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UPDATE

Effectiveness and safety of sodium–glucose cotransporter 2 inhibitors in Asian populations

Sodium–glucose cotransporter 2 inhibitors (SGLT2is) comprise a class of glucose-lowering drugs that enhance urinary glucose excretion, leading to metabolic improvements. Furthermore, SGLT2is offer cardiovascular and chronic kidney disease benefits. Given the cardiorenal advantages of SGLT2is, their usage is increasing globally, including in Asia[1,2]. However, it is important to note that SGLT2i outcome trials included <25% Asian participants, which restricts the generalizability of their efficacy in this population[3]. Furthermore, individuals with diabetes in Asia show ethnicity-specific characteristics, such as impaired β-cell function relative to insulin resistance and a higher propensity for visceral obesity, as well as early-onset diabetes. Consequently, previous studies have assessed the efficacy and safety of SGLT2is in Asian populations, and compared them with non-Asian individuals in randomized controlled trials (RCTs). Nevertheless, RCTs might not fully represent individuals in real-world clinical practice. In the case of Japanese individuals with type 2 diabetes, baseline characteristics varied between RCTs and non-RCTs, including the proportion of older adults, obesity and disease duration[4]. Therefore, a comprehensive evaluation of both RCTs and non-RCTs is warranted.

In terms of improving metabolic profiles, the meta-analysis, encompassing seven SGLT2i outcome trials in Asian individuals and 10 in non-Asian individuals, indicated a similar clinical metabolic efficacy of SGLT2is in both groups. This resulted in reduced glycated hemoglobin, fasting glucose, bodyweight and blood pressure[5]. The cardiometabolic benefits of SGLT2is in Asians have also been observed in real-world clinical practice settings. A retrospective cohort study using the Japan Medical Data Center claims database found that SGLT2i users showed greater improvements in metabolic profiles, including glycated hemoglobin, body mass index, blood pressure and lipid levels, in comparison with dipeptidyl peptidase-4 inhibitor users[6]. Additionally, SGLT2i users required fewer new prescriptions for antihypertensive users compared with users of other glucose-lowering drugs[7].

Regarding the effectiveness of cardiovascular outcomes, the meta-analysis of three SGLT2i outcome trials showed that the risk of major adverse cardiovascular events was similar between Asian and whites people (hazard ratio 0.81, 95% confidence interval 0.57–1.04; hazard ratio 0.90, 95% confidence interval 0.80–1.00; P for interaction = 0.46)[8]. In two SGLT2i outcome trials involving individuals with heart failure and reduced ejection fraction, the benefit of preventing hospitalization for heart failure or cardiovascular death was more significant in Asian patients compared with white patients (hazard ratio 0.60, 95% confidence interval 0.47–0.74; hazard ratio 0.82, 95% confidence interval 0.73–0.92; P for interaction = 0.01)[8]. The effects of SGLT2is were also confirmed in real-world clinical practice settings in three east Asian countries (Japan, South Korea and Taiwan)[9].

In terms of the effectiveness of renal outcomes, SGLT2is are known to delay the decline in renal function in diabetic kidney disease in both SGLT2i outcome trials and in large real-world clinical practice settings[10]. These renoprotective effects in diabetic kidney disease have also been observed in Asian paople[10]. In recent SGLT2i trials, a reduction in the risk of composite outcome, including a decline in estimated glomerular filtration rate (eGFR), end-stage kidney disease or death from renal causes, was also shown among Asian people[11,12]. In the Asian subanalysis of SGLT2i outcome trials, there were comparable incidences of renal-related adverse events, such as acute kidney injury, renal impairment, eGFR decline, increased creatinine levels and renal failure, between the SGLT2i and placebo groups[13]. Using hospital medical records in Japan, the initiation of SGLT2is in the early stage of type 2 diabetes improved the eGFR slope in individuals with both rapid and moderate eGFR decline, and these renoprotective effects were more pronounced in individuals with rapid eGFR declines[14].

Most SGLT2i outcome trials have shown a similar incidence rate or no increased risk of adverse events between the SGLT2i and control groups in Asian individuals. Furthermore, these incidence rates are relatively low in Asian people compared with those in other countries[13]. In real-world clinical practice settings, the initiation of SGLT2i therapy did not result in an increased risk of fracture in South Korea or lower-limb amputations in Japan[15,16]. In older adults aged ≥65 years in South Korea, the initiation of SGLT2i therapy did not increase the risk of diabetic ketoacidosis, fracture or severe hypoglycemia. However, the initiation of SGLT2i therapy had a higher risk of genital infection and urinary tract infection compared with the initiation of dipeptidyl peptidase-4 inhibitor therapy[17]. Table 1 summarized the effectiveness and safety of SGLT2 inhibitors in Asian populations.

