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Glycated Hemoglobin Assessment in Clinical Practice: Comparison of the A1cNow™ Point-of-Care Device with Central Laboratory Testing (GOAL A1C Study)

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ABSTRACT

Background: The Glycemic Optimization with Algorithms and Labs At Po1nt of Care (GOAL A1C) Study assessed the effect of titration monitoring strategies and methods of A1C testing on glycemic control in patients with type 2 diabetes failing oral therapy and beginning basal insulin glargine. The availability of both point-of-care (POC) and central laboratory A1C values provided an opportunity to evaluate correlation and statistical agreement between these methods of testing. This analysis forms the basis of the current report.

Methods: This is a 24-week, randomized, four-arm, open-label study conducted in 7,758 subjects enrolled at 2,130 sites. At baseline, patients had A1C measurements both by POC testing using the A1cNow™ device (Metrika, Inc., Sunnyvale, CA), which applies an immunoassay method, and by central laboratory analysis using ion exchange high-performance liquid chromatography. These measures were compared statistically.

Results: An *r* value of 0.72 was calculated for POC and laboratory A1C assessments. Although the mean POC A1C values were in agreement with the central laboratory values, there was a large range in individual POC A1C values.

Conclusions: POC testing of A1C in predominantly primary care settings using the A1cNow device was correlated with central laboratory results. The correlation was less than expected based on each method's reproducibility data. Although there was agreement between the average POC A1C values and the corresponding central laboratory values, the dispersion of individual POC A1C values was large. Thus, we conclude that these two methods of A1C testing should not be used interchangeably.

INTRODUCTION

In type 1 and type 2 diabetes, improved glycemic control reduces the development and progression of microvascular and neuropathic complications.[1,2] Hemoglobin A1C (A1C) measures a patient's average glycemia over the preceding 2–3 months and predicts the risk of complications.[3–6] American Diabetes Association guidelines recommend A1C measurements

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twice per year in patients who are meeting glycemic goals, and quarterly in patients whose therapy has changed or who are not meeting goals.[7] Despite established guidelines and well-recognized clinical utility, A1C remains an underutilized test in clinical practice.[8] A1C assays that yield immediate results on testing in an office visit may facilitate more timely treatment modification or intensification.[9–12] Immediate feedback also provides an opportunity for improved interaction between physicians and patients with diabetes.[9,12]

The A1cNow™ device (Metrika, Inc., Sunnyvale, CA),[13] a rapid A1C testing device, was used in the Glycemic Optimization with Algorithms and Labs At Po1nt of Care (GOAL A1C) Study. The GOAL A1C study enrolled subjects with type 2 diabetes who had not achieved an A1C of <7.0% on oral antidiabetes agent therapy and were starting basal insulin glargine. The primary objectives were to assess the impact of two different titration monitoring strategies, as well as two different methods of A1C testing on glycemic control, and will be reported in full elsewhere. A post hoc analysis was conducted to evaluate the correlation and agreement between point-of-care (POC) A1C results and central laboratory results, and is the focus of this report.

SUBJECTS AND METHODS

Patients

The criteria for enrollment included type 2 diabetes of at least 1 year's duration, age 18 years or older, an A1C level >7.0%, current treatment with diet, exercise, oral antidiabetes agents, and eligibility for insulin therapy. All participants provided written informed consent. There was no formal screening period for this study; thus patients proceeded directly to randomization if they met the study criteria and the investigator determined that insulin therapy should be initiated.

Investigators

The study investigators (n = 2,685) were primarily internal medicine (42.42%) or primary care (33.52%) providers. Fewer than 10% were endocrinologists/diabetologists (9.61%), and the remainder were from another (i.e., pediatrics) or unidentified specialty.

