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COMMENTARY

Pleiotropic effects of SGLT2 inhibitors beyond the effect on glycemic control

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Abstract

The risk cardiovascular disease is markedly increased in patients with type 2 diabetes mellitus (T2DM). Recently, the EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in T2DM Patients-Removing Excess Glucose) trial showed, for the first time, that a glucose lowering drug, the sodium-glucose cotransporter-2 (SGLT2) inhibitor empagliflozin decreased cardiovascular events, cardiovascular mortality, and overall mortality in patients with T2DM at establish cardiovascular disease. Following to EMPA-REG OUTCOME trial, the CANVAS (Canagliflozin Cardiovascular Assessment Study) Program also showed that the SGLT2 inhibitor canagliflozin decreased cardiovascular events in patients with T2DM at high cardiovascular risk. These results suggest the class effects rather than drug-specific effects on cardiovascular risk. In addition, these two clinical trials showed that empagliflozin and canagliflozin improved renal outcomes. With regard to adverse events, the rate of urinary tract infection and genital infection significantly increased in patients receiving SGLT2 inhibitor such as empagliflozin or canagliflozin. Notably, the lower limb amputation significantly increased in the only canagliflozin group. However, the possibility that increased amputation risk might be a class effect remains open and in need of further research. This report discusses the results of cardiovascular and renal outcomes from the two landmark trials.

Keywords Sodium-glucose cotransporter 2 (SGLT2) inhibitor · Empagliflozin · Canagliflozin · Cardiovascular disease · Renal outcome

Type 2 diabetes mellitus (T2DM) is associated with increased cardiovascular morbidity and mortality. Previously, major landmark trials with glucose lowering interventions in the patients with T2DM have failed to demonstrate any benefits in macrovascular events at the end of the intervention period such as the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial [1] and the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) trial [2].

Sodium-glucose cotransporter 2 (SGLT2) are a new class drug approved for glucose lowering in patients with T2DM in the United States since 2012. In Japan, ipragliflozin was been initially approved for T2DM in 2014 and up to the present, six SGLT2 inhibitors—ipragliflozin, dapagliflozin, luseogliflozin, tofogliflozin, canagliflozin, and empagliflozin—have been approved. SGLT2 inhibitors increase urinary glucose excretion by reducing the reabsorption of filtered glucose in the renal proximal tubule and, in turn, improve hyperglycemia in patients with T2DM. The mechanism of SGLT2 inhibition occurs independently of insulin secretion, and is not affected by pancreatic β-cell function or the degree of insulin resistance. SGLT2 inhibitors also provide in mild osmotic diuresis and net caloric loss, contributing to a reduction in body weight and blood pressure.

Recently, two major cardiovascular trials, the EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in T2DM Patients-Removing Excess Glucose) trial [3] and the CANVAS (Canagliflozin Cardiovascular Assessment Study) [4], which were clinical trials of a glucose lowering drugs to demonstrate superiority to the reduction of cardiovascular diseases in the patients with T2DM, have been reported.

The EMPA-REG OUTCOME trial [3] randomized patients with T2DM at high cardiovascular risk to receive either empagliflozin (10 mg or 25 mg) or placebo in addition

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to standard care. More than 99% of patients had established cardiovascular disease. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke, the so-called three-point major adverse cardiovascular events (MACE). In the empagliflozin group, there was a 14% relative risk reduction in primary outcome, in particular a 38% relative risk reduction in cardiovascular death. In addition, there were a 32% relative risk reduction in all-cause mortality and a 35% relative reduction in the incidence of hospitalization for heart failure. However, there was no significant difference in the incidence of nonfatal myocardial infarction or nonfatal stroke between the empagliflozin group and the placebo group. These results demonstrated the cardiovascular benefits of empagliflozin in patients with T2DM and preexisting cardiovascular disease and, as a result, have dramatically increased the prescription number of empagliflozin. The cardiovascular benefits of empagliflozin are presumed the possibility of multiple potential mechanisms. These include metabolic factors, such as reductions in HbA1c, body weight, blood pressure, uric acid, and visceral adiposity.

