

DIABETES

Severe hypoglycemia associated with risk of vascular events and death

Patients with type 2 diabetes mellitus who have severe hypoglycemia are at increased risk of major macrovascular and microvascular events and death, report researchers from the ADVANCE Collaborative Group.

Intense glucose control in patients with type 2 diabetes has been associated with increased incidence of severe hypoglycemia. Concerns have thus been raised that intensive antidiabetic therapy might increase the risk of severe complications and death in this patient population. Results from the ACCORD study, published in early 2010, established a link between severe hypoglycemia and increased mortality in a large population of patients with diabetes. This link, however, was not likely to explain the increased mortality found among patients receiving intensive antidiabetic therapy compared with those receiving standard treatment.

The ADVANCE study was a multicenter, international trial in which the effects of intensive and standard glucose-lowering approaches were compared in 11,140 patients with type 2 diabetes in an open-label fashion. The median follow-up was 5 years. Of note, intensive glucose control to a target glycated hemoglobin level of <6.5% was not associated with increased mortality

in this trial. A new analysis of data from ADVANCE shows that patients with severe hypoglycemia—whose blood glucose levels were <2.8 mmol/l or who had typical signs and symptoms of hypoglycemia and were unable to care for themselves owing to transient nervous system dysfunction—had a significant increase in the adjusted risk of major macrovascular events (hazard ratio [HR] 3.45, $P < 0.0001$), major microvascular events (HR 2.07, $P < 0.001$), cardiovascular-related death (HR 3.78, $P < 0.0001$), and all-cause death (HR 3.30, $P < 0.0001$). The risks of adverse nonvascular outcomes, such as certain respiratory, digestive, or skin disorders, were also significantly ($P < 0.05$) increased among patients with severe hypoglycemia. These associations were independent of the treatment group, although the presence of severe hypoglycemia was more frequent among patients under intensive glucose control.

The researchers have also identified several risk factors for severe hypoglycemia in patients with type 2 diabetes. Among the patients studied, those who were older, had had diabetes for longer, had renal impairment, lower BMI, lower cognitive function, used two or more glucose-lowering agents, had history of smoking or microvascular disease, or had been



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assigned to intensive glucose control were at increased risk.

Whether severe hypoglycemia has a direct causal role in triggering adverse events in patients with type 2 diabetes is still not clear. In fact, severe hypoglycemia might instead be a marker of a vulnerable state, in which patients are more susceptible to a variety of adverse clinical outcomes. “The experience of severe hypoglycemia should prompt investigation for [its] underlying cause, as well as review of glucose-lowering management, including diet and drug therapy,” concludes study investigator Sophia Zoungas.

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Original article Zoungas, S. *et al.* Severe hypoglycemia and risks of vascular events and death. *N. Engl. J. Med.* **363**, 1410–1418 (2010)