A1C analysis

At baseline, A1C was assessed in each patient using both the POC A1cNow device (to determine eligibility) and laboratory A1C testing (used for efficacy assessments). Sample collection frequency was based on treatment arm assigned. For laboratory testing, blood samples for A1C were collected via fingerstick and capillary collection tube (Bio-Rad Laboratories, Hercules, CA), added to reagent, and transported to a central laboratory for measurement (Quest Diagnostics Clinical Trials, Van Nuys, CA). The central laboratory provided all supplies for specimen collection to the study sites. Blood samples were shipped within 24 h under ambient conditions via a Quest Diagnostics courier or FedEx if no courier was available in that area. All medical technologists who performed the testing were required by the State of California to have been licensed as Clinical Laboratory Scientists. Two levels of quality control are run per batch. Currently those levels are 5.7% and 9.8%, with target coefficients of variation (CVs) of 1.9% and 1.8%, respectively, for those levels. The maximum allowable CVs defined in the standard operating procedure and derived from the test validation for those levels 1 and 2 are 2.5% for the range of 4.0–6.5% and 3.0% for the range of 7.0–13.0%. Thus, the assay in routine operation is meeting the criteria as defined in the standard operating procedure for the method. The controls are Bio-Rad lyophilized A1c controls. Westgard rules are used to evaluate the control values and acceptability. Results from the Bio-Rad Variant ion exchange method used by the central laboratory were unaffected by interference from samples that contain hemoglobin C trait (HbC), but there may have been interference from the hemoglobin S trait (HbS). The A1C peak was separated and read by the photometer. If the peak could not be separated for any reason, no result was sent, and the sample was reported as having interference present.

The A1cNow is a small, single-use, disposable, POC, immunoassay device. A drop of blood obtained by a fingerstick is added to a reagent provided with the test kit, mixed by shaking, and then transferred with a pipette to a sample well in the device. Results are displayed in 8 min. Training on the use of the A1cNow was provided to all sites at the investigator meetings. The devices were sent from the manufacturer to a central location and dispensed to study sites as needed. Devices were kept refrigerated until they were used and were then discarded. The investigator or a designated trained sub-investigator or nurse coordinator performed the test with the device. More than 25 internal chemical and electronic control checks are built into the A1cNow software so that quality control checks are performed at several stages of device operation and result in display of error messages if there are any electronic, sample, chemistry, strip, or temperature problems. According to the manufacturer, the reportable range is 3.0–13.0% and normal range is 3.9–6.5%. At the time of this study, the CV was 6.8% for an A1C of 6.0%, and 6.0% for an A1C of 9.0%.[13] Samples with HbS and HbC may yield unreliable values.[14]

Statistical analysis

Least-squares means regression analysis (calculated on A1C values 8.0–12.0%) was used to assess agreement between the two methods of A1C testing; 95% confidence intervals on the estimate were also calculated. This range was chosen because regression analyses assume a normal distribution at each value. Since POC A1C levels <7.0% were not sent to a central laboratory (as these patients were excluded from the trial), and the upper limit of the A1cNow device was 13.0% (i.e., values greater than 13.0% would be displayed as ">13.0%" and thus would be excluded from analysis), the wider range of 7.0% and 13.0% could not be used without skewing the data in the tails of the distribution plot. The correlation coefficient (r) was calculated to describe the strength of association between POC and central laboratory A1C values. Bland-Altman differences (calculated on all available A1C values)[15] were determined as an additional measure of agreement. The Bland-Altman plot[15] is a graphical method used to compare two measurement techniques. Using this method, the differences (or, alternatively, the ratios) between POC A1C values and central laboratory were plotted against the central laboratory values.

Table 1. Baseline Demographics and Disease Characteristics

Characteristic	*Mean (SD)*
Age (years)	56.8 (11.8)
Sex	
Male	3,138 (50.4)[a]
Female	3,093 (49.6)[a]
Race	
White	4,366 (70.2)[a]
Black	986 (15.9)[a]
Hispanic	660 (10.6)[a]
Asian	153 (2.5)[a]
Other	54 (0.8)[a]
Body mass index (kg/m^2)	34.6 (7.5)
Duration of diabetes (years)	8.5 (6.4)
Fasting SMBG (mg/L)	208 (67.7)
POC A1C (%)	8.9 (1.4)
Laboratory A1C (%)	8.8 (1.3)

A total of 6,226 patients were enrolled. Variations in patient numbers are due to missing and/or outlying data points. SMBG, self-monitored blood glucose.

[a]Number (%).

