

## Hypoglycemia: Culprit or Bystander?

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In 2012, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes published a position statement on the management of hyperglycemia in patients with type 2 diabetes. This position statement emphasizes the need to individualize both glycemic targets and treatment strategies, with an emphasis on patient-centered approach and shared decision making [1]. In particular, although the ADA's "Standards of medical care in diabetes" recommends lowering glycosylated hemoglobin (HbA1c) to <7.0% as a general target to reduce the risk of microvascular complication, less strict HbA1c goals are allowed for patients with a history of severe hypoglycemia [2].


To date, there are a lot of epidemiologic and interventional studies showing the association between hypoglycemia and cardiovascular and all-cause mortality. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, total mortality was significantly higher in the intensive therapy group compared with conventional therapy group, which was mainly due to increased cardiovascular mortality [3] for which increased hypoglycemic event was suggested as a plausible explanation for the finding.

However, there is still much debate regarding whether hypoglycemia directly causes cardiovascular diseases or if it is just a marker of frailty and multiple comorbidities prone to adverse clinical outcomes. In a retrospective cohort study performed with patients admitted to general wards, hypoglycemia was associated with 1.7-fold increased in-hospital mortality. However, this greater risk was confined to patients with spontaneous hypoglycemia, whereas those with drug-associ-

ated hypoglycemia were independent from this risk factor. In addition, the association between spontaneous hypoglycemia and mortality became insignificant after adjusting for patient comorbidities. Therefore, the authors speculated that spontaneous hypoglycemia may be a marker of disease burden and susceptibility of hosts to multiple comorbidities, but it might not be a direct cause of mortality [4]. Similarly, increased mortality in patients with acute myocardial infarction was confined to patients who developed hypoglycemia spontaneously. In contrast, iatrogenic hypoglycemia after insulin therapy was not associated with higher mortality risk [5].

In this regards, Cha et al. [6] investigated the association between severe hypoglycemia and the risk of cardiovascular or all-cause mortality in 1,260 patients aged 25 to 75 years with type 2 diabetes. As a result, severe hypoglycemia was significantly associated with increased risks of all-cause mortality and cardiovascular mortality after adjusting for sex, age, diabetic duration, hypertension, mean HbA1c levels, diabetic nephropathy, lipid profiles, and insulin use. However, cardiovascular events comprised only 24.4% of all-cause death, whereas sepsis or infection and malignancy were the major causes of death in this population. Furthermore, the median time from the onset of severe hypoglycemia to the first cardiovascular death or death from any cause was within 3 years, thus severe hypoglycemia appears to reflect combined critical comorbidity or patients' vulnerability to any cause of death.

Some cautions are needed in interpreting current results. First, patients that are possibly more vulnerable to hypoglycemia and/or any cause of death were excluded from this study

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including elderly, mentally ill, unable to undertake self-care behaviors, previous episode of severe hypoglycemia, cognitive dysfunction, alcoholism, or any medical illness. Second, approximately 30% of participants were lost to follow-up, making it impossible to determine the hypoglycemic events and fate of this population. Third, the effect of minor hypoglycemia episodes on mortality was not evaluated.

In conclusion, although hypoglycemia is associated with cardiovascular or all-cause mortality, it is still elusive whether hypoglycemia directly causes adverse outcomes or if it simply reflects frailty and multiple comorbidities prone to adverse outcomes. There is some evidence that hypoglycemia is a marker of bad outcomes rather than being the direct cause for bad outcomes, and therefore physicians should pay attention to patients with hypoglycemia to prevent adverse outcomes.

## CONFLICTS OF INTEREST

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

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