Less-Stringent HbA_{1c} Goal May Be Appropriate

BY MITCHEL L. ZOLER

NEW YORK — Physicians need to be judicious in choosing a treatment goal for controlling glycemia in patients with type 2 diabetes, three studies have shown.

It may not always be necessary or appropriate to focus on treating a patient to achieve a hemoglobin A_{1c} level of less than 7.0%, Dr. John B. Buse said at a meeting sponsored by the American Diabetes Association.

In some patients, reaching a goal of less than 7.0% may require intensive treatment with multiple oral antidiabetes drugs, regimens that may cause more harm than good. And many patients are not good candidates for intensive, multidrug regimens because of comorbidities or a limited life expectancy.

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The recent study results were "a call to clinical judgment," said Dr. Buse, professor of medicine and director of the diabetes care center at the University of North Carolina at Chapel Hill. "A less stringent A_{1c} goal than less than 7.0% may be appropriate for patients with a history of severe hyperglycemia and a limited life expectancy," he said. "Do the best you can [in lowering a patient's HbA_{1c} level], but don't be a lunatic about it."

Another important message to physicians who treat patients with type 2 diabetes is to "deal with blood pressure and lipids at least as aggressively as you deal with glycemia," he said.

Dr. Buse gave the example of a patient with type 2 diabetes on a regimen of metformin and 60 U/day insulin who has an HbA_{1c} level of 7.2%, with a systolic blood pressure of 127 mm Hg and a serum LDL cholesterol level of 65 mg/dL. The patient maintains a good diet and regular exercise.

"I wouldn't add another oral antidiabetes drug to try to get this patient to an A_{1c} of 6.9%," he said. "I don't believe that for this patient it will make much difference to go from 7.2% to 6.9%." But, he added, he would probably take a different approach to adding more treatment if the patient's HbA_{1c} level was 7.8%, "or especially if it was 8.5%" on the same regimen of metformin and insulin.

"The [percentage] of patients with an A_{1c} of less than 7.0%, a systolic blood pressure of less than 130 mm Hg, and a serum level of [LDL] cholesterol of less than 100 mg/dL who are on daily aspirin and getting an annual flu shot is really small—less than 10%" of all U.S. patients with type 2 diabetes, Dr. Buse said in an interview. "This shows how complicated it is to take care of patients with diabetes."

The three studies he cited, which had their results reported last year or early this year, were the ACCORD, ADVANCE, and VADT trials. The results of all three showed that setting and reaching a target HbA_{1c} level of less than 7.0% in patients with type 2 diabetes did not uniformly result in improved patient outcomes.

The ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial randomized more than 10,000 patients with an average HbA_{1c} at baseline of 8.1% to a target HbA_{1c} of less than 6.0% or a target of 7%-8%. The HbA_{1c} level that was achieved during the study was an average of about 6.4% in the intensive-intervention group and an average of about 7.5% in the control group. During an average follow-up of 3.5 years, there was no significant difference in the rate of the primary outcome (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) in the two groups, but the intensively treated group did show a statistically significant increased rate of all-cause mortality (N. Engl. J. Med. 2008;358:2545-59). This finding led to a premature stop to the study. The researchers who ran the study concluded that the findings "identify a previously unrecognized harm of intensive glucose lowering in high-risk patients with type 2 diabetes."

The ADVANCE (Action in Diabetes and Vascular Disease) trial randomized more than 11,000 patients with an aver-

age baseline HbA_{1c} of 7.5% to an intensive regimen with a target HbA_{1c} of less than 6.5% or to a standard regimen. The achieved HbA_{1c} level was 6.5% with intensive treatment and 7.3% in the standard-treatment arm. After a median of 5 years, the intensive regimen led to a statistically significant reduction in the combined rate of macrovascular and microvascular events, and a significant cut in the rate of major microvascular events.

Nephropathy was the type of event most frequently prevented with intensive treatment. But the two treatment arms showed no significant differences in the rates of macrovascular events alone (MI, stroke, or cardiovascular death) or in the rates of cardiovascular death or death from any cause (N. Engl. J. Med. 2008;358:2560-72).

The VADT (Veterans Affairs Diabetes Trial) randomized nearly 1,800 patients with an average baseline HbA_{1c} level of 9.4% to either a standard regimen or an intensive regimen with a target HbA_{1c} level of 1.5% less than what would be achieved in the standard-treatment arm.

After 3 months, this goal was reached, with an average achieved HbA_{1c} level of 6.9% in the intensive-regimen group and an average level of 8.4% in the standard-treatment patients. After an average of 5.6 years, there was no significant difference in the primary outcome (the rate of major cardiovascular events, including MI, stroke, heart failure, surgery for vascular disease, cardiovascular death, or other cardiovascular events).

The two groups also showed no significant differences in the rate of cardiovascular death or the rate of all-cause death. And there were no significant differences in the rates of microvascular complications between the two groups (N. Engl. J. Med. 2009;360:129-39).

The results from these three studies led to a statement from an expert panel organized by the American Diabetes Association, the American College of Cardiology, and the American Heart Association (Diabetes Care 2009;32:187-92). In part, the statement said: "Less stringent A_{1c} goals than the general goal of less than 7% may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, or extensive comorbid conditions or [for] those with long-standing diabetes in whom the general goal is difficult to attain." ■