Algorithm Improves Diagnostic Value of HbA_{1c}

BY MIRIAM E. TUCKER

FROM THE ANNUAL MEETING OF THE EUROPEAN ASSOCIATION FOR THE STUDY OF DIABETES

STOCKHOLM – Use of a "rule-in" hemoglobin A_{1c} cut point of 6.8% and a "rule-out" value of 5.8%, with glucose testing for individuals who fall in the middle of the diagnostic cutoff, was more accurate in diagnosing type 2 diabetes than was a single cutoff value of 6.5%.

The finding from a multiethnic cohort study of 8,696 previously undiagnosed primary care patients addresses some of the concerns about false-positive and false-negative diagnoses associated with using a single measure of hemoglobin A_{1c}. Multiple studies have shown that the 6.5% cutoff may be discordant with the results of an oral glucose tolerance test (OGTT), which is considered to be the standard diagnostic test for type 2 diabetes, said Dr. Samiul A. Mostafa, a clinical research fellow in the diabetes research unit of the University of Leicester (England).

In July 2009, an international expert committee recommended the use of hemoglobin A_{1c} for diagnosing diabetes, with a diagnostic cutoff of 6.5% or above following a repeat confirmatory A_{1c} test (Diabetes Care 2009;32:1327-34). In January 2010, the American Diabetes Association endorsed that recommendation (Diabetes Care 2010;33[suppl. 1]:S62-9). The European Association for the Study of Diabetes and the World Health Organization are expected to issue similar statements soon.

The study participants were identified from two systematic screening programs during 2002-2008. Three-quarters (75%) were white Europeans and 23% were South Asians from Pakistan, Bangladesh, and India. The mean HbA_{1c} for the entire cohort was 5.7%. All underwent an OGTT and also had their HbA_{1c} levels measured. Using the WHO criteria (a 2-hour plasma glucose level of 200 mg/dL or above, following a 75-g glucose load), the OGTT detected 291 individuals (3.3% of 8,696 study participants) with type 2 diabetes.

Among the white Europeans, use of the 6.5% A_{1c} cutoff had a sensitivity of 62% and a positive predictive value of 45%. Based on an Australian study published earlier this year, the investigators chose to compare those values with a rule-out A_{1c} cutoff of 5.5% and a rule-in cutoff of 7.0%, with a confirmatory OGTT used for those falling in between (Diabetes Care 2010;33:817-9).

That method gave an improved sensitivity of 98% and positive predictive value of 76% in the white European group. With either method, specificity and negative predictive values were close to 100%. For the South Asians, the 6.5% cutoff gave a sensitivity of 79% and positive predictive value of 36%, both of which improved to 99% and 68%, respectively, with the two–cut-point criteria. Again, specificity and negative predictive values were strong with either method, Dr. Mostafa reported.

"Impaired HbA_{1c}," the term used for the values between the two cutoffs (5.6%-6.9%), was found in 59% of the total cohort, who thus required confirmatory tests. Noting that those in the impaired HbA_{1c} group (55% of the total cohort) had A_{1c} values between 5.6% and 6.4% (that is, lower than 6.5%), they tried various cut points and arrived at a rule-out value of 5.8% or below and a rule-in value of 6.8% or above. That left 28% of the total cohort in the "impaired HbA_{1c}" category when defined as an HbA_{1c} of 5.9%-6.7%.

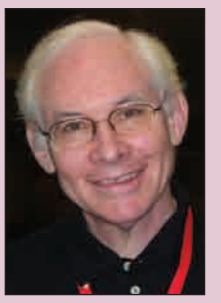
"We believe [a rule-out value of 5.8% and a rule-in value of 6.8%] would be a more feasible strategy to implement in clinical practice," Dr. Mostafa said.

These cutoffs gave sensitivities of 92% for white Europeans and 98% for South Asians, and positive predictive values of 70% and 54%, respectively, while maintaining the nearly 100% specificity and negative predictive values for both ethnicities. Despite the slight reductions in positive predictive values, "overall, we feel using the cut points of 5.8% and 6.8% is still diagnostically accurate, with the major advantage that only a quarter of the population would have to return for a subsequent test," he said.

Dr. Mostafa stated that he had no disclosures. ■

VIEW ON THE NEWS

Blood Glucose Tests Are Still Crucial



This study assesses a strategy that I think is quite reasonable, and was suggested in the American Association of Clinical Endocrinologists' position statement a number of months ago.

