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INTRODUCTION TO MINI-REVIEWS

Current understanding of the effect of sodium–glucose co-transporter-2 inhibitors in Asian patients with diabetes mellitus

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The two fundamental defects in type 2 diabetes mellitus are reduced insulin sensitivity and impaired pancreatic β-cell function. Thus, enhancing insulin sensitivity and/or insulin secretion has been considered to be a reasonable therapeutic strategy for this disease. Diet and exercise therapy eventually enhance insulin sensitivity, and drugs that directly increase insulin resistance or secretion have been used as the primary treatments for type 2 diabetes.

Sodium–glucose co-transporter-2 (SGLT2) is mainly expressed in the proximal renal tubules, and is responsible for renal glucose reabsorption. SGLT2 inhibitors enhance glucosuria and reduce blood glucose independent of insulin action; thus, this drug does not fit with the drug for primary treatment for type 2 diabetes. However, the concept of using SGLT2 inhibitors for the treatment of diabetes mellitus is not new. Phlorizin, a SGLT1 and SGLT2 inhibitor, has been used for several decades in animal research on diabetes. Phlorizin reduces blood glucose without affecting insulin secretion or insulin action. As a result, if it improves any phenomena in diabetic model rodents, these phenomena will probably be due to hyperglycemia, and not necessarily to decreased insulin action. By modifying the chemical structure of phlorizin used in animal studies, SGLT2-specific inhibitors have been developed for clinical use in humans. Before SGLT2 inhibitors were administered in clinical settings, their mode of action raised concerns about adverse effects caused primarily by increased glucosuria. In addition, it is very difficult to differentiate the effects of these drugs from those of low carbohydrate intake, and it was unclear which approach would be more effective. However, most patients with type 2 diabetes mellitus in western countries are obese. Also, in Japan, the prevalence of obesity in type 2 diabetes has been increasing. Obese patients often do not maintain a proper diet, and they were expected to benefit from SGLT2 inhibitors. However, before these drugs were launched, probably only a few diabetologists imagined them having an effect other than general effect by reduction of energy intake in the patients with diabetes mellitus.

In 2013, canagliflozin became the first SGLT-2 inhibitor to be approved by the Food and Drug Administration in the United States. In Japan, with the launch of SGLT2 inhibitors in 2014, a recommendation on the proper use of SGLT2 inhibitors was issued. This guideline was based on the mechanism of action of the drug, not on research-based evidence. It identified risks that clinicians should be aware of, and particularly emphasized dehydration, complications secondary to dehydration, and use of the drug in the elderly. Since then, SGLT2 inhibitors have been carefully administered in Japan.

Recent antidiabetic drugs launched in the United States have required proof of cardiovascular safety. Indeed, the cardiovascular safety of several dipeptidyl peptidase-4 (DPP-4) inhibitors was proved in large-scale cardiovascular outcome trials. Regarding SGLT2 inhibitors, the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial was the first to report results on safety [1]. This trial was conducted to investigate the effects of empagliflozin on cardiovascular morbidity and mortality in patients with type 2 diabetes at

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high cardiovascular risk. A total of 7020 patients were randomly allocated to the treatment group, which received two doses of empagliflozin, or the placebo group. The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. In contrast with trials of DPP-4 inhibitors that proved non-inferiority for cardiovascular events but failed to prove superiority, the primary outcome in the empagliflozin group was 14% less common than in the placebo group, indicating a significant difference. Intriguingly, while there were no significant differences in the rates of myocardial infarction or stroke, the empagliflozin group showed a 38% lower rate of death from cardiovascular causes, as well as a 35% relative risk reduction for hospitalization for heart failure, indicating significant differences. Another study of the same subjects investigated the effects of empagliflozin on prespecified renal outcomes, including incident or worsening nephropathy (for instance progression to macroalbuminuria), doubling of the serum creatinine level, initiation of renal replacement therapy, or death from renal disease. That study found that incident or worsening nephropathy in the empagliflozin group was 39% less common than in the placebo group, indicating a significant difference [2].

