

HbA_{1c} for Diabetes Diagnosis Now Mainstream

International Expert Committee's consensus opinion endorsed by three major U.S. associations.

BY SHERRY BOSCHERT

SAN FRANCISCO — The use of a hemoglobin A_{1c} level of 6.5% or higher to diagnose type 2 diabetes is now mainstream, with formal endorsements from three major U.S. medical associations in 2010 supporting an International Expert Committee's 2009 consensus recommendations.

The World Health Organization and other groups are likely to follow suit, though with greater emphasis on this as an alternative to conventional means of diagnosing diabetes in regions that don't have easy access to standardized assays for HbA_{1c}. Dr. Richard M. Bergenstal said at a meeting sponsored by the American Diabetes Association.

He welcomed the change, and the rationale for using HbA_{1c} to diagnose diabetes. "Why do we follow it so closely once you're diagnosed, but pay no attention to it before you're diagnosed?" asked Dr. Bergenstal, president of medicine and science for the ADA and executive director of the International Diabetes Center, Saint Louis Park, Minn.

The International Expert Committee, with members appointed by the ADA, the European Association for the Study of Diabetes, and the International Diabetes Federation, got the ball rolling by publishing a consensus opinion in July 2009 to make HbA_{1c} the preferred test for diagnosing type 2 diabetes (Diabetes Care 2009;32:1327-34).

The ADA translated the international

consensus into clinical practice recommendations that were published in its annual update on standards of care in January 2010 (Diabetes Care 2010;33:S11-61). The ADA backed away from calling HbA_{1c} the preferred test, instead saying it's one of four diagnostic options, but acknowledged that it may become the most popular diagnostic test for type 2 diabetes.

The other, conventional diagnostic criteria are a fasting plasma glucose level of at least 126 mg/dL, an oral glucose tolerance test result of 200 mg/dL or higher, or classic symptoms of hyperglycemia plus a randomly obtained glucose level of at least 200 mg/dL.

The Endocrine Society endorsed the ADA clinical practice recommendations in a separate statement issued Jan. 20, 2010. The American Association of Clinical Endocrinologists followed with its own supportive statement on Feb. 1, 2010.

Inevitably, clinicians will have patients whose HbA_{1c} and glucose results conflict, Dr. Bergenstal noted. If one is abnormal and the other is not, repeat the abnormal test, the ADA recommendations say. "If that is still abnormal, you've made the diagnosis," he said. If, instead, you perform a third test method for con-

firmed and the result meets diagnostic criteria, diabetes is confirmed, he added.

Results are less clear when a patient has one normal and one abnormal test result, and repeating the abnormal test produces a normal result. "Then you have someone who is obviously on the edge" and who should be retested again in 3-6 months, he said.

Another gray area is the use of HbA_{1c} to define prediabetes (patients at high risk for developing diabetes or cardiovascular disease). The statements from the various groups differ somewhat in how they address this.

"I think everyone agrees that for at-risk patients, that's a little bit more of a judgment call," Dr. Bergenstal said.

The International Expert Committee suggested avoiding the concept of prediabetes because the risk is a continuum with a fairly steady rise in risk as HbA_{1c} levels increase. They identified HbA_{1c} levels of 6.0%-6.4% as "very high risk" while noting that people with lower HbA_{1c} levels also may have increased risk for diabetes if other risk factors are present. The Committee recommended starting preventive strategies depending on the intensity with which a clinician wants to deploy any available resources, he said.

The ADA's 2010 clinical practice recommendations declare HbA_{1c} levels of 5.7%-6.4% to be indicative of high risk,

and state that patients with these levels may be referred to as having prediabetes, Dr. Bergenstal said. "At 5.7% we thought the risk was really quite high, and that people deserved to have some kind of program" to prevent diabetes.

The American Association of Clinical Endocrinologists suggested that an HbA_{1c} level of 5.5%-6.4% may be a better cut-off to identify higher-risk patients.

Unlike the glucose tests, HbA_{1c} testing does not require patients to fast before testing, and carries several other advantages. Each of the statements supporting HbA_{1c} testing for diabetes diagnosis acknowledged a number of caveats, however, such as recognition that marginally elevated HbA_{1c} values in certain ethnic groups do not necessarily indicate diabetes. HbA_{1c} testing should not be used for diabetes diagnosis in patients with conditions that impair the correlation between HbA_{1c} and average blood glucose, such as iron deficiency or renal disease.

