

University of Groningen

One in Five Laboratories Using Various Hemoglobin A(1c) Methods Do Not Meet the Criteria for Optimal Diabetes Care Management

Lenters-Westra, Erna; Weykamp, Cas; Schindhelm, Roger K.; Siebelder, Carla; Bilo, Henk J.; Slingerland, Robbert J.

Published in:
Diabetes technology & therapeutics

DOI:
[10.1089/dia.2010.0148](https://doi.org/10.1089/dia.2010.0148)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2011

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Lenters-Westra, E., Weykamp, C., Schindhelm, R. K., Siebelder, C., Bilo, H. J., & Slingerland, R. J. (2011). One in Five Laboratories Using Various Hemoglobin A(1c) Methods Do Not Meet the Criteria for Optimal Diabetes Care Management. *Diabetes technology & therapeutics*, 13(4), 429-433.
<https://doi.org/10.1089/dia.2010.0148>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

One in Five Laboratories Using Various Hemoglobin A_{1c} Methods Do Not Meet the Criteria for Optimal Diabetes Care Management

Erna Lenters-Westra, B.Sc.,^{1,2} Cas Weykamp, Ph.D.,³ Roger K. Schindhelm, M.D., Ph.D., MEPI,¹ Carla Siebelder, B.Sc.,³ Henk J. Bilo, M.D., Ph.D.,^{4,5} and Robbert J. Slingerland, Ph.D., EURCLINCHEM^{1,2}

Abstract

Background: We assessed the reference change value (RCV) of currently available hemoglobin A_{1c} (HbA_{1c}) laboratory assays, which is defined as the critical difference between two consecutive HbA_{1c} measurements representing a significant change in health status.

Methods: We examined the individual laboratory coefficients of variation (CVs) in the Dutch/Belgian quality scheme based on 24 lyophilized samples and calculated the RCV per laboratory ($n = 220$) and per assay method. In addition, two pooled whole blood samples were sent to the participating laboratories. The individual laboratory results were compared to the assigned value \pm an allowable total error (TE_a) of 6%.

Results: At HbA_{1c} values of 41.0 mmol/mol (5.9%-Diabetes Control and Complications Trial [DCCT]) and 61.8 mmol/mol (7.8%-DCCT), 99% and 98%, respectively, of the laboratories reported a value within a TE_a limit of 6%. The analytical CV of the HbA_{1c} method used in 78% of the laboratories is $<2.4\%$. The mean RCV at an HbA_{1c} value of 53 mmol/mol (7.0%-DCCT) for methods of Bio-Rad is 5.9 mmol/mol (0.59%-DCCT); for Arkray/Menarini, 4.3 mmol/mol (0.43%-DCCT); for Roche, 6.5 mmol/mol (0.65%-DCCT); for Tosoh, 3.3 mmol/mol (0.33%-DCCT); and for other methods, 6.3 mmol/mol (0.63%-DCCT).

Conclusions: The analytical performance of the majority of laboratory HbA_{1c} methods is within the clinical requirements. However, based on the calculated RCV, 21.8% of the laboratories using different HbA_{1c} methods are not able to distinguish an HbA_{1c} result of 59 mmol/mol (7.5%-DCCT) from a previous HbA_{1c} result of 53 mmol/mol (7.0%-DCCT). It can be presumed that differences in HbA_{1c} results of 5 mmol/mol (0.5%-DCCT) do influence treatment decisions.

Introduction

MONITORING GLYCEMIC CONTROL by using glycated hemoglobin A_{1c} (HbA_{1c}) measurements is one of the hallmarks in the management of diabetes mellitus to adjust therapy regimens and to aid in patient education.¹ In general, a target value of HbA_{1c} of less than 53 mmol/mol (7.0%-Diabetes Control and Complications Trial [DCCT]) is considered by many to be the treatment goal in order to reduce the risk of diabetes-related complications.^{2,3} The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) consensus algorithm for the initiation and adjustment of therapy states that a sustained HbA_{1c} level above 53 mmol/mol (7.0%-DCCT) should prompt the healthcare provider to consider changing therapy in order to reach the predefined target value.⁴ Indeed, the

ADA recommends performing HbA_{1c} testing at least twice a year in patients with stable glycemic control or four times per year in patients with changes in therapy or with HbA_{1c} levels above the target value.¹ The changes in therapeutic regimens are therefore guided by (relevant) changes in serial measurements of HbA_{1c} testing.

