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Update on the efficacy and safety of sodium–glucose cotransporter 2 inhibitors in Asians and non-Asians

Sodium–glucose cotransporter 2 (SGLT2) inhibitors are a novel class of antidiabetic drugs for the treatment of diabetes; they reduce plasma glucose concentrations and bodyweight by inhibiting glucose reabsorption in the kidney[1]. As the action of SGLT2 inhibitors is unique, they have been receiving attention regarding their efficacy and safety from well before their launch. In clinical use, further insights on the efficacy and cautions on the safety of SGLT2 inhibitors have been accumulating. Meta-analysis suggests that SGLT2 inhibitors, as well as glucagon-like peptide 1 analogs, lead to comparable bodyweight decreases in type 2 diabetes patients[2]. Bodyweight loss is a major target for treatment of patients with type 2 diabetes, especially because overweight is associated with insulin resistance and cardiovascular risk factors.

Based on the evidence of several major mega-trials, which showed that SGLT2 inhibitors also exert preventive effects on major adverse cardiovascular events, heart failure hospitalization and progression of renal impairment, they were prioritized among other second-line oral drugs after metformin for patients with cardiovascular disease and chronic kidney disease in the consensus reports of the American Diabetes Association and the European Association for the Study of Diabetes[3].

These consensus reports were edited based on evidence targeted primarily to Caucasians. It is widely recognized that type 2 diabetes in Asians, especially East Asians, is characterized by β-cell dysfunction and less obesity compared with Caucasians[4]. These pathophysiological differences might have an impact on the therapeutic consideration of SGLT2 inhibitors. Cai *et al.*[5] carried out a meta-analysis to compare the efficacy and adverse effects of SGLT2 inhibitors between Asian and non-Asian type 2 diabetes patients. They found no significant difference in the reduction of glycated hemoglobin or bodyweight. Furthermore, no disparity was found in the risk of all-cause mortality or hypoglycemia[5]. Subgroup analysis in the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA-REG OUTCOME) showed that the reductions in the risk of cardiovascular events and mortality by empagliflozin were consistent between Asians and the overall population[6]. These reductions were also consistent between East Asians and the overall population; however, a statistical test was not carried out, because the number of East Asian patients with cardiovascular events was small.

Clinical findings using SGLT2 inhibitors in Asian patients have been accumulating. Luseogliflozin added to liraglutide improves glycemic control and leads to a reduction in bodyweight (especially fat mass) in Japanese patients[7]. This suggests that combination therapy could be an attractive treatment approach for overweight Japanese patients with type 2 diabetes. Tofogliflozin showed better improvement of glycemic control and an increase in insulin secretion, especially in subgroups with high insulin levels at baseline[8]. These data suggest that SGLT2 inhibitors might facilitate recovery from impaired -cell dysfunction in patients in whom insulin secretion capacity is preserved to a certain extent. Furthermore, administration of SGLT2 inhibitors with or without dipeptidyl peptidase-4 inhibitor decreased nocturnal hypoglycemia when taking basal–bolus insulin therapy, suggesting that SGLT2 inhibitors might increase the insulin counter-regulatory hormone concentrations, including glucagon, growth hormone, cortisol and catecholamine[9]. SGLT2 inhibitors also have the effect of reducing blood pressure comparable to that of low-dose thiazide diuretics in patients with both type 2 diabetes and hypertension[10].

Regarding safety concerns, empagliflozin was found to be well tolerated in pooled analysis of East Asian patients with type 2 diabetes, which is consistent with results from the safety data in overall population pooled analysis from placebo-controlled trials[11]. In Japan, shortly after six SGLT2 inhibitors were launched, safety became a major concern due to reports of several serious adverse events. These led to a "recommendation on the appropriate usage of SGLT2 inhibitors" by a committee of Japanese experts in June 2014. This statement recommended that all patients aged ≥65 years starting the drugs within 3 months after the launch should be registered in a post-marketing study. The clinical incidence of adverse reactions to tofogliflozin in patients aged ≥65 years differed little from that noted in preapproval clinical trials[12]. Recently, prevention of sarcopenia, which might accompany aging in patients with diabetes, has been given special attention[13]. Luseogliflozin was found to produce beneficial changes in

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Table 1 | Major benefits and risks of sodium–glucose cotransporter 2 inhibitors use

Benefits	Risks
• Plasma glucose ↓	• GTI
• Bodyweight ↓	• UTI
• Body fat ↓	• DKA (especially used in type 1 diabetes)
• Blood pressure ↓	• Hypoglycemia (with insulin or SU)
• MACE ↓	• Volume depletion
• HF hospitalization ↓	• Skin lesion
• Renal protection	

DKA, diabetic ketoacidosis; GTI, genital tract infection; HF, heart failure; MACE, major adverse cardiovascular events; SGLT2, sodium–glucose cotransporter 2; SU, Sulfonylureas; UTI, urinary tract infection.

body composition in moderately obese Japanese type 2 diabetes patients, including body fat reduction with minimal muscle reduction, and the signs of sarcopenia were not observed after treatment[13]. The latest edition of "recommendations" updated in July 2019 notes safety concerns, such as diabetic ketoacidosis, especially when the drug is used in type 1 diabetes patients, hypoglycemia when used with sulfonylurea or insulin, volume depletion, skin lesion and urogenital infections.

One of the most common adverse effects of SGLT2 inhibitors is genital tract infection. The rate of developing positive colonization and symptomatic vaginitis by the use of SGLT2 inhibitors in women who attended outpatient clinics in Japan appears to be higher in real-world practice than in clinical trials[14]. Meta-analysis of the efficacy and safety profiles of SGLT2 inhibitors in East Asian patients with type 2 diabetes showed that the drugs significantly increased the risk of genital tract infection, but did not significantly increase the risk of hypoglycemia, urinary tract infection, hypotension or mortality[15].

The major benefits and risks of using SGLT2 inhibitors are listed in Table 1; they should be carefully considered for appropriate use of the drugs[3,5,15]. Reports regarding the clinical use of SGLT2 inhibitors are accumulating for both Asians and non-Asians, and are expected to further clarify the risks and benefits of these drugs.

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