doctors often experience clinical situations in which they want to change prescriptions to SGLT2 inhibitors for various reasons including glucose control. Moreover, switching therapy may be a relatively common use pattern in Korea, where insurance coverage is restricted by number of drug classes used.
Suggested clinical parameters associated with better glucose-lowering effectiveness of SGLT2 inhibitors are higher baseline HbA1c, shorter diabetes duration, and higher estimated glomerular filtration rate [15,16]. Hong et al. [12] demonstrated that switching to SGLT2 inhibitors showed the same efficacy in weight loss, blood pressure reduction, and decrease in triglyceride level with a half reduction of HbA1c compared to add-on therapy in inadequately controlled T2DM patients. This confirms the glucose-independent mechanism of SGLT2 inhibitors in previous studies [5,15].

Current pharmacologic treatment strategies for T2DM emphasizes a patient-centered approach. To choose the appropriate anti-diabetic drugs, doctors must consider efficacy, safety, patient comorbidities, costs, and patient preferences. In this context, there are still many unanswered questions about the usefulness of SGLT2 inhibitors. The cardio-renal benefit of the SGLT2 inhibitor is significant, but it appeared to vary across the diabetes continuum [17]. Although SGLT2 inhibitors are strongly considered in T2DM patients with prior atherosclerotic cardiovascular disease or heart failure, it is not yet known whether SGLT2 inhibitors are effective or safe for those with recent acute coronary syndrome with decompensation or acute stroke, like those with past history of cardiovascular disease in stable condition. Further, it is not yet known whether SGLT2 inhibitors provide similar benefits if used in individuals not requiring additional glucose lowering on their current therapy. In addition, at what stage and what characteristics of diabetic nephropathy the SGLT2 inhibitors are most effective and safe, what happens in case of acute kidney injury, what the best combination regimen for SGLT2 inhibitors is to achieve the highest efficacy and safety in patients with T2DM, and whether SGLT2 inhibitors are safe for long-term use are not yet established. More research is needed to define a “personalized” target for patients with T2DM.

SGLT2 inhibitors increase the risks of urinary frequency, dehydration, genital infection, and rare diabetic ketoacidosis (DKA). Serum glucose in SGLT2 inhibitor-associated DKA is often lower than in traditional DKA because of increased renal clearance of glucose by the SGLT2 inhibitors, which can delay recognition by both the affected individual and clinician. Although the incidence is very low, one Korean study found that DKA patients using SGLT2 inhibitors needed longer ICU treatment than non-users [18]. Caution should be taken before initiating SGLT2 inhibitor therapy in individuals with a predisposition to hypovolemia or a history of urinary tract infection, those who have decreased insulin secretion capacity or borderline kidney function, or those who are taking concomitant diuretics or nephrotoxic medications. Patients may not mention the side effects unless the doctor informs them in advance or asks them during treatment. In retrospective data, there is a possibility that side effects were not recorded in detail and were thus underestimated in the medical chart. Indications of SGLT2 inhibitors are likely to gradually expand to patients without T2DM if they have heart failure or chronic kidney disease after completion of ongoing studies [19-22]. During the writing, it was announced that dapagliflozin had a protective effect against heart failure with reduced ejection fraction even in nondiabetic patients [23]. Optimal prescription of SGLT2 inhibitors requires full understanding of the benefits and risks. Better understanding is needed to achieve this goal.

CONFLICTS OF INTEREST
No potential conflict of interest relevant to this article was reported.

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