Based on the cardiorenal benefits observed in RCTs and observational studies in real-world clinical practice settings, SGLT2is have led to a shift in the

*Correspondence
Dae Jung Kim
Tel.: +82-31-219-5128
Fax: +82-31-219-4497
E-mail address: djkim@ajou.ac.kr

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Table 1 | Summary of the effectiveness and safety of sodium–glucose cotransporter 2 inhibitors in Asian populations

Outcomes	Study	Findings
Metabolic profiles	Meta-analysis of randomized controlled trials[5]	Placebo-corrected difference (95% CI): HbA_{1c} (%), −0.60 (−0.68 to −0.53) Fasting glucose (mmol/L), −1.37 (−1.53 to −1.22) Bodyweight (kg), −1.60 (−1.84 to −1.37) SBP (mmHg), −4.53 (−5.53 to −3.53)
	Japan Medical Data Center claims database[6, 7]	Mean difference of SGLT2i vs DPP-4i: HbA_{1c} (%), −0.89 vs −0.75 BMI (kg/m^2), −1.12 vs −0.22 SBP (mmHg), −5.20 vs −2.80 Total cholesterol (mg/dL), −8.7 vs −13.8 Triglycerides (mg/dL), −29.9 vs −29.2 LDL-C (mg/dL), −8.6 vs −10.1 HDL-C (mg/dL), 4.0 vs 0.5 Risk ratio (95% CI) for prescription (vs other GLDs): Antihypertensive drug, 0.66 (0.47–0.93) Lipid-lowering drug, 1.43 (1.12–1.82)
Cardiovascular outcomes	Meta-analysis of randomized controlled trials[8]	Hazard ratio (95% CI; vs placebo): Major adverse cardiovascular events, 0.81 (0.57–1.04) HHF or cardiovascular death, 0.60 (0.47–0.74)
	Routine care in Japan, South Korea and Taiwan[9]	Hazard ratio (95% CI; vs DPP-4i): HHF or all-cause mortality, 0.76 (0.67–0.86) MI, stroke, or all-cause mortality, 0.74 (0.61–0.88) HHF, 0.82 (0.71–0.94) All-cause mortality, 0.64 (0.50–0.81) MI, 0.89 (0.62–1.26) Stroke, 0.77 (0.55–1.09) Coronary revascularization procedure, 0.81 (0.69–0.95)
Renal outcomes	DAPA-CKD and EMPA-KIDNEY trial[11, 12]	Hazard ratio (95% CI) of composite outcome including a decline in eGFR, end-stage kidney disease, or death from renal or cardiovascular causes (only in DAPA-CKD trial; vs placebo): DAPA-CKD trial 0.66 (0.46–0.93) EMPA-KIDNEY trial; China and Malaysia, 0.67 (0.53–0.85); Japan, 0.50 (0.33–0.76)
	Hospital medical records in Japan[14]	Mean annual eGFR slope (mL/min/1.73 m^2 per years; vs control) Rapid decliners, −1.00 to −4.36 Moderate decliners, −1.42 to −3.48
Adverse events	Korean National Health Insurance Service database[15]	Hazard ratio (95% CI) of fracture (vs DPP-4i): As-treated analysis, 0.98 (0.92–1.04) Intention-to-treat analysis, 0.94 (0.89–1.00)
	Medical Data Vision administrative claims database[16]	Hazard ratio (95% CI) of amputation (vs metformin): 1.34 (0.80–2.24)
	Korean National Health Insurance Service database[17]	Hazard ratio (95% CI) of fracture (vs DPP-4i): Diabetic ketoacidosis, 0.96 (0.63–1.46) Fracture, 0.95 (0.88–1.02) Severe hypoglycemia, 0.93 (0.81–1.07) Genital infection, 2.44 (2.22–2.67) Urinary tract infection, 1.05 (1.00–1.11)

BMI, body mass index; CI, confidence interval; DAPA-CKD, dapagliflozin and prevention of adverse outcomes in chronic kidney disease; DPP-4i, dipeptidyl peptidase 4 inhibitors; eGFR, estimated glomerular filtration rate; EMPA-KIDNEY, study of heart and kidney protection with empagliflozin; GLDs, glucose-lowering drugs; HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HHF, hospitalization for heart failure; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; SBP, systolic blood pressure; SGLT2i, sodium–glucose cotransporter 2 inhibitors.

paradigm, moving beyond glucose control toward a more comprehensive strategy for reducing cardiorenal risk in individuals with type 2 diabetes. Furthermore, their effectiveness and safety appear to be consistent in both Asian and non-Asian populations. Therefore, active consideration of SGLT2i utilization is necessary, taking into account their cardiorenal benefits and potential adverse events in Asian populations.

DISCLOSURE

Dae Jung Kim is an editorial board member of *Journal of Diabetes Investigation* and a co-author of this article. To minimize bias, they were excluded from all editorial decision-making related to the acceptance of this article for publication. The authors declare no conflict of interest.

Kyoung Hwa Ha, Dae Jung Kim
Department of Endocrinology and Metabolism, Ajou University School of Medicine, Suwon, Korea

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