# ADA Officially Endorses $HbA_{1c}$ for Diagnosis

BY MIRIAM E. TUCKER

The American Diabetes Association has officially endorsed the use of hemoglobin $A_{1c}$ as an option for diagnosing diabetes.

In its Standards of Medical Care in Diabetes, updated annually, the ADA for the first time is officially endorsing the use of $HbA_{1c}$ as one of four options for diagnosing diabetes, with a cut-point of 6.5% or greater. Recommendations for use of the three previous diagnostic criteria remain unchanged, including a fasting plasma glucose (FPG) of 126 mg/dL or above, a 2-hour plasma glucose of 200 mg/dL or greater following a 75-g oral glucose tolerance test, or a random plasma glucose of 200 mg/dL or greater in an individual with classic symptoms of hyperglycemia (Diabetes Care 2010; doi: 10.2337/dc10-S011).

**The ADA decision is based in part on the fact that $HbA_{1c}$ assays are now highly standardized, and 'results can be uniformly applied both temporally and across populations.'**

In June 2009, the use of $HbA_{1c}$ for diabetes diagnosis was endorsed in a consensus statement by an expert panel comprising members of the ADA, the European Association for the Study of Diabetes, and the International Diabetes Federation (INTERNAL MEDICINE NEWS, June 15, 2009, p. 1). However, that statement was not the official position of the respective organizations (Diabetes Care 2009;32:1327-34).

The new ADA endorsement is based in part on the fact that $HbA_{1c}$ assays are now highly standardized, and "their results can be uniformly applied both temporally and across populations." In addition, epidemiologic data show a relation between $HbA_{1c}$ and the risk of retinopathy similar to that shown for corresponding FPG and 2-hour postprandial glucose thresholds. The $HbA_{1c}$ is also more convenient because fasting is not required, and is likely to be more stable than glucose measurements, the statement said.

The ADA acknowledged the greater cost of $HbA_{1c}$ testing, and the incomplete correlation between $HbA_{1c}$ and mean glucose levels in some individuals. Also, the $HbA_{1c}$ can be misleading in patients with certain forms of anemia and hemoglobinopathies. Indeed, unpublished data suggest that an $HbA_{1c}$ of 6.5% or higher identifies one-third fewer cases of undiagnosed diabetes than does a FPG of 126 mg/dL or greater.

However, the ADA said, "in practice, a large portion of the diabetic population remains unaware of their condition. Thus, the lower sensitivity of $A_{1c}$ at the designated cut-point may well be offset by the test's greater practicality, and wider application of a more convenient test ($A_{1c}$) may actually increase the number of diagnoses made."

Not everyone agrees. Dr. Zachary T. Bloomgarden of Mount Sinai School of Medicine, New York, said in an interview that although it may be appropriate to use $HbA_{1c}$ as a screening tool to determine who would be asked to return for an oral glucose tolerance test, he believes that using it for diagnosis is not appropriate because it could lead to overdiagnosis among people with high hemoglobin glycation, or "high glycators," and underdiagnosis of "low glycators."

## Criteria for the Diagnosis of Diabetes

1. Hemoglobin $A_{1c}$ 6.5% or greater.*

**or**

2. FPG 126 mg/dL or greater (fasting is defined as no caloric intake for at least 8 hours).*

**or**

3. Two-hour plasma glucose of 200 mg/dL or greater during an oral glucose tolerance test.*

**or**

4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose of 200 mg/dL or greater.

*In the absence of unequivocal hyperglycemia, criteria 1-3 should be confirmed by repeat testing.

Source: Diabetes Care 2010 (doi: 10.2337/dc10-S011).

For example, he said, older individuals have higher $HbA_{1c}$ levels than do younger people, and blacks have higher $HbA_{1c}$ levels than do whites for a given level of glucose tolerance, so these individuals might be systematically overdiagnosed. On the other hand, many ill persons seeing a physician for chronic kidney disease or other conditions associated with anemia might be low glycators, leading to underdiagnosis. "These are rather common, each certainly affecting 10% of the population," said Dr. Bloomgarden, editor of the Journal of Diabetes.

The ADA's decision to endorse the $HbA_{1c}$ as a diagnostic tool is "overall, not to my mind satisfactory," he added.

But Dr. Mayer Davidson, who was part of the expert panel that endorsed $HbA_{1c}$ for diagnosing diabetes last summer, is on the opposite end of the spectrum. He said the recommendation to use $HbA_{1c}$ for diabetes diagnosis is long overdue, and that the ADA erred in not removing glucose criteria as diagnostic options. The International Expert Committee had recommended use of the glucose criteria only if a standardized $HbA_{1c}$ assay was not available, he noted in an interview.