From an analytical point of view, the difference between two serial HbA_{1c} measurements depends on the coefficient of variation (CV): the intra-individual biological variation (CV_w) and the analytical variation (CV_a) of the HbA_{1c} laboratory assay. These two sources of variation can be combined in the so-called reference change value (RCV), which is the critical difference in the change in a patient's serial test results that can be considered significantly different at a probability of 95%.^{5,6} In other words, this means that if an RCV of 7.0 mmol/mol (0.7%-DCCT) HbA_{1c} units is found, an HbA_{1c} value of 58 mmol/mol

Departments of ¹Clinical Chemistry and ⁴Internal Medicine, Isala Klinieken, Zwolle, The Netherlands.

²European Reference Laboratory for Glycohemoglobin, Zwolle, The Netherlands.

³European Reference Laboratory for Glycohemoglobin, Winterswijk, The Netherlands.

⁵Department of Internal Medicine, University Medical Centre, Groningen, The Netherlands.

(7.5%-DCCT) would not be significantly different from a previous HbA_{1c} value of 53 mmol/mol (7.0%-DCCT).

Currently there are more than 30 HbA_{1c} laboratory methods available on the market, and information on the analytical performance of each assay method may not be readily available. In addition, the same HbA_{1c} assay may have different performance characteristics within and between various laboratories. External HbA_{1c} quality schemes reveal average analytical performance of the different HbA_{1c} methods used in the field and do not make available the results of individual laboratories to others besides the laboratory concerned. Indeed, the aggregated results, in general, indicate sufficient analytical performance of the majority of the methods but provide no insight in the performance of all laboratories individually.⁷

The aim of the current study was to present the analytical performance of a large portion of available HbA_{1c} laboratory assays currently available on the market, based on the individual results of the HbA_{1c} values of the participating laboratories in the Dutch and Belgian external quality scheme. Moreover, the results of a separate ring survey with fresh whole blood are presented. Based on this information we calculated the RCV, which may aid the healthcare professional to interpret differences in serial HbA_{1c} measurement results.

Research Design and Methods

The results of two External Quality Assurance Services (EQAS)—the Stichting Kwaliteitsbewaking Medische Laboratoria (SKML) in The Netherlands and the Wetenschappelijk Instituut voor de Volksgezondheid (WIV) in Belgium—and the results of a ring survey with two pooled fresh whole blood samples were used to assess the individual laboratory performance of various HbA_{1c} laboratory methods.⁸ Not all laboratories ($n = 550$) participated in the ring survey with two pooled fresh whole blood samples, and therefore only the results of the laboratories that submitted results in both surveys (SKML/WIV and fresh whole blood samples) were used ($n = 220$).

The design of the Dutch SKML and Belgian WIV scheme is based on 24 lyophilized interconnected samples. The samples are sent annually to all participating laboratories and stored at -20°C or below. Each sample is requested to be analyzed every fortnight, and the results are to be submitted to the website of SKML/WIV. The 24 samples were in fact 12 samples in duplicate. The duplicates were blinded to prevent any influence on results. From the duplicates the CV_a was calculated, using the following formula:

$$CV_a = \frac{\sqrt{\frac{\sum(\Delta)^2}{n}}}{\bar{x}\sqrt{2}} \times 100\% \quad (1)$$

where CV_a is the analytical CV, Δ is the difference between duplicates, n is the number of duplicates, and \bar{x} is the mean of the duplicates.

The CV_a was used to calculate the RCV, which is the critical difference in the change in a patient's serial test results that can be considered significantly different at a probability of 95%. The RCV is calculated with the following formula:^{5,6}

$$RCV (\%) = \sqrt{2} \times 1.96 \times \sqrt{[(CV_a)^2 + (CV_w)^2]} \quad (2)$$

where CV_a is the analytical CV and CV_w is the intra-individual or within-person biological CV.

For a healthcare provider to be able to conclude that a significant difference of 5.0 mmol/mol (0.5%-DCCT) at a medical decision point of 53 mmol/mol (7.0% DCCT) was caused by significant changes in glycemic control of a patient instead of analytical imprecision of the HbA_{1c} method, the percentage RCV should be $<7.1\%$ ($[0.5/7.0] \times 100 = 7.1\%$). This RCV results in a CV_a of 2.4% when applying a CV_w of 1%. We used a CV_w of 1%, in line with the data presented by Rohlfing et al.,⁹ who stated that in patients with diabetes, fluctuations in HbA_{1c} levels are not random, but should be considered pathologic, i.e., caused by changes in glycemic state. Furthermore, we calculated the RCV with a CV_w of 3.4%, in line with the data presented by Ricos et al. available on the Westgard website.¹⁰ Based on the percentage RCV and the HbA_{1c} medical decision point of 53 mmol/mol (7.0%-DCCT), the absolute RCVs of the various methods were derived (in mmol/mol and %-DCCT).

