Severe Hypoglycemia Signals Mortality Risk

BY MARY ANN MOON

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Severe hypoglycemia in patients with long-standing type 2 diabetes is strongly associated with adverse outcomes, including death from cardiovascular and noncardiovascular causes, according to a large analysis.

However, there is no close temporal relation between episodes of severe hypoglycemia and such adverse events, nor is there a dose-response relation in which more frequent episodes carry increasingly higher risks.

"Although our findings cannot exclude the possibility that severe hypoglycemia has a direct causal link with these outcomes, they suggest that it is as likely to be a marker of vulnerability to a wide range of clinical outcomes. In either case, the presence of severe hypoglycemia should raise clinical suspicion of the patient's susceptibility to adverse outcomes and prompt action to address this possibility," said Dr. Sophia Zoungas of the George Institute for International Health, University of Sydney, and her associates in the ADVANCE trial.

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation assessed 11,140 patients aged 55 years and older who had type 2 diabetes and were followed at 215 medical centers in 20 countries for a median of 5 years.

The study subjects were randomly assigned to receive either intensive or standard glucose-lowering therapy. A total of 231 (about 2%) reported experiencing 299 severe hypoglycemic events: 150 (2.7%) receiving intensive therapy reported 195 events and 81 (1.5%) receiving standard therapy reported 104 events.

Major macrovascular or microvascular events oc-

curred in 2,125 subjects, 87 of whom reported severe hypoglycemic events. And 1,031 subjects died, 45 of whom reported severe hypoglycemic events.

Nearly 17% of subjects who reported severe hypoglycemia subsequently had a major macrovascular event, 12% had a subsequent major microvascular event, and 20% died. In contrast, the corresponding proportions for subjects who did not report severe hypoglycemia were 10%, 10%, and 9%, respectively, the investigators said (N. Engl. J. Med. 2010;363:1410-8).

Also, risks for disorders of the respiratory system, digestive system, and skin were higher in patients who had severe hypoglycemic episodes than in those who did not.

Hypoglycemia conceivably could have contributed to both cardiovascular and noncardiovascular disorders and death by means of sympathoadrenal activation, abnormal cardiac repolarization, increased thrombogenesis, inflammation, or vasoconstriction. However, it is also possible, and more likely, that hypoglycemia merely reflected the effects of "coexisting conditions and unmeasured or incompletely quantified confounding variables," making it a marker rather than a direct cause of adverse outcomes, the investigators noted. ■

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Major Finding: Patients with type 2 diabetes who had episodes of severe hypoglycemia were at increased risk of major macrovascular events (hazard ratio, 2.88), major microvascular events (HR, 1.81), death from cardiovascular causes (HR, 2.68), and death from any cause (HR, 2.69), compared with patients who did not have severe hypoglycemia episodes.

Data Source: ADVANCE, an international, double-blind, randomized clinical trial comparing standard vs. intensive glucose-lowering therapy in 11,140 adults with longstanding type 2 diabetes.

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