Only standardized, validated laboratory assays for HbA_{1c} were endorsed. Some of the newer point-of-care tests may be sufficiently accurate, but others are not, and more testing is needed before these can be endorsed for diabetes diagnosis, he said.

Dr. Bergenstal has held stock in Merck & Co. and participated in research or consulted for Abbott Diabetes Care, Amylin Pharmaceuticals, Bayer, Eli Lilly & Co., Intuity Medical, Lifescan (Johnson & Johnson), Mannkind, Medtronic, Merck, Novo Nordisk, ResMed, Roche Diagnostics Corp., Sanofi-Aventis, Pfizer, and Takeda Pharmaceuticals. ■

Push to Lower Hemoglobin A_{1c}, Back Off if No Response

BY SHERRY BOSCHERT

SAN FRANCISCO — It's okay to push for a rapid drop in high hemoglobin A_{1c} levels and tight glycemic control in patients with diabetes, but it's probably smart to ease up if there's no response within a year.

That's the key message from the recent major trials of aggressive glycemic control, Dr. Richard M. Bergenstal said at a meeting sponsored by the American Diabetes Association.

Many patients—but not all—can get their HbA_{1c} level below 7% and help prevent microvascular disease, if that's a goal the patient embraces and the physician provides the right therapies.

"Push hard, work with a team, make good choices, and if there's no response, be careful. Don't keep pushing, pushing, pushing," said Dr. Bergenstal, president of medicine and science for the ADA and executive director of the International Diabetes Center in Saint Louis Park, Minn.

HbA_{1c} levels plummeted in the first year of intensive treatment in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (N. Engl. J. Med. 2008;358:2545-59) but decreased more gradually in the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) trial (N. Engl. J. Med. 2008;358:2560-72).

Contrary to what many have presumed, however, the increased risk of death in the ACCORD trial in the in-

tensive-therapy group compared with the standard-therapy group was not associated with the fast decrease in HbA_{1c}, he said.

In a yet-to-be-published analysis, there was no increased mortality in ACCORD patients whose HbA_{1c} declined in the first year, and there was increased mortality if the HbA_{1c} did not drop. "It's just the opposite of what you might think. If you drop rapidly, you do fine. If you don't drop, you are at risk of dying," probably because "there's something going on in your life or in your physiology" that increases risk, Dr. Bergenstal said.

Pushing hard to get the HbA_{1c} level below 6% may be overkill if the patient is not responding, he added. This was the goal of intensive therapy in the ACCORD trial, which was associated with increased cardiovascular risk. The unpublished analysis, however, showed that patients on intensive therapy who achieved lower HbA_{1c} levels were less likely to die.

"So, yes, the ACCORD intensive group had higher mortality" compared with the standard-therapy group "but it was people who could not get to goal," Dr. Bergenstal explained. "If you are working hard, hard, hard and not getting a response, that is the person you back off on. They're not going to get to goal, and you're probably going to cause more harm than benefit." This shouldn't be an excuse for not trying to get HbA_{1c} down initially, however, at least to less than 7%, he added.

Lessons to be learned from these studies and the other recent major trial of tight glucose control, the Vet-

erans Affairs Diabetes Trial (VADT), go far beyond management of HbA_{1c}, Dr. Bergenstal said. "I think relying on the A_{1c} alone is causing part of the problem" in getting too few patients to glycemic goals, he said.

Organizing a clinical practice for success is a team effort that should include a nurse, educator, and/or pharmacist who can help monitor patients between physician visits and initiate a change in therapy according to an agreed-upon algorithm that serves as a checklist, not a cookbook, he suggested. A team helps motivate patient lifestyle changes and helps patients cope with pain or depression.

It's very important that patients and physicians agree on the goals of therapy, and that the right therapies are chosen to meet those goals, he added. Some patients, for example, may be more afraid of increasing their risk for hypoglycemic episodes with intensive therapy than of the risk for complications from higher HbA_{1c} levels. Others may be more concerned about avoiding the weight gain associated with some medications than about lowering HbA_{1c} levels.

Dr. Bergenstal has held stock in Merck & Co. and participated in research or been a consultant for that company as well as Abbott Diabetes Care, Amylin Pharmaceuticals, Bayer, Eli Lilly and Co., Intuity Medical, LifeScan (Johnson & Johnson), Mannkind Corp., Medtronic, Novo Nordisk, ResMed, Roche Diagnostics Corp., Sanofi-Aventis, Pfizer, and Takeda Pharmaceuticals. ■



If tests are inconclusive, a patient 'who is obviously on the edge' should be retested again in 3-6 months.

DR. BERGENSTAL