To avoid discussions about commutability of lyophilized samples for certain methods with respect to systematic error (bias), we used two pooled fresh whole blood samples that were sent halfway through the interval of the SKML/WIV scheme (in May) to the laboratories, similar to the College of American Pathologists' (CAP) survey.⁷ The values were assigned with five International Federation of Clinical Chemistry (IFCC) Secondary Reference Measurement procedures on two days in duplicate.¹¹ The acceptance limit of an allowable total error (TE_a) of 6% was used.¹² TE_a is calculated as follows:

$$TE_a (\%) = \text{bias} (\%) \pm 1.96 CV_a (\%) \quad (3)$$

Statistics

Computations were performed using Microsoft[®] Excel 2002 (Microsoft, Redmond, WA) software.

Results

Figures 1 and 2 show the results of the ring survey of two pooled fresh whole blood samples at respective HbA_{1c} values of 41.0 mmol/mol (5.9%-DCCT) and 61.8 mmol/mol (7.8%-DCCT). Of the laboratories, 99% and 98%, respectively, met the criterion of TE_a $<6\%$.

The calculated CV_a in the SKML survey gives an impression of the CV used in the laboratory over a longer time, as both duplicate samples are assayed over a period of several months. Of the HbA_{1c} laboratory methods, 69%, 78%, and 86% have a CV_a of $\leq 2.0\%$, $\leq 2.4\%$, and $\leq 3.0\%$, respectively (Table 1). One of the remarkable findings is that 41.9% of the laboratories using immunoassays have a CV_a $>3.0\%$ compared with only 10.4% of the laboratories using a high-performance liquid chromatography-based method.

Table 2 shows the results of the mean and the range of the absolute RCVs calculated at an HbA_{1c} value of 53 mmol/mol (7.0%-DCCT) with different intra-individual biological variations (1% and 3.4%). Fifty-nine percent of the laboratories using a method from Bio-Rad, 93% of the laboratories using a method from Arkray/Menarini, 42% of the laboratories using a method from Roche, and 95% of the laboratories using a method from Tosoh were able to meet the criterion of having a RCV of $<7.1\%$ at an HbA_{1c} value of 53 mmol/mol (7.0%-DCCT) calculated with a CV_w of 1%. Overall, almost 22% of

