ISCP Guest Editorial

Cardiovascular Disease Prevention in Diabetes

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Type 2 diabetes is a major risk factor for the development of cardiovascular disease (CVD) such as MI, and cerebrovascular incidents such as stroke. A substantial body of evidence has indicated that the proper management of blood glucose in people with diabetes can inhibit the progression of microvascular disease such as retinopathy and nephropathy.

Nevertheless, whether strict blood glucose control is effective at reducing the risk of CVD in people with diabetes has long been debated. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, the overall mortality significantly increased by strict control of blood glucose (target HbA_{1c} < 6.0 %) compared with a less stringent control (target HbA_{1c} of approximately 7 %).¹ Strict glucose control resulted in a significantly higher likelihood of developing severe hypoglycaemia, leading to adverse events. Severe hypoglycaemia itself was associated with death due to CVD.²

The important point is that the risk of developing CVD increases from the early stages of an impairment in glucose tolerance. Previous epidemiological data have revealed that the risk of CVD or death begins to increase at an HbA_{1c} level of approximately 5 %.³ The risk of developing coronary artery disease in European and American men with an HbA_{1c} 5–5.4 % is 1.56 times higher than the risk in those with an HbA_{1c} < 5.0 %.⁴

In the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial, the administration of acarbose (an alpha-glucosidase inhibitor) to patients with impaired glucose tolerance prevented the progression to type 2 diabetes and significantly reduced the onset of CVD and hypertension.⁵

Sodium glucose cotransporter 2 (SGLT2) inhibitors lower blood glucose levels by reducing glucose reabsorption in the kidneys and eliminating glucose in the blood via urine. The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose (EMPA-REG OUTCOME) trial involved approximately 7,000 patients with type 2 diabetes and a history of CVD.⁶ The primary endpoint in this trial was a composite cardiovascular endpoint (cardiovascular death, MI or stroke), the incidence of which was significantly reduced by empagliflozin, an SGLT2 inhibitor. In particular, the incidence of cardiovascular death decreased by approximately 40 %. Among the trials involving patients with type 2 diabetes, the EMPA-REG OUTCOME trial was the first to find such a substantial reduction in cardiovascular events.

The detailed mechanism by which SGLT2 inhibitors effectively inhibit a composite cardiovascular endpoint is unclear. In addition to reducing plasma volume, improving haemodynamics and lowering blood glucose levels, SGLT2 inhibitors promote weight loss, reduce visceral fat, lower blood pressure, increase HDL cholesterol and decrease triglycerides and uric acid levels. As an overall consequence, SGLT2 inhibitors probably reduce oxidative stress and the hyperactivity of the sympathetic nervous system.

The Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors (CVD-REAL) study is an international large-scale observational study that retrospectively verified the efficacy of SGLT2 inhibitors in patients with type 2 diabetes.⁷ In that trial, hospitalisation due to heart failure decreased by 31 % in patients receiving SGLT2 inhibitors compared with patients treated with a hypoglycaemic drug other than SGLT2 inhibitors. This inhibition is

presumably related largely to the antihypertensive and diuretic actions of SGLT2 inhibitors. The trial also found that the overall mortality rate of patients decreased by 51 %. In that study, 87 % of the overall study population possessed no prior history of CVD. The mechanisms by which SGLT2 inhibitors reduce total mortality in patients both with and without CVD requires further study.

The results of epidemiological studies demonstrate that CVD risk increases before the onset of type 2 diabetes.^{3,4} Instead of blood glucose control in advanced diabetes, active intervention in patients in the early stages of impaired glucose tolerance may therefore be crucial for the inhibition of cardiovascular events. Thus, a more effective use of alpha-glucosidase inhibitors and SGLT2 inhibitors in such patients should be considered. ■

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