Intensive Glucose Control May Be Overrated

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Intensive glucose control isn't any more effective than standard therapy at reducing the rates of major cardiovascular events, death, or microvascular disease in patients with poorly controlled type 2 diabetes, a large prospective study has concluded.

In fact, patients assigned to intensive therapy were significantly more likely to experience hypoglycemia, dyspnea, and other serious adverse events, according to Dr. William Duckworth of the Phoenix Veterans Affairs Health Care Center and his colleagues.

Given these findings, the authors recommended that preventive efforts focus on factors more directly tied to cardiovascular health. "For now, appropriate management of hypertension, dyslipidemia, and other cardiovascular risk factors appears to be the most effective approach to preventing cardiovascular morbidity and mortality" in these patients, the investigators wrote (N. Engl. J. Med. 2009, 360[2]:129-39).

The Veterans Affairs Diabetes Trial (VADT) examined the effect of intensive glucose control in 1,791 military veterans (mean age, 60 years) who had poorly controlled type 2 diabetes. Patients were randomized to either standard or intensive glucose control therapy. In both groups, obese patients (those with a body mass index of 27 kg/m^2 or greater) began with metformin plus rosiglitazone, and lean patients (with a BMI less than 27) began with glimepiride plus rosiglitazone. Intensive therapy groups began with maximum doses, whereas standard therapy groups started with half the maximum doses. The glucose targets were different for each group: The goal for the intensive therapy group was a hemoglobin A_{1c} (HbA_{1c}) level of less than 6%; the goal for the standard therapy group was less than 9%.

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The primary outcome was the time from randomization to a first major cardiovascular event, heart failure, surgery for vascular disease, or amputation for ischemic gangrene.

At 3 months, median HbA_{1c} had decreased in both groups; by 6 months, it had stabilized at 8% in the standard therapy group and 7% in the intensive therapy group.

After a median follow-up of 6 years, the investigators found that those in the intensive therapy group were 12% less likely than those in the standard care group to have had a cardiovascular event (not a significant difference). Nor were there significant differences in any of the individual cardiovascular end points, or in the rate of cardiovascular deaths.

Intensive therapy did not significantly affect any of the outcomes associated with microvascular disease. There were no significant between-group differences in amputation. And although the investigators found a slight reduction in diabetic retinopathy in the intensive therapy group, it was nonsignificant.

Intensive therapy did not significantly improve renal function or slow its decline, and was associated with a nonsignificant increase in autonomic neuropathy.

Patients in the intensive therapy group had significantly more adverse events than did those in the standard therapy group. The most common was hypoglycemia (1,566 vs. 432 incidents per 100 patient-years). Significantly more patients in the intensive therapy group had at least one serious adverse event (24% vs. 18%).

Among these, dyspnea was the most commonly reported.

There were 95 deaths from any cause in the standard therapy group, and 102 in the intensive therapy group, which was not a significant difference.

The results of VADT agree with those of two other large trials—ACCORD (Action to Control Cardiovascular Risk in Diabetes) and ADVANCE (Action in Diabetes and Vascular Disease)—that examined the effect of intensive glucose control, the authors said.

"Intensive glucose control did not reduce cardiovascular events [in these trials]. The ACCORD study was terminated at 3.5 years because of increased mortality in the intensive therapy group. The ADVANCE study showed a reduction in the progression of albuminuria, but there were no changes in the rates of severe nephropathy, retinopathy, or cardiovascular events."

The American Association of Clinical Endocrinologists (AACE) presented its perspectives of the VADT findings on the AACE Web site (www.aace.com). "All subjects were intensively treated to reduce LDL-cholesterol and blood pressure, to use antiplatelet therapies, and to stop tobacco use," AACE's Scientific Advisory Committee noted in a statement. "The cardiovascular event rate was much lower than anticipated, likely because of aggressive use of nonglycemic therapies, so that the study became underpowered for observing a difference in outcome based on glycemic control. Intensive glycemic control was associated with a three- to fourfold increase in hypoglycemia and with weight gain, but only with a modest reduction in cardiovascular events, nephropathy, and retinopathy."

For now, appropriate management of cardiovascular risk factors is the most effective approach to preventing cardiovascular mortality.

The study was sponsored by the Department of Veterans Affairs, the American Diabetes Association, and the National Eye Institute, with additional funding from various pharmaceutical companies.

Dr. Duckworth and his coauthors reported numerous financial connections with those companies. ■