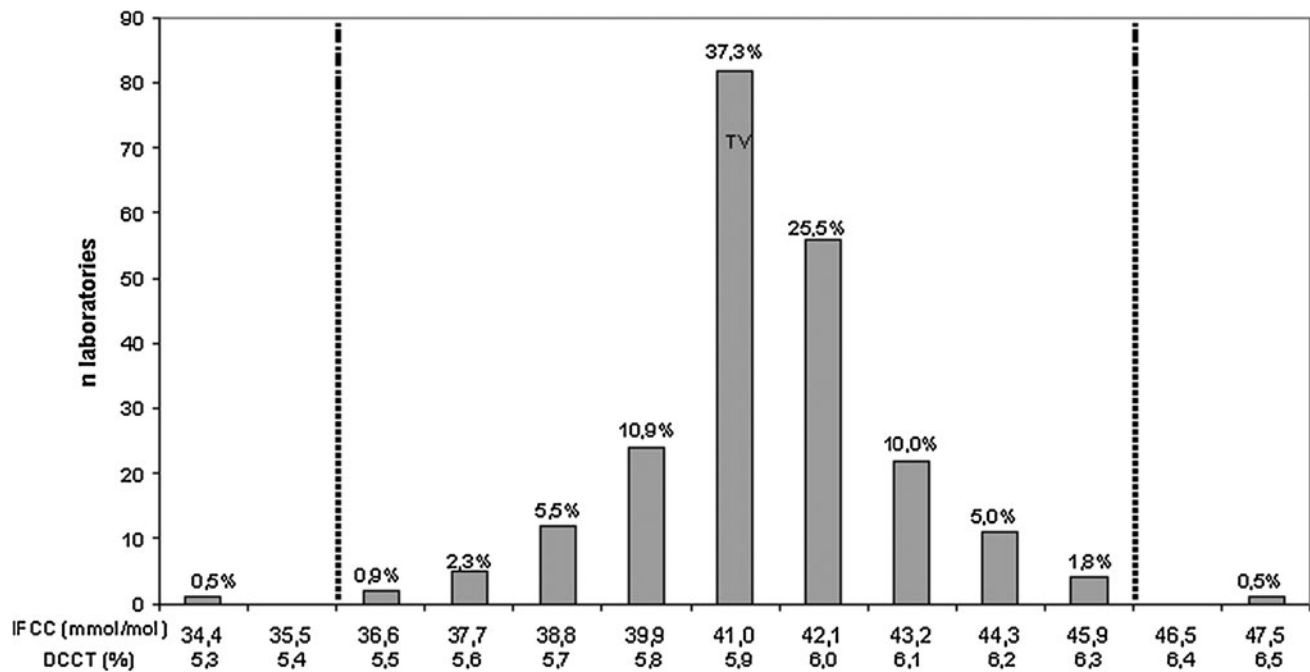


FIG. 1. Measured hemoglobin A_{1c} results compared with the target value (TV) of 41.0 mmol/mol (5.9%-Diabetes Control and Complications Trial [DCCT]) \pm allowable total error of 6%. IFCC, International Federation of Clinical Chemistry.

the methods used in laboratories were not able to distinguish an HbA_{1c} result of 59 mmol/mol (7.5%-DCCT) from a previous HbA_{1c} result of 53 mmol/mol (7.0%-DCCT). This means that one in five laboratories using various HbA_{1c} methods do not meet the criteria for optimal diabetes care management.

Discussion

In this study we derived the CV_a from the individual participating laboratories in the Dutch SKML/Belgian WIV

external quality scheme. Almost every laboratory was able to report HbA_{1c} results within a TE_a limit of 6%. However, based on the calculated RCVs, almost 22% of HbA_{1c} methods are not able to distinguish an HbA_{1c} result of 59 mmol/mol (7.5%-DCCT) from a previous HbA_{1c} result of 53 mmol/mol (7.0%-DCCT). This may have a profound impact on the management of patients with diabetes if changes in medication are made due to changes in serial HbA_{1c} measurements. Indeed, the International Diabetes Federation recommends starting insulin therapy above an HbA_{1c} value 58 mmol/mol

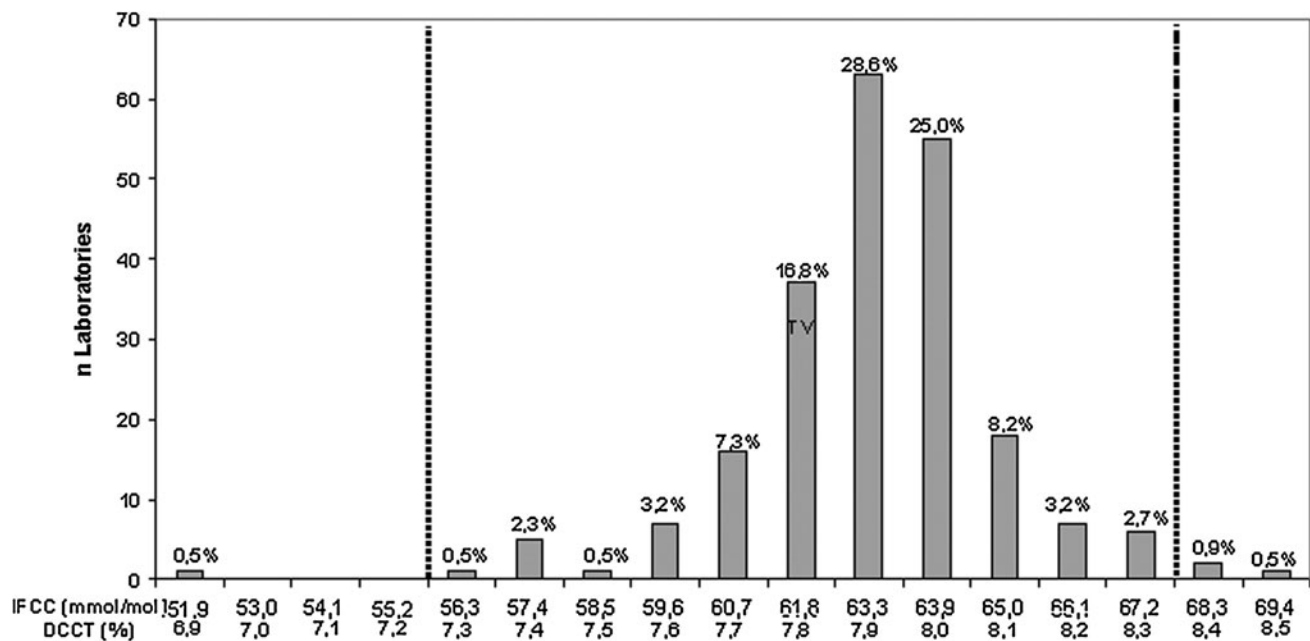


FIG. 2. Measured hemoglobin A_{1c} results compared with the target value (TV) of 61.8 mmol/mol (7.8%-Diabetes Control and Complications Trial [DCCT]) \pm allowable total error of 6%. IFCC, International Federation of Clinical Chemistry.

