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Analysis of Point-of-Care and Over-the-Counter Testing Methods for Hemoglobin A1c: How Good Do They Need To Be?

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Abstract

In this issue of Journal of Diabetes Science and Technology, Chang and colleagues evaluate the performance of the A1CNow® SELFCHECK device for measurement of hemoglobin A1c (HbA1c). The authors discuss the potential advantages of point-of-care (POC) HbA1c testing and also mention the importance of accuracy and precision and provide some data to document the device's performance. There are specific criteria for HbA1c method evaluation and proficiency testing used by the National Glycohemoglobin Standardization Program and the College of American Pathologists. Chang and colleagues mention these criteria but chose wider performance limits for their evaluation of the A1cNow SELFCHECK. Given the available data on the relationship between HbA1c and risk for complications, assay method performance is a vital consideration when HbA1c results, including those from POC methods, are used in the management of patients with diabetes.

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The prevalence of diabetes is increasing and currently affects more than 250 million people worldwide.[1] Measurement of hemoglobin A1c (HbA1c) is fundamental to the management of patients with diabetes and has recently been recommended for diabetes and prediabetes diagnosis as well.[2,3] There has therefore been much attention focused on performance criteria for this very important test.

Results from several large-scale prospective trials, most notably the Diabetes Control and Complications Trial (DCCT)[4] and the United Kingdom Prospective Diabetes Study[5] (UKPDS) have shown that HbA1c levels are directly related to risks for diabetic complications and that a relatively small difference in HbA1c levels (<1% HbA1c) represents a significant difference in outcome risks. After these trials, most clinical organizations recommended specific treatment goals based on the HbA1c results obtained during the studies. HbA1c levels of 6.5 and 7% (depending on the specific clinical organization) have been recommended as general goals.[3,6] This is a level that can be achieved by most patients without an unacceptable risk for hypoglycemia. In addition, some recommendations include a change in therapy if the HbA1c changes by 0.5%.[7]

The National Glycohemoglobin Standardization Program (NGSP) maintains a certification program whereby

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Abbreviations: (CAP) College of American Pathologists, (DCCT) Diabetes Control and Complications Trial, (HbA1c) hemoglobin A1c, (NGSP) National Glycohemoglobin Standardization Program, (POC) point-of-care, (PT) proficiency testing, (UKPDS) United Kingdom Prospective Diabetes Study

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manufacturers of HbA1c tests must show traceability to the results reported in these trials, and they must be traceable within specified limits.[8] The College of American Pathologists (CAP) has adopted the NGSP accuracy base to grade their proficiency testing (PT) results for HbA1c.[9] Both the NGSP and the CAP incorporate total error (combining accuracy and imprecision) for evaluation of results as passing or failing.

The difficult question is how accurate and precise does an assay method need to be for optimal clinical utility? This is a difficult question to answer. Many physicians assume that a result of 7% is exactly 7% and can be distinguished from 7.1 or 6.9%. Clearly this may not be a reasonable assumption, but how much variability is acceptable? Certainly, one would want to distinguish between an HbA1c of 7%, a general goal for most patients, and 8%, once labeled an "action limit." The difference between the mean HbA1c of the conventional and intensive groups in the UKPDS was <1% HbA1c (7 vs 7.9% HbA1c), and this represented statistically and clinically important differences in risks for complications. Most available assay methods can provide adequate bias and precision to give a clear distinction between these two results.

The NGSP criterion for manufacturer certification is that the 95% confidence interval of the differences between the method and the NGSP (in a 40-sample comparison with samples analyzed in duplicate during 5 days) be within ±0.75% HbA1c.[8] The CAP currently requires a PT result to be within ±8% of the NGSP-assigned value[9] and will tighten this to ±7% for 2011. More than 90% of participating laboratories are using methods that can meet these limits. Both NGSP and CAP criteria may be tightened again in the future.

In an article entitled *Evaluation of an Over-the-Counter Glycated Hemoglobin (A1C) Test Kit* in this issue of *Journal of Diabetes Science and Technology*, Chang and colleagues[10] evaluate the performance of the A1CNow® SELFCHECK device (Bayer HealthCare, LLC, Tarrytown, NY) for measurement of HbA1c by lay users and health care professionals. In their study, the potential benefits of POC HbA1c testing are discussed, and laboratory results from a venous blood sample are compared with A1CNow results. In the discussion, Chang and colleagues state that "to be effective in POC testing, it is important that an A1C test. . .provide accurate results comparable to laboratory analysis. . ." There are, of course, other important characteristics of POC devices such as ease of use and ability to have a result at the time of a clinic visit. But providing accurate results is paramount.

The authors mention that the A1CNow assay passes NGSP certification with the current 0.75% criteria, but they do not use these criteria for the evaluation presented here. They mention the 2008 CAP criterion of ±12%, but again, they don't use this for their method evaluation. Instead, the authors report that most results (93.2%) were within a range of ±13.5% of the laboratory value.

The authors do clearly show that there is very little bias throughout the clinically important HbA1c range, and this is important. However, their Figures 1 and 2 also show that there is a large amount of variability. Several results were outside ±1% HbA1c compared to the laboratory result. Also of concern is the fact that the average within-subject coefficient of variation was 4.57% (for subjects that tested twice). This is actually quite high, especially given that the all-method coefficient of variation (including between-laboratory and between-method variability) on the CAP survey is approximately 4.5%.

Another issue mentioned is the interference from hemoglobin variants. At least 300,000 Americans with diabetes have hemoglobin C or S trait.[11] Many do not know that they have these traits because there are generally no clinical symptoms associated with them. The A1CNow has been shown to exhibit both statistically and clinically significant positive biases in the presence of both C and S traits.[11] This overestimation of HbA1c could lead to overly aggressive treatment with a consequent increase in risk for hypoglycemia. Certainly any new version of the method should be reevaluated. Other methods have also shown interference from specific hemoglobin variants, and it is important for end users to know if their method has this type of interference. With some methods, such as immunoassays, the user would have no indication that a hemoglobin variant is present.

In summary, accurate and precise HbA1c measurement is essential to optimal diabetes care. Accuracy and precision limits that are based on clinical trial data and clinical recommendations have been set by both the NGSP and the CAP. Although there are specific advantages in the use of POC devices in some settings, they must still be held to the same standards as other HbA1c methods when they are used for the management of patients with diabetes.

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