"Unfortunately, the ADA kept the glucose criteria, which will lead to the confusing situation of people who have diabetes by one criterion but not by the other when both are measured, which is likely to occur frequently," said Dr. Davidson, professor of medicine, Charles Drew University and University of California, Los Angeles.

Based on the expert committee's deliberations, it's likely that the ADA and the other organizations will ultimately transition to the use of $HbA_{1c}$ alone for diagnosis, but it may take time. Until then, he advises physicians who want to use repeat testing for diagnosis to stick to the a single test to avoid confusion. Bottom line: "One should not intermingle the glucose and $A_{1c}$ criteria."

Along with the 6.5% cutoff for diabetes diagnosis, the ADA now categorizes patients with $HbA_{1c}$ levels of 5.7%-6.4% under the new heading "Categories of Increased Risk for Diabetes," replacing "Diagnosis of Pre-Diabetes." The 5.7% threshold was derived from unpublished data suggesting that it has the best combination of sensitivity (39%) and specificity (91%) to identify cases of impaired fasting glucose.

Dr. Bloomgarden and Dr. Davidson reported having no financial disclosures. ■

# $HbA_{1c}$ Levels Above 8% Pose All-Cause Mortality Risk

BY MIRIAM E. TUCKER

MONTREAL — No difference in mortality was found at 4 years between baseline hemoglobin $A_{1c}$ levels of less than 6.5% and levels of 6.5%-7.0% in a prospective observational study of nearly 3,000 unselected patients with type 2 diabetes.

However, the Diabetes in Germany (DIG) study also found a dramatically increased risk of mortality for those with baseline $HbA_{1c}$ levels greater than 8%, compared with those who began the study with lower $HbA_{1c}$ values. Other baseline predictors of mortality included age, smoking, cardiovascular disease, and systolic blood pressure, Dr. Markolf Hanefeld reported at the World Diabetes Congress.

"In a diabetes population rather well controlled for hemoglobin $A_{1c}$, smoking status and good blood pressure control are of utmost importance for survival. However, at a level greater than 8%, [the degree of] glucose control becomes a serious risk factor for all-cause mortality," said Dr. Hanefeld of the Center for Clinical Studies, Technical University, Dresden, Germany.

Of an initial 4,020 unselected patients aged 35-80 years with type 2 diabetes from 238 sites in Germany, 2,784 completed the study at a median of 3.7 years and 175 died during that time. Most (86%) had no history of a major adverse cardiovascular event (MACE) at baseline, while 251 (8.5%) reported a first MACE during follow-up.

The average baseline $HbA_{1c}$ for the entire group was 7.0%. Thirty-seven percent met the International Diabetes Federation's and American Association of Clinical Endocrinologists' target $HbA_{1c}$ of less than 6.5%, whereas 57% met the American Diabetes Association's target of less than 7.0%. However, 29% had $HbA_{1c}$ values above 7.5%. The average $HbA_{1c}$ level for the entire group did not change over the 4-year period, Dr. Hanefeld said.

**Among those who died, 6% had baseline $HbA_{1c}$ values of less than 6.5%; 5.3% had values of 6.5%-6.9%; 5.1% had values of 7.0%-7.9%; and 7.6% had values of 8% or higher.**

Among those who died during the study period, 6% had baseline $HbA_{1c}$ values of less than 6.5%; 5.3% had values of 6.5%-6.9%; 5.1% had values of 7.0%-7.9%; and 7.6% had values of 8% or higher. The same trend was seen in MACE.

In a multivariate analysis, the most significant factor predicting mortality was MACE at baseline, conferring a twofold greater risk. Also significant were smoking, age, and systolic blood pressure. Female gender cut the risk by half. $HbA_{1c}$ did not contribute significantly to mortality, he said.

A comparison of these DIG findings with the standard care arms of the recent randomized, controlled glucose-lowering trials ADVANCE (Action in Diabetes and Vascular Disease), ACCORD (Action to Control Cardiovascular Risk in Diabetes), and VADT (Veterans Affairs Diabetes Trial) shows no link between $HbA_{1c}$ and mortality. In fact, the standard care arm of the ADVANCE study had the highest annual death rate (1.92%) but the second-lowest average $HbA_{1c}$ (7.5%). The 7.0% average $HbA_{1c}$ in DIG was the lowest of the four trials, but its annual mortality rate was 1.59% (for the entire group, since all were in "standard" care), higher than the 1.14 annual death rate in the standard care arm of ACCORD. That death rate in ACCORD's standard care arm was the lowest of the four studies, while the mean $HbA_{1c}$ was the second highest (8.3%, vs. 9.4% in VADT).

Dr. Hanefeld said he had no conflicts of interest. ■