Severe Hypoglycemia and Cardiovascular Disease in Type 2 Diabetes

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Cardiovascular disease (CVD) is the main cause of morbidity and mortality in subjects with diabetes mellitus (DM). Strict glycemic control has been shown to reduce the risk of microvascular complications of DM, but its effects on the risk of CVD appear less conclusive. Recent large randomized trials have demonstrated that intensive glycemic control failed to show significant benefits on the macrovascular outcomes. In particular, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study has shown that participants in intensive therapy had 22% higher mortality with 3-fold higher incidence of severe hypoglycemia than those in standard therapy, suggesting a possible association between hypoglycemia and increased mortality [1]. However, the post hoc analysis of ACCORD study suggested that the high mortality in the intensive treatment group was not directly explained by higher rate of hypoglycemia [2]. In contrast, a retrospective analysis of the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study has shown that severe hypoglycemia is strongly associated with an increased risk of macrovascular events, presenting hypoglycemia as a possible cause for adverse cardiovascular events and deaths [3]. Furthermore, several epidemiologic studies have demonstrated that symptomatic or severe hypoglycemia is associated with an increased risk of cardiovascular events and mortality in patients with type 2 diabetes mellitus (T2DM) [4,5].

Hypoglycemia occurs commonly during the treatment of DM and is also a major hurdle to attaining better glycemic control. Experience of hypoglycemic episodes can discourage subjects with DM from achieving their glycemic goals, breaking patients’ will to keep optimal glycemic control. Among the categories of hypoglycemia, severe hypoglycemia is generally defined as an event that requires the assistance of another person to overcome hypoglycemia, posing a serious health problem in subjects with DM [6]. As discussed earlier, hypoglycemia appears to be associated with adverse cardiovascular events and deaths in large clinical trials and several epidemiologic studies, even though no direct evidence of causal relationship between hypoglycemia and increased cardiovascular mortality has been found in patients with DM until now. There are potential mechanisms by which acute hypoglycemia may increase cardiovascular events and deaths. Acute hypoglycemia induces sympathoadrenal activation, endothelial dysfunction, vasoconstriction, prolongation of QT interval, enhanced inflammation, and increased thrombogenesis [7-9]. All of these physiological changes may trigger myocardial ischemia and cardiac arrhythmia in patients with DM, which could cause adverse cardiovascular events and deaths (Fig. 1).

The major causes of hypoglycemic episodes in patients with T2DM are changes related to diet, exercise, or glucose-lowering medications. In addition, clinical factors that predispose to hypoglycemia include advanced age, polypharmacy, low education level, poor cognitive function, intensive glycemic control, longer duration of DM, and longer duration of insulin therapy. Peripheral or autonomic neuropathy is also associated with hypoglycemia [10]. In particular, hypoglycemia unawareness or a
A history of previous hypoglycemia may increase the risk of severe hypoglycemia. Albuminuria or impaired renal function is associated with hypoglycemia in patients with DM [11,12].

In this issue, Yun et al. [13] presented an article showing that a history of CVD might be an independent risk factor for the development of severe hypoglycemia in Korean patients with T2DM. They enrolled 894 patients with T2DM aged 25 to 75 years without chronic kidney disease and conducted a prospective cohort study. A total of 624 patients completed the follow-up with a median time of 9.5 years (5,814 person-years). They showed that the development of severe hypoglycemia was associated with a history of CVD after adjustment for age, sex, duration of T2DM, diabetic complications, insulin use, and glycosylated hemoglobin level. In a previous study from the same cohort, they demonstrated that the presence of definite cardiovascular autonomic neuropathy (CAN) was a prognostic factor for the development of severe hypoglycemia [10]. They found in this study that even after adjusting further for the presence of CAN, patients with a history of CVD had nearly 2-fold higher risk of future development of severe hypoglycemia compared with those without.

In accordance with these findings, several case-control or population-based studies in patients with T2DM have demonstrated that the presence of coronary heart disease or stroke might be an independent risk factor for severe hypoglycemia [14-16]. Moreover, a retrospective study in T2DM patients who were admitted for severe hypoglycemia has shown that patients with a history of coronary artery disease (CAD) are at an increased risk for recurrent hypoglycemia during the first 48 hours after admission compared with those without [17]. On the contrary, several conflicting data suggested that a history of prior CVD did not predict hypoglycemia in patients with DM [18-20]. Therefore, further studies in other races or ethnic groups will be necessary to confirm these findings.

As the authors noted, there are several limitations in this study. First, though the follow-up time is quite long, the size of study patients is relatively small. Second, the definition of CVD is narrow, which includes CAD and stroke but excludes peripheral artery disease. Moreover, plausible mechanisms relating a history of CVD to an elevated risk of severe hypoglycemia remain thus far speculative. Despite some limitations, the current study provides valuable information suggesting that a history of prior CVD is an independent risk factor for the future development of severe hypoglycemia in patients with T2DM, prompting practitioners to address this possibility in vulnerable patients. In addition, studies to explore the underlying mechanisms linking CVD with severe hypoglycemia are needed.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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