Asian Perspective of the EMPA-REG OUTCOME Study

Yasuko K. Bando, MD, PhD; Toyoaki Murohara, MD, PhD

In Japan, 3.2 million people have been diagnosed with type 2 diabetes (T2DM) and its prevalence is increasing. According to an estimation by the WHO, Eastern Asia is on the way to become another global epicenter for T2DM as dietary culture changes more rapidly and people become less active and obese. Cardiovascular (CV) complications are very common in patients with T2DM and are related to the severity and duration of hyperglycemia. Because hyperglycemia plays a central role in both the microvascular and macrovascular complications of T2DM, stable control of hyperglycemia is an important means of preventing the vascular complications in T2DM.

Many clinical studies have been undertaken to test whether intensive glucose-lowering using multiple drugs is effective for the prevention of CV events. However, the use...
of intensive therapy to target glycated hemoglobin levels lower than 6% for 3.5 years paradoxically increased all-cause mortality and did not significantly reduce major composite CV events compared with standard therapy. These findings suggest a previously unrecognized risk of intensive and rapid glucose-lowering using polytherapy in high-risk patients with T2DM. However, it is also true that the same trial confirmed that the incidence of nonfatal myocardial infarction was significantly lower in the intensive glucose-lowering group compared with the standard group. Moreover, UKPDS 80 demonstrated that better control of blood glucose levels was associated with a risk reduction not only for microvascular complications but also myocardial infarction and death from any cause during 10 years of post-trial follow-up, a phenomenon referred to as the “legacy effect”. Considering these clinical findings on the prevention of CV events in T2DM, it is desirable to use drugs that can stably lower blood glucose levels while not inducing severe hypoglycemia in high-risk patients with T2DM. One of these candidate drugs is a sodium glucose cotransporter 2 inhibitor (SGLT2i).

In this issue of the Journal, Kaku and co-workers present striking data of their subanalysis of the EMPA-REG OUTCOME study that tested the efficacies of a SGLT2i, empagliflozin, on CV outcomes in Asian T2DM patients with high CV risk (Table S1). The CV protective mechanisms mediated by SGLT2i have attracted much attention and many potential factors are presented (Figure 1). One of the most interesting actions is the diuretic effect without a secondary increase in plasma renin activity (PRA). Loop diuretics, such as furosemide, have played a primary role in the management of systemic congestion observed in symptomatic heart failure patients. However, cardiologists should remember the harmful consequence of diuretics that can promote activation of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (Figure 2). Consistently, as previously demonstrated by a comparison of the changes in systolic blood pressure (SBP) between SGLT2i and hydrochlorothiazides, the SGLT2i lowered daytime SBP more markedly than did hydrochlorothiazides without elevating PRA. In contrast, hydrochlorothiazide lowered night-time BP, whereas the SGLT2i did not. Because PRA is enhanced in a posture-dependent manner and diuretics, including thiazide, are known to augment this posture-dependent increase in PRA, the daytime-dominant action on SBP by the SGLT2i may explain the lack of unwanted activation of the RAAS. Indeed, Gilbert et al predicted that the renoprotective effect of the SGLT2i is mediated by its mechanism of RAAS blockade.

In the era of evidence-based medicine, a randomized controlled trial with a global setting is one of the most powerful forms of clinical trial to examine drug safety and efficacy. Asian populations reveal a higher prevalence of T2DM and CV events than Caucasian populations. The present study demonstrates a beneficial effect of empagliflozin on CV protection in an Asian population exposed to higher CV risk because of impaired insulin excretion with a genetic background.
model repeat measurement, which is generally applied to analysis of longitudinal data, especially when missing data is a matter of concern and missing at random is assumed. Presumably as a result of this limitation, there were no significant differences between the placebo and empagliflozin-treated arms in terms of CV events, including heart failure hospitalization, which is currently thought to be the primary factor of CV protection observed in the original EMPA-REG-OUTCOME study. Second, there was a distinct trend in the effect of empagliflozin on blood glucose control. In the EMPA-REG OUTCOME study, empagliflozin ameliorated hyperglycemia independent of its dosage. In the present subanalysis, the change in HbA1C levels from the baseline mediated by empagliflozin exhibited a trend of dose-dependency. To date, several studies, including the EMPA-REG OUTCOME study, have revealed that SGLT2i ameliorate HbA1C in a dose-independent manner. Further prospective study will be required to provide evidence that contributes to practical medical care of T2DM patients in Asia.

At the first introduction of SGLT2i into the clinical arena in Japan, both diabetologists and cardiologists hesitated to use this new antidiabetic drugs because of predictable concerns such as an increase in stroke incidence. Later, several studies reported that adverse events actually resulted from inappropriate prescriptions for diabetic patients with advanced age and/or low body weight. The EMPA-REG OUTCOME study overcame these initial concerns, which do not really matter at this moment in time. The EMPA-REG OUTCOME study has changed the balance between these prejudices and the practical effect(s) and we will soon learn from the evidence that will be provided by other ongoing clinical trials.

Acknowledgments
None.

Conflicts of Interest / Disclosure
T.M. has received research grants and lecture fees from Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Daiichi-Sankyo, Kowa, MSD, Pfizer, Takeda, and Tanabe-Mitsubishi. Y.K.B. received lecture fees and research grants from Asteras, AstraZeneca, Boehringer Ingelheim, MSD, Takeda, and Tanabe-Mitsubishi.

References