Table 2. Correlation Between POC (A1cNow) and Laboratory A1C Testing

Population	*Correlation coefficient* (r)
Overall	0.72
Age (years)	
<50	0.71
50–65	0.72
>65	0.70
Gender	
Male	0.72
Female	0.72

RESULTS

Patients

A total of 7,758 subjects were enrolled from 2,130 sites.[16] At the time of this analysis, baseline POC and central laboratory A1C values were provided by 6,231 subjects (1,984 sites). Baseline demographic data from the study sample are presented in Table 1. About half of

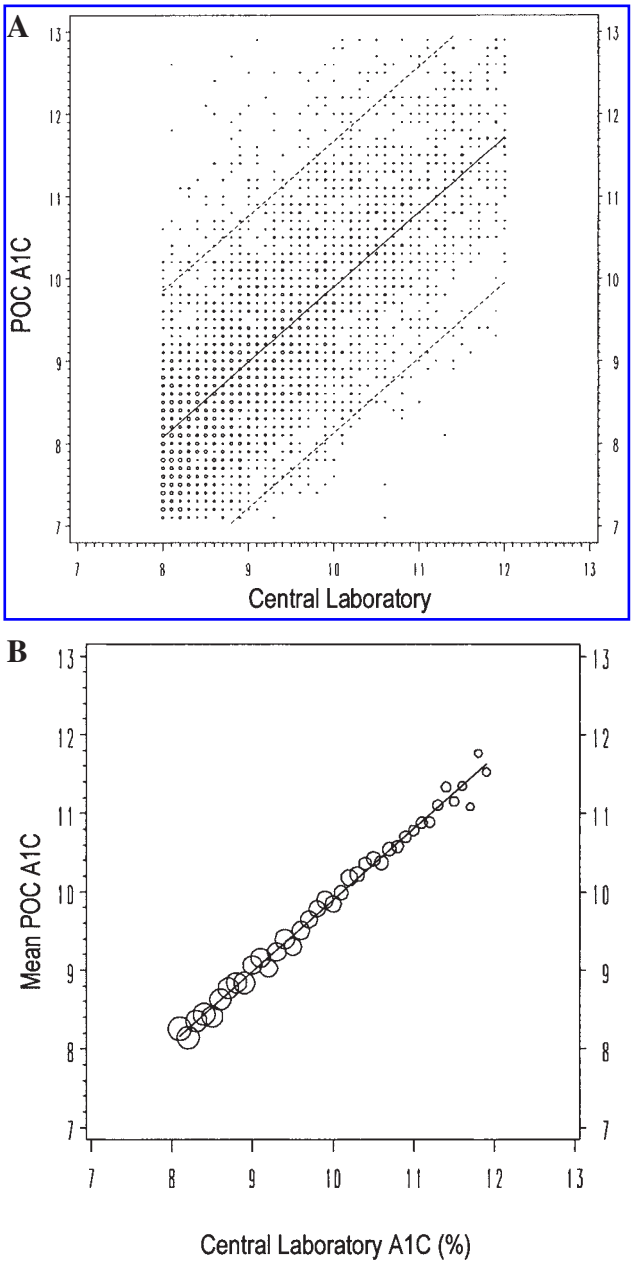

FIG. 1. Regression analysis of POC (A1cNow) versus central laboratory testing of A1C values. Solid line indicates estimated outcome [POC A1C = 0.79 + 0.91(Laboratory A1C)]; dashed lines indicate 95% confidence interval for the estimated outcome. The size of each bubble is indicative of the number of subjects with the corresponding value. **A:** Scatter plot of central laboratory A1C values and the corresponding individual POC A1C values. **B:** Agreement between the mean POC A1C values and central laboratory A1C values.

patients were women. Overall, the mean age of subjects was 57 years, with an average disease duration of 8.5 years. The majority of subjects were white (70%), followed by black (16%), Hispanic (11%), and other races.

