Few Point-of-Care Hemoglobin A$_{1c}$ Assay Methods Meet Clinical Needs

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Accurate and timely measurements of hemoglobin A$_{1c}$ (Hb A$_{1c}$)$^2$ are an increasingly important challenge for clinical laboratories. As Hb A$_{1c}$ measurements are being used to answer new clinical questions, each new use of Hb A$_{1c}$ imposes requirements for the analytical performance of the methods used to measure it. Until recently, Hb A$_{1c}$ was used only as a key test for monitoring glycemic control in people with diabetes. More recently, it has been proposed as the preferred test for the diagnosis of diabetes ($1, 2$), and it is being used in many areas to calculate an estimated average glucose (eAG) concentration ($3, 4$).

The analytical requirements differ in these 3 uses of the test. In monitoring glycemic control, as with any test used for monitoring therapy, the reproducibility of Hb A$_{1c}$ is critical. Freedom from bias, however, has also become critical, because fixed cutpoints are being used as targets for glycemic control. When Hb A$_{1c}$ is used for measuring eAG concentrations, errors in the measurement may produce unexpectedly large changes in eAG. In the diagnosis of diabetes, fixed cutpoints are used, again requiring particular attention to the effect of bias on diagnostic accuracy. In addition to analytical requirements, there is pressure for rapid return of results in view of evidence that improved glycemic control can be achieved when Hb A$_{1c}$ results are made available at the point of care (POC) ($5, 6$). It is against this background that an important new report addresses the analytical performance of POC assays for Hb A$_{1c}$.

In this issue of *Clinical Chemistry*, Lenters-Westra and Slingerland ($7$) report on the imprecision, bias, and total error of 8 POC Hb A$_{1c}$ analyzers. The study used well-defined protocols from the CLSI and 3 appropriate secondary reference measurement procedures. Two of the 8 manufacturers withdrew from the study after initial unpromising results with their POC methods. Only 2 methods met an acceptance criterion of a total CV $<3\%$ in the clinically relevant concentration range, and only these 2 methods met the $<0.85\%$ error criterion of the National Glycohemoglobin Standardization Program (NGSP) with 2 different lots of reagent. These results have important clinical implications for monitoring therapy, calculating the eAG, and diagnosing diabetes or estimating the risk of developing diabetes.

**Hb A$_{1c}$ in Monitoring of Glycemic Control and Calculation of eAG**

When monitoring serial results for an assay, laboratories commonly follow the guideline that analytical imprecision should be less than one half the biological within-person imprecision ($8$). The CV for the mean within-person variation of Hb A$_{1c}$ derived from 6 studies is approximately 3.5\% ($http://www.westgard.com/guest17.htm; accessed October 27, 2009$). Thus, under this guideline the desirable analytical variation for Hb A$_{1c}$ would be a CV of $<2\%$. Although this $<2\%$ criterion can be met by several laboratory-based analyzers, only 2 of the POC analyzers evaluated by Lenters-Westra and Slingerland met this criterion. Statistical-modeling studies have also questioned the ability of POC devices to detect clinically important changes in Hb A$_{1c}$ ($9$).

For the use of Hb A$_{1c}$ in calculating eAG ($3$), it is important to consider total error. The data of Lenters-Westra and Slingerland showed total-error estimates that ranged from $−1.56\%$ to $+1.20\%$ Hb A$_{1c}$ units. At an underlying Hb A$_{1c}$ of 7\%, these total errors translate into relative errors of $−22\%$ to $+17\%$ in Hb A$_{1c}$. Such errors give even larger errors in eAG, $−29\%$ to $+22\%$. Such errors exceed the International Organization for Standardization total-error limit of 20\% that is currently used for glucose meters, a limit that itself has been criticized as too lax to meet medical needs ($10$).

**Hb A$_{1c}$ in the Diagnosis of Diabetes**

Hb A$_{1c}$ is recommended as the preferred test for the diagnosis of diabetes ($1$). This recommendation reflects, among other things, the important advances in the harmonization and standardization of Hb A$_{1c}$ assays that have been achieved by manufacturers working with national and international groups [e.g., ($11, 12$)].

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Received October 30, 2009; accepted November 2, 2009.  
Preceding published online at DOI: 10.1373/cinchem.2009.199865  
*Nonstandard abbreviations: Hb A$_{1c}$, hemoglobin A$_{1c}$; eAG, estimated average glucose; POC, point of care; NGSP, National Glycohemoglobin Standardization Program; CAP, College of American Pathologists.*
The International Expert Committee report on the role of Hb A1c in the diagnosis of diabetes (1) recommended that testing be performed in a central laboratory, noting that POC instruments have not yet been shown to be sufficiently accurate or precise for diagnosing diabetes (1). The data of Lenters-Westra and Slingerland (7) reinforce this viewpoint and suggest that most POC analyzers are not up to the task.

