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Optimizing glucose control for diabetic patients undergoing percutaneous coronary intervention

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Diabetes mellitus (DM) is a major risk factor for atherosclerotic cardiovascular disease. Lowering blood glucose is an important medical intervention to prevent recurrence in patients with established atherosclerotic cardiovascular disease. However, lower has not been always better, until now.

Intensive glucose lowering improved the microvascular complications of DM, but not the macrovascular complications [1], with increased risks of hypoglycemia and mortality [2]. The paradoxical increase in mortality with aggressive glucose lowering, a U-shaped curve, has been reported in the general DM population [3,4]. Hypoglycemia during aggressive glucose lowering therapy has adverse effects on the cardiovascular system and worsens clinical outcomes [5].

There are several proposed explanations for worse outcomes with aggressive glucose lowering in DM patients. Patients experiencing hypoglycemic events generally have a poor nutritional state. Hypoglycemia causes oxidative stress and vascular inflammation. In addition, hypoglycemia activates the adrenergic system, and a hyperadrenergic state increases arrhythmogenic potential.

The relationship between hemoglobin A1c (HbA1c) and clinical outcome after percutaneous coronary intervention (PCI) is still debated. Hwang et al. [6] reported that a lower HbA1c level 2 years after PCI was associated with a decreased risk of major adverse cardiovascular events, mostly driven by a lower rate of target lesion revascularization. Corpus et al. [7] showed an association between a lower HbA1c level at the time of PCI and a decreased rate of target vessel revascularization, but another study by Lemesle et al. [8] failed to show a benefit of a lower HbA1c level.

The association between aggressive glucose lowering and an increased risk of mortality is not as evident in PCI patients as in the general DM population. Two recent studies reported worse outcomes after intensive glucose lowering in PCI patients. A Japanese study showed that tight glycemic control was associated with a higher risk of cardiovascular death compared with mild glycemic control in diabetics who underwent PCI [9]. A recently published single-center retrospective study in diabetics undergoing PCI showed that a low HbA1c level was associated with an increased risk of mortality, whereas a higher level was associated with an increased risk of myocardial infarction (MI) [10].

In this issue of the *Korean Journal of Internal Medicine*, Bae et al. [11] showed a lower incidence of major adverse cardiac and cerebrovascular events in patients with aggressive glycemic control.

The benefit of a lower Hb1Ac was driven mainly by a lower rate of stroke. Poor glycemic control induces pro-thrombotic states and causes thrombotic adverse events such as MI and revascularization. An increased risk of stroke in the uncontrolled group in this study is consistent with previous studies that showed an increased risk of thrombotic events in poorly controlled DM.

Compared with previous studies, this study has several strengths. The authors used the mean HbA1c level during follow-up instead of the initial HbA1c level at the time of PCI. Previous studies used the HbA1c level at a single time point such as at the time of PCI or 2 years after PCI. In this study, the average HbA1c level during follow-up reflected better the true levels of blood glucose during the study period compared with other studies. Another strength is the long-term follow-up duration (median duration > 6 years).

This study also had limitations, inherent in the retrospective study design. The groups were divided according to the achieved HbA1c level, and not by actual intensity of the glucose lowering treatment. Thus, the low HbA1c level in the active control (AC) group in this study was not necessarily the result of aggressive diabetes control but may also be because cases of easily controlled diabetes were included. The duration of DM was shorter in the AC group, and fewer patients in this group were on either an oral hypoglycemic agent or insulin treatment at baseline. Thus, there is the possibility that patients in the AC group may have had a lower atherosclerotic burden; therefore, a further randomized study is warranted to address these limitations.

The advent of antidiabetic medications with proven cardiovascular benefits is changing the DM treatment paradigm in the PCI population, from a focus on the blood glucose level to use of drug combinations tailored to improve cardiovascular outcomes. The DM treatment guidelines recommend the use of specific drugs with proven cardiovascular benefits for established cardiovascular disease, independent of the baseline HbA1c level [12].

Nonetheless, the challenge against the U-shaped curve will not cease in the era of new DM agents with less hypoglycemic side effects and proven cardiovascular benefits.

Conflict of interest

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

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