On the other hand, the CANVAS Program was designed similar to EMPA-REG OUTCOME trial, enrolling individuals who either had preexisting cardiovascular disease or were high risk for cardiovascular disease. The CANVAS Program integrated data from two trials involving CANVAS and CANVASS-R. The CANVAS randomized patients with T2DM at high cardiovascular risk to receive either canagliflozin (100 mg or 300 mg) or placebo in addition to standard care, and CANVAS-R randomized patients with T2DM at high cardiovascular risk to receive either canagliflozin (initial dose of 100 mg and optional increase to 300 mg starting from 13 weeks) or placebo in addition to standard care [4]. Cardiovascular disease had been established in 65.8% of patients. The primary endpoint of CANVAS Program was the composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. In the canagliflozin group, the relative risk of the primary outcome significantly decreased by 14%, whereas there was no significant difference in cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke compare with the placebo group. Following the results from EMPA-REG OUTCOME, the results from CANVAS Program lends support to a class effect of the SGLT2 inhibitors on cardiovascular risk. The cardiovascular benefits of canagliflozin are presumed the possibility of multiple potential mechanisms. These include metabolic factors, such as reductions in HbA1c, body weight, blood pressure, uric acid, and visceral adiposity.

In addition, CANVAS Program demonstrated that the relative risk of progression of albuminuria and the relative risk of a composite renal endpoint of sustained 40% reduction in eGFR, requirement for renal-replacement therapy, or renal death significantly decreased by 23% and by 40%, respectively, in the canagliflozin group [4]. Moreover, EMPA-REG OUTCOME also investigated renal outcomes in patients with T2DM, established cardiovascular disease, and an estimated glomerular filtration rate (eGFR) $\geqq$ 30 mL/min/1.73 m^2 [5]. The empagliflozin group showed a sharp initial decline in eGFR in the first 4 weeks of treatment, but this decline in eGFR was a later plateau and was superior to placebo over time. Finally, in the empagliflozin group, there were a 39% relative risk reduction in the incident or worsening nephropathy, a 38% relative risk reduction in the progression of macroalbuminuria, a 44% relative risk reduction in the doubling of serum creatinine, and a 55% relative risk reduction in the initiation of the renal-replacement therapy [5]. The potential mechanism of renal effects in SGLT2 inhibitors is multifactorial, and the direct renal vascular and hemodynamic effects are presumed to play an important role. SGLT2 inhibitors decrease the reabsorption of proximal tubular sodium and, therefore, increase sodium delivery to the macula densa, which activate tubule-glomerular feedback and afferent arteriolar vascular regulation, resulting in decreased glomerular hyperfiltration [6]. Reduction of glomerular hyperfiltration and glomerular pressure clinically contributes as acute reduction of albuminuria and eGFR.

With regard to adverse event, there was no difference between SGLT2 inhibitor and placebo for severe hypoglycemia, thromboembolic events, or ketoacidosis in EMPA-REG OUTCOME trial or CANVAS Program. However, the rate of urinary tract infection and genital infection significantly increased in patients receiving SGLT2 inhibitor such as empagliflozin or canagliflozin, particularly in women [3, 4]. Notably, the lower limb amputation significantly increased in patients receiving canagliflozin in CANVAS Program, although these events may not have been fully studied in EMPA-REG OUTCOME trial [3, 4]. However, the possibility that increased amputation risk might be a class effect remains open and in need of further research.

In summary, at first, EMPA-REG OUTCOME trial demonstrated that empagliflozin enables significant reductions in cardiovascular and all-cause mortality as well as in renal outcomes in patients with T2DM and established cardiovascular disease [3]. It was unknown whether the benefits observed in EMPA-REG OUTCOME are specific to empagliflozin or are a class effect of SGLT2 inhibitors. However, following the results from EMPA-REG OUTCOME trial, the CANVAS Program reduced the risk of three-point MACE. As a result of these two trials, a significant reduction in three-point MACE by these two SGLT2 inhibitors lends to support class effects rather than drug-specific effects on cardiovascular risk. On the basis of the primary cardiovascular outcomes reported in these two trials, American Diabetes Association (ADA) guideline recognizes the cardiovascular protective effects of empagliflozin and canagliflozin in patients with T2DM and established cardiovascular disease

[7, 8]. The kidney benefits of SGLT2 inhibitors as well as the cardiovascular benefits of SGLT2 inhibitors should be considered in the selection of glucose lowering drugs for the management of patients with T2DM and established cardiovascular disease. However, in neither study was there a reduction in nonfatal myocardial infarction. These considerations suggest that the benefit of SGLT2 inhibitors is not due to improvement in the underlying atherosclerotic process. In addition, it is unknown whether SGLT2 inhibitor can improve cardiovascular outcome in preexisting T2DM patients without cardiovascular disease or preexisting cardiovascular disease patients without T2DM. Therefore, it would require many large trails of without cardiovascular disease.

In conclusion, the results from EMPA-REG OUTCOME and CANVAS trials indicate that SGLT2 inhibitors offer a promising therapeutic option in the future management of patients with T2DM. However, many questions have yet to be resolved and further research is needed in the future.

Compliance with ethical standards

Conflict of interest The author declares that they have no conflict of interest.

Ethics policy This article does not contain any studies with human or animal subjects performed by the author.

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