The danger of the use of POC Hb A1c analyzers for diagnosis can be appreciated by examining Hb A1c results for the general population of people with no history of diabetes, that is, the population of individuals who would be tested for the diagnosis of diabetes. At the recommended cutpoint of 6.5% for the diagnosis of diabetes, \(2.4 \times 10^6\) US adults are projected to have diabetes (13) (Fig. 1). Errors of measurement of Hb A1c will dramatically alter that prevalence. If, for example, Hb A1c is measured with a bias of +0.5% Hb A1c units (so that the true Hb A1c concentration is 0.5% units lower than the measured value), the prevalence of diabetes would nearly triple, from \(2.4 \times 10^6\) to \(7.1 \times 10^6\) people (Fig. 1). Among the POC devices tested by Lenters-Westra and Slingerland, biases ranged from approximately \(-0.9\%\) to \(0.4\%\) Hb A1c units. If such biases were present in diagnostic testing, either tens of millions of people would be wrongly diagnosed with diabetes, with the accompanying costs, or millions would not receive diabetes treatment of proven value.

Similarly, a study of POC analyzers reported that “18% of patients with HbA1c more than 7% by laboratory analysis were not identified as such by the POC test” (14). Thus, the accumulating evidence further supports the recommendation (1) that no POC device for measuring Hb A1c be used for the diagnosis of diabetes in the absence of evidence that it can meet analytical requirements appropriate for that use.

**Are Current Quality Specifications for Hb A1c Measurement Adequate to Meet Clinical Needs?**

The current quality specifications are not congruent with a desirable imprecision criterion based on biological variation. Currently, the NGSP requires that total error be demonstrated to be \(<0.85\%\) Hb A1c units for certification of Hb A1c assays by manufacturers. At an Hb A1c of 7% and with an Hb A1c assay with zero bias, this criterion translates into a total error of \(<12.1\%\) and thus to an assay imprecision CV of less than approximately 6%. This CV is more than 3 times the desirable criterion of a CV \(<2\%\) described above.

There is increasing recognition of a need to improve the precision of Hb A1c assays, in view of the low biological variability of Hb A1c. The NGSP plans to reduce the acceptability specification for level 1 laboratories to 0.70\% and for manufacturers of all Hb A1c methods to \(<0.75\%\) in 2010 (http://www.ngsp.org/...
ngsp/prog/News/manuf09.html; accessed October 28, 2009). The College of American Pathologists (CAP) also has recognized the need to tighten total error criteria for Hb A1c and is in the process of revising the criteria used in grading proficiency tests (http://www.ngsp.org/ngsp/prog/News/manuf09.html; accessed October 28, 2009). In 2007, the limit specified by the CAP for acceptability on Hb A1c proficiency testing was ±15% of the target value. This limit was lowered to ±12% in 2008 and to ±10% in 2009, and it will be lowered to ±8% in 2010 and to ±6% in 2011.

The CAP’s 2011 criterion of ±6% translates to an expected assay CV for imprecision of no more than 3%, and to even lower CV values in the presence of bias. These limits approach the desirable CV of <2% based on within-person biological variation. The data of Lenters-Westra and Slingerland (7) indicate that the manufacturers of most POC analyzers have their work cut out for them. The advances made in the analytical performance of laboratory-based Hb A1c analyzers suggest that meeting this criterion may be possible.

For the diagnosis of diabetes, it is clear from Fig. 1 that even small biases, especially positive biases, translate into misdiagnoses in large numbers of people. More consideration of this issue is needed, but it is clear that the biases of most POC Hb A1c analyzers reported by Lenters-Westra and Slingerland preclude their use for the diagnosis of diabetes.

The work of Lenters-Westra and Slingerland (7) should bring attention to the issues surrounding all Hb A1c analyzers, both POC-based and laboratory-based. We suggest that the marketing and sale of Hb A1c devices be contingent on the demonstration of analytical characteristics consistent with the intended uses of Hb A1c test results. The performance of some devices may be found adequate for one use (such as monitoring of therapy in diabetes) and not for another (e.g., diagnosis of diabetes). In places where payments are made to clinicians for testing, it would seem foolhardy to pay for Hb A1c testing of patients for the diagnosis of diabetes by a method that is not adequate for the purpose. Thus, the data of Lenters-Westra and Slingerland may take on significance for agencies such as the Food and Drug Administration and the Centers for Medicare and Medicaid Services in the US, and similar agencies elsewhere.

Lenters-Westra and Slingerland are to be thanked for providing a study that brings attention and facts to these important issues.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

References