Glycemic Goals Are Reaffirmed

HbA_{1c} *from page 1*

The three organizations conducted a careful reexamination of glycemic control guidelines in light of the findings from the Action to Control Cardiovascular Risk in Diabetes (ACCORD), the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE), and the Veterans Affairs Diabetes Trial (VADT). All showed no significant reduction in cardiovascular outcomes with intensive glucose control, but the ACCORD caused particular concern—and was halted early—because it showed a 22% increase in mortality among subjects randomized to a strategy of very intensive glycemic control with a target HbA_{1c} of less than 6% (N. Engl. J. Med. 2008;358:2545-9).

Still, "The evidence obtained from ACCORD, ADVANCE, and VADT does not suggest the need for major changes in glycemic control targets, but rather additional clarification of the language that has consistently stressed individualization," Dr. Jay S. Skyler and his associates wrote (Diabetes Care 2009;32:187-92).

Those clarifications include:

► To prevent microvascular and neuropathic complications in people with both type 1 and type 2 diabetes, the HbA_{1c} goal for nonpregnant adults in general remains less than 7%. This recommendation is based on robust data from long-term studies including the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS).

The American Association of Clinical Endocrinologists (AACE), which was not part of the group issuing the statement, recommends aiming for an HbA_{1c} level of 6.5% or less.

► The general HbA_{1c} goal of less than 7% also "appears reasonable" for prevention of macrovascular disease among those with recent onset of diabetes, based on long-term follow-up of the DCCT and UKPDS cohorts.

► For selected individual patients, even lower HbA_{1c} goals than the general goal of less than 7% might be reasonable, provided that this target can be achieved without significant hypoglycemia or other adverse effects of treatment. Such individuals might include those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease. This recommendation was based on subgroup analyses of the DCCT, UKPDS, and the microvascular evidence from the ADVANCE trial.

► Conversely, less stringent HbA_{1c} goals may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, or extensive comorbid conditions or those with longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management and education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents, including insulin.

► For primary and secondary cardiovascular risk reduction in patients with diabetes, providers should continue to follow the evidence-based recommendations for blood pressure treatment, lipid-lowering with statins, aspirin prophylaxis, smoking cessation, and healthy lifestyle behaviors delineated in the ADA Standards of Medical Care in Diabetes (Diabetes Care 2008;31[suppl 1]:s12-54) and the AHA/ADA guidelines for primary CVD prevention (Circulation 2007;115:114-26).

Dr. Gonzalez-Campoy, who serves on the AACE board of directors, agreed with the recommendations. "The ACCORD, ADVANCE, and VADT emphasize the need to individualize care. … The recent publications that show no benefit in cardiovascular outcomes with attempts at normalizing glycemic control were all done on people with [longstanding] type 2 diabetes. Therefore, these findings are not applicable to people with type 1 diabetes, nor do they apply to people with new-onset diabetes mellitus."

"People with type 2 diabetes who may achieve normal A_{1c} values with lifestyle changes alone, or with weight management, should not increase their A_{1c} values," Dr. Gonzalez-Campoy added.

Indeed, a substudy of VADT presented at the ADA's annual meeting in June suggested that individuals earlier in their history of type 2 diabetes had the most benefit of improved glycemic control, noted Dr. Daniel Einhorn, head of the Sharp Diabetes Treatment and Research Center, San Diego.

"The key is not to throw out the baby with the bathwater. The VADT and ACCORD suggest that some populations may not benefit from tight glycemic control and there may be risks associated with tight control in these same populations, i.e with cardiovascular disease and/or increased risk of hypoglycemia. This does not detract from the wealth of information that good glycemic control confers benefit on microvascular disease and, given a long enough window, cardiovascular disease," said Dr. Einhorn, also on the AACE board of directors.

Dr. Einhorn is a consultant to Takeda, Eli Lilly, Amylin Pharmaceuticals, and Merck.

Seven of the 11 members of the document's writing committee disclosed financial dualities of interest with companies that manufacture diabetes-related products. Dr. Skyler of the University of Miami reported receipt of fees totaling $10,000 per year or more from Amylin Pharmaceuticals, Dexcom Corp., Novo Nordisk, and Nutrition 21. Dr. Gonzalez-Campoy receives all grant support from the MNCOME Foundation. ■

Intensive Glucose Control Fails to Cut CV Risks, Mortality

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

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 prospective study of nearly 1,800 such patients has indicated.

In fact, patients assigned to intensive therapy were significantly more likely to experience hypoglycemia, dyspnea, and other serious adverse events, the investigators wrote.

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, wrote Dr. William Duckworth of the Phoenix Veterans Affairs Health Care Center and his colleagues (N. Engl. J. Med. 2008 Dec. 17 [doi:10.1056/NEJMoa0808431]).

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%.

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."

'Appropriate management of … risk factors appears to be the most effective approach.'

DR. DUCKWORTH

The American Association of Clinical Endocrinologists (AACE) presented its view of the VADT results 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. "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."

The committee emphasized that "AACE... continue[s] to advocate good glycemic control for diabetic patients, recognizing that treatment targets and strategies have to be individualized."

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. ■