SGLT2 inhibitors reduce body weight due to the energy loss caused by enhanced glucosuria. This effect could be especially beneficial for obese patients. If so, the use of this drug could be more effective in non-Asians because Asians are known to be leaner than members of other races. In this regard, the effects of empagliflozin in Asian patients were investigated in a post hoc analysis of the EMPA-REG OUTCOME trial. Of the 7020 patients in this trial, 21.6% were Asians. The study found that the reduction in cardiovascular events in Asians was similar to that in the overall population [3].

After the EMPA-REG OUTCOME trial was completed, the results of the Canagliflozin Cardiovascular Assessment Study (CANVAS) program were reported. This trial included 10,142 patients with type 2 diabetes and high cardiovascular risk. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Canagliflozin significantly reduced the primary outcome by 14% relative to placebo. In addition, the canagliflozin group demonstrated a beneficial effect of hospitalization for heart failure as well as positive renal outcomes [4]. Subsequently, the results of the Dapagliflozin Effect on Cardiovascular Events (DECLARE)-TIMI 58 trial were reported. Unlike the EMPA-REG OUTCOME trial and CANVAS program, a significant proportion of the DECLARE-TIMI 58 trial population, specifically 10,186 of the 17,160 enrolled patients, did not have atherosclerotic cardiovascular disease. As a result, this trial failed to demonstrate a lower rate of cardiovascular events in the dapagliflozin group. On the other hand, patients in the dapagliflozin group demonstrated a 17% lower rate of cardiovascular death or hospitalization for heart failure than the placebo group; this was a significant difference that was mainly due to the lower rate of hospitalization for heart failure in the dapagliflozin group. This group also had a 24% lower incidence of renal events than the placebo group, indicating a significant difference [5].

SGLT2 inhibitors reduce blood glucose levels, blood pressure, triglyceride levels, uric acid levels, body weight, and possibly ameliorate visceral obesity. These combined effects seem to be beneficial for the prevention of cardiovascular diseases. However, the aforementioned large-scale cardiovascular outcome studies demonstrated only a modest suppressive effect of SGLT2 inhibitors on the onset of atherosclerotic disease. Instead, these clinical trials supported these drugs' beneficial effects on heart failure and diabetic kidney disease, both of which are frequently observed in elderly patients. Clinicians prescribing SGLT2 inhibitors should be familiar with all recent evidence on the outcomes and mode of action of these drugs. Furthermore, the subjects included in most of the aforementioned studies were not Asian. Thus, in caring for Asian patients with diabetes, we need to know whether the findings observed in previous trials are applicable to this race. In this mini review series, two experts were each invited to write a review of a topic in this field, taking the above background into account. I hope this report will provide you with valuable information regarding SGLT2 inhibitors.

Compliance with ethical standards

Conflict of interest HW received honoraria from Astellas Pharma, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Fujifilm, Kyowa Kirin, Merck Sharp and Dohme, Mitsubishi Tanabe Pharma, Novo Nordisk, Ono Pharmaceutical, Sanofi, Sanwa Kagaku Kenkyusho, Sumitomo Dainippon Pharma, Takeda Pharmaceutical and Terumo, also received subsidies or donations from Boehringer Ingelheim, Eli Lilly, Kowa, Novartis, Sanofi, Sanwa Kagaku Kenkyusho and Yakult Honsha, also received subsidies or donations from Abbott Japan, Astellas Pharma, Boehringer Ingelheim, Daiichi Sankyo, Kissei Pharmaceutical, Kyowa Kirin, Merck Sharp and Dohme, Mitsubishi Tanabe Pharma, Novartis Pharma, Novo Nordisk, Ono Pharmaceutical, Pfizer, Sanofi, Sumitomo Dainippon Pharma, Taisho Toyama Pharmaceutical and Teijin, and belongs to endowed departments by Boehringer Ingelheim, Kowa, Merck Sharp and Dohme, Mitsubishi Tanabe Pharma, Ono Pharmaceutical, Sanwa Kagaku Kenkyusho, Soiken and Takeda Pharmaceutical.

Ethical approval This article does not contain any studies with human or animal subjects performed by any of the authors.

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