Measures of A1C

The mean and median baseline A1C levels were 8.8% (SD 1.3) and 8.6% (interquartile range, 7.7–9.6%), respectively, with central laboratory testing. Similarly, mean and median baseline A1C levels for POC testing were 8.9% (SD 1.4) and 8.6% (interquartile range, 7.7–9.8%), respectively. There was a positive but clinically low correlation between the POC and the central laboratory technique ($r = 0.72$) that did not appear to be affected by age or gender (Table 2). Results of least-squares means regression analysis are presented in Figure 1. A large range was observed for the individual POC A1C values corresponding to each given central laboratory A1C value (Fig. 1A), although regression analysis demonstrated agreement between average POC A1C values and the central laboratory values (Fig. 1B). Figure 2 illustrates agreement of these values by using the Bland-Altman difference. The average of the POC and laboratory A1C was used as the best statistical estimate for "true value" of A1C. Of the patients, 32% and 20% were outside the limits of 0.75% and 1.0%, respectively.

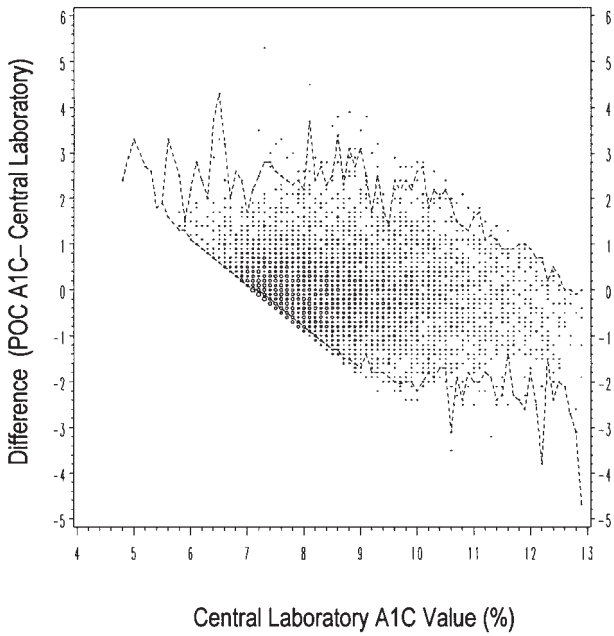

FIG. 2. Bland-Altman[15] analysis of the difference in A1C values [POC testing (A1cNow) vs. laboratory] by laboratory A1C values. The size of each bubble is indicative of the number of subjects with the corresponding value. The dashed lines indicate the 95th and 5th percentile of the difference.

CONCLUSIONS

POC measurement of A1C in the primary care office setting using the A1cNow device demonstrated a positive correlation with central laboratory measurements of A1C regardless of the age or gender of the patient. However, the correlation coefficient of 0.72 was not ideal. At the time this study was conducted, the A1cNow device had not yet received National Glycohemoglobin Standardization Program (NGSP) certification.[17] Metrika has since made improvements to its product, and the A1cNow device is now NGSP-certified, with a better reported correlation.[17–19] At the time of the study, Quest Diagnostics Clinical Trials was a Level II NGSP-certified laboratory (requires an accuracy of ±1.0% A1C to the NGSP secondary reference laboratory, which is checked annually); Quest is now level I NGSP-certified (requires an accuracy of ±0.75% A1C, with quarterly monitoring checks). The current correlation between A1C testing results obtained from these two methods would most likely be closer to 1.0%.

In this analysis, results obtained from the POC method may have been influenced by operator technique. Thus, another important source of variation is that more than 2,000 investigators were involved in the study. The aim of the overall study was to emulate standard clinical practice; thus A1C testing was not done in replicate, and more in-depth statistical evaluation of the relationship between the two methods of A1C testing was not possible. This also may have contributed to the variability in the data, but reflects "real world" use (such as home use) of this POC device.

These results suggest that, although the mean A1C values obtained using the POC device demonstrated agreement with the corresponding mean central laboratory A1C values, the dispersion of individual POC A1C values was very large, which raises concerns about the clinical utility of POC measurements obtained with a non–NGSP-certified device (Fig. 1B). The observed correlation between central laboratory A1C testing and non–NGSP-certified POC A1C testing is insufficient to support interchangeable use of these methods. Future studies with NGSP-certified POC devices may demonstrate better correlation with central A1C testing.

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