One must recognize that a "negative" hemoglobin A_{1c} level (below 6.5%) misses from one-third to one-half of those with diabetes by glucose tolerance test criteria, whereas a "positive" value (6.5% or greater) may not be the result of diabetes in persons who have greater degrees of hemoglobin glycation.

Because high glycation is present in blacks, older populations, and people with iron deficiency, and also is a common variant in the overall population, I would even suggest that blood glucose confirmation – although not necessarily with glucose tolerance testing – should be done in all persons with high HbA_{1c}, regardless of the level.

Similarly, there are people whose degree of hemoglobin glycation is lower than average. Thus, if there is clinical reason to look for diabetes, it is reasonable to perform glucose tolerance testing even with rather low HbA_{1c} levels.

Given this inherent variability in glycation, just as the 6.5% diagnostic cutoff is incorrect for many persons whose diabetes status is being ascertained, the use of a specific HbA_{1c} goal of, say, 6.5% or 7.0%, may not be appropriate for all patients with known diabetes. Again, assessment of actual blood glucose levels is crucial in the management of diabetes.

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FDA Wants Controlled tQT Study of Long-Acting Exenatide

BY EMILY HAYES

A long-acting formulation of exenatide has failed to pass muster with the Food and Drug Administration, which is asking the manufacturer Amylin for its most recent clinical trial results and a new QT prolongation analysis.

The FDA issued a complete response letter for the formulation, called Bydureon, the company announced last month. This is the agency's second complete response letter for Bydureon. The first, issued in March, had straightforward requirements, and Amylin responded within a month. However, the new request for a thorough QT prolongation study, which assesses effects on cardiac repolarization, could push the resubmission back by more than a year.

Complete response letters are not made public by the agency, and only the company can reveal contents at its discretion.

The FDA is also asking for results of a recently completed clinical trial, known as DURATION-5, which can be pulled together rapidly.

Amylin initially submitted the Bydureon new drug application (NDA) in May 2009, supported by the DURATION-1 head-to-head study of Bydureon vs. exenatide twice daily (Byetta), safety data from the DURATION-2 trial, and more than 7 years of clinical data.

DURATION-1 comprised 295 patients who did not achieve adequate glucose control either with use of diet and exercise or with oral glucose-lowering drugs. Exenatide once-weekly showed a statistically significant improvement in hemoglobin A_{1c} of approximately 1.9% from baseline, compared with an improvement of 1.5% for Byetta. About three-fourths of the study subjects who were treated with the long-acting drug achieved a hemoglobin A_{1c} level of 7% or less.

Regulatory requirements for diabetes drugs have tightened since the Byetta program began, however. In 2008, the FDA issued guidelines requiring manufacturers to monitor potential for cardiovascular events in new diabetes drugs, but this was not an issue for the Bydureon application.

Since 2005, the FDA has required thorough QT prolongation studies to support all NDAs – for all therapeutic categories – and this was at the heart of the FDA's complete response letter. Prolongation of the QT interval may signify increased risk of cardiac arrhythmia, a recurrent safety concern for new drugs.

Amylin executives said that they conducted extensive preclinical and clinical QT prolongation studies on Byetta, but did not find any signs of risk. A QT prolongation study was also conducted to support the Bydureon filing. But the study consisted of administration of a single 10-mcg dose of Byetta in healthy volunteers, and did not have a control arm.

In addition, a QT assessment had been done for Bydureon as part of the DURATION-1 study, including patients with mild to moderate renal impairment, and showed no signs of QT prolongation.

The FDA now wants Amylin to analyze exposures higher than typical therapeutic levels of Bydureon in a controlled thorough QT (tQT) study.

"The complete response letter was the first indication that this was an approvability issue," Amylin CEO Daniel Bradbury asserted during a conference call with investors and press.

Exenatide is cleared through the kidneys and the chief issue with Bydureon, which underlies regulators' concerns, appears to be that the drug persists in elevated levels in patients with renal impairment.

The agency has requested that the new tQT study include patients with pharmacokinetic concentrations consistent with levels seen in patients with renal impairment. ■

Emily Hayes is with "The Pink Sheet" which, along with this newspaper, is published by Elsevier.