Severe hypoglycemia predicts major adverse outcomes in diabetic patients undergoing glycemic control regimes

Vascular diseases are the major causes of morbidity and mortality in patients with diabetes mellitus. Better glycemic control reduces microvascular and macrovascular complications in patients with diabetes mellitus. The two large clinical trials of glycemic control in patients with type 1 and type 2 diabetes mellitus, namely the Diabetes Control and Complications Trial (DCCT) and UK Prospective Diabetes Study (UKPDS), both showed significant decreases in microvascular complications with better glycemic control. In long-term extension studies, observations in both the DCCT and UKPDS showed reductions in macrovascular events in the intensively treated cohort. Since then, striving to achieve near normoglycemia became the key objective in the management of diabetes mellitus. Recently, the beneficial effects of more aggressive glycemic control in reducing vascular complications were investigated in the Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE), and Veterans Affairs Diabetes Trial (VADT) trials. In these trials, the HbA1c goals were set nearer to normal than that in the DCCT and UKPDS studies. All three studies failed to show any significant benefit of aggressive glycemic control in reducing the rate of primary outcome compared with standard therapy. In the ACCORD study, there were more deaths from any cause (primarily cardiovascular) and fewer non-fatal myocardial infarctions. Furthermore, a greater number of severe hypoglycemic episodes was reported in the intensive therapy group.

In the recently published comprehensive *post hoc* analysis of the ADVANCE trial, Zoungas *et al.*[1] examined the associations between severe hypoglycemia and adverse clinical outcomes among 11,140 patients with type 2 diabetes using Cox proportional hazards models with adjustment for covariates measured at baseline and after randomization. They found that at a median 5 years follow-up, 2.1% of patients had had one or more episodes of severe hypoglycemia. Multivariate analyses showed that severe hypoglycemia was associated with an increased risk of major macrovascular and microvascular events and death, complications previously attributed to hyperglycemia. Similar associations were apparent for a range of non-vascular outcomes, including respiratory, digestive, and skin conditions. However, no relationship was found between repeated episodes of severe hypoglycemia and vascular outcomes or death. Independent risk factors for severe hypoglycemia included variables such as older age, longer duration of diabetes, higher creatinine levels, lower body mass index, lower cognitive function, the use of two or more oral glucose-lowering drugs, a history of smoking or microvascular disease, and assignment to intensive glucose control.

Hypoglycemia is the most common side effect of treatment with insulin or sulphonylurea for diabetes, and is the single greatest barrier to drug adherence and the achievement and maintenance of good glycemic control. During an acute episode, hypoglycemia may precipitate and aggravate a vascular event via activation of the sympathetic nervous system and hemodynamic changes. Recently, Gill *et al.*[2] reported QT prolongation and cardiac rhythm disturbances in response to nocturnal hypoglycemia in ambulatory patients with type 1 diabetes, which may support the idea of an arrhythmic basis for sudden nocturnal death. In one study involving diabetic patients with coronary heart disease who were monitored continuously for blood glucose concentrations and electrocardiographic changes, it was demonstrated that there was chest pain associated with hypoglycemia in 20% of patients, of whom 40% had concomitant electrocardiogram (ECG) changes consistent with ischemia[3]. Asymptomatic hypoglycemia was also associated with ECG changes of ischemia in 14% of patients.

In the long term, repeated occurrences of hypoglycemic episodes may have cumulative effects that are detrimental to inflammation-based processes, such as atherogenesis and its thrombotic complications. Abnormalities in coagulation, fibrinolysis, and inflammation associated with the abnormalities in coagulation could be related to the induction and progression of atherosclerosis. In one case control study, Gimenezm *et al.*[4] found that the maximal flow-mediated brachial dilatation (FMD) was lower in diabetic patients with severe hypoglycemia than in those without. A significantly higher intima–media thickness (IMT) was also observed at both carotid and femoral sites.

In both the ADVANCE and ACCORD studies, annual mortality among patients who reported severe hypoglycemia was higher in the group receiving standard therapy than in the group receiving intensive treatment (Table 1). Despite the higher rate of severe hypoglycemia in the latter group, hypoglycemia was not considered a likely explanation for the excessive mortality associated with the intensive control in the ACCORD trial[5]. Although Zoungas *et al.*[1] did not find a consistent

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Table 1 | Annual rate of episodes of severe hypoglycemia and mortality according to glycemic control regimes

	Intensive	Standard	HR (95% CI)
Episode rate/person	0.007	0.004	1.86 (1.40–2.40)
Mortality rate* (%)	3.6	5.1	0.67 (0.37–1.21)

Data are modified from Zoungas *et al.*[1].
*In those with one or more episodes of severe hypoglycemia. HR, hazard ratio; CI, confidence interval.

dose–response or temporal relationship between severe hypoglycemia and adverse outcomes, suggesting that hypoglycemia is not a causal factor, the associations should not be ignored. The fact that hypoglycemia may often be asymptomatic leaves us with the possibility that it may be underreported. Thus, physicians should individualize treatment to avoid hypoglycemia. In adults with type 2 diabetes, treatment strategies should avoid therapeutic agents that can produce severe hypoglycemia. Many classes of pharmaceutical agents are not associated with severe hypoglycemia. Patients should be routinely questioned about hypoglycemic episodes and taught how to recognize, prevent, and treat hypoglycemia. Finally, it is plausible to take severe hypoglycemia as a marker of vulnerability to a wide range of adverse clinical outcomes, and the pathogenesis of diabetic vascular complications and their relationships with hypoglycemia have to be tackled with greater urgency.

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