TABLE 1. ANALYTICAL COEFFICIENT OF VARIATION FROM DIFFERENT HEMOGLOBIN A_{1c} METHODS

	n	Range CV _a	Mean CV _a	CV _a ≤3.0%	CV _a ≤2.4%	CV _a ≤2.0%
Bio-Rad (HPLC)						
D-10 A1c Program	14	0.9–6.4	3.1	10 (71%)	8 (57%)	3 (21%)
Variant II HbA1c	6	2.0–7.0	3.6	4 (67%)	3 (50%)	2 (33%)
Variant II Dual A1C Program	4	1.7–3.6	2.0	2 (50%)	1 (25%)	1 (25%)
Variant II Turbo A1C Program	8	1.6–2.7	2.0	8 (100%)	7 (88%)	5 (63%)
Arkray/Menarini (HPLC)						
HA-8140 DM	11	0.8–5.8	2.0	10 (91%)	9 (82%)	6 (55%)
HA-8160 TP	6	1.1–4.6	2.3	4 (67%)	4 (67%)	3 (50%)
HA-8160 VP	98	0.5–7.7	1.5	93 (95%)	89 (91%)	82 (84%)
Roche (immunoassay)						
Cobas (501-311-111)*	10	1.7–4.5	2.9	5 (50%)	3 (30%)	1 (10%)
Integra 400/800	14	0.7–14.8	3.3	11 (79%)	7 (50%)	6 (43%)
Tosoh (HPLC)						
G7	20	0.6–5.4	1.5	19 (95%)	18 (90%)	17 (85%)
G8	17	0.5–1.5	1.0	17 (100%)	17 (100%)	17 (100%)
Others [†]	12	1.1–6.1	3.0	7 (58%)	6 (50%)	6 (50%)

Bio-Rad, Hercules, CA; Arkray/Menarini, Kyoto, Japan and Florence, Italy, respectively; Roche, Basel, Switzerland; Tosoh, Tokyo, Japan.
*Whole blood and hemolysate mode.

[†]Beckman Coulter (Brea, CA) Synchron LX, Beckman Unicel DxC, Siemens (Munich, Germany) Dimension RxL, Vitros[®] 5,1 FS (Johnson & Johnson, Raritan, NJ), Trinity Biotech (Bray, County Wicklow, Ireland) Ultra² HPLC and PDQPlus, Roche Hitachi (902-911-912-Modular) Tina-quant.

CV_a, analytical coefficient of variation; HPLC, high-performance liquid chromatography.

(7.5%-DCCT),¹³ and the ADA/EASD consensus statement states that therapy changes should be initiated if HbA_{1c} levels are above 53 mmol/mol (7.0%-DCCT).⁴ However, if the analytical variability of the laboratory assay is >2.4%, corresponding to an RCV of >5.0 mmol/mol (>0.5%-DCCT), a clear distinction based on patient health status between 53 mmol/mol (7.0%-DCCT) and 58 mmol/mol (7.5%-DCCT)

is not possible. It is important that the limitations of current HbA_{1c} laboratory methods are understood by healthcare professionals as these may have important clinical implications.

The design of the Dutch/Belgian SKML/WIV scheme differs in approach compared with the CAP survey. The CAP survey sends three fresh pooled samples to all participating laboratories

TABLE 2. ABSOLUTE REFERENCE CHANGE VALUES (%-DIABETES CONTROL AND COMPLICATIONS TRIAL) AT A HEMOGLOBIN A_{1c} VALUE OF 53.0 MMOL/MOL (7.0%-DIABETES CONTROL AND COMPLICATIONS TRIAL) CALCULATED WITH DIFFERENT INTRA-INDIVIDUAL BIOLOGICAL VARIATIONS

	n	CV _w 1%		CV _w 3.4%	
		Range RCV	Mean RCV	Range CV	Mean RCV
Bio-Rad (HPLC)					
D-10 A1c Program	14	0.26–1.25	0.63	0.68–1.40	0.91
Variant II HbA1c	6	0.33–1.37	0.73	0.71–1.51	1.00
Variant II Dual A1C Program	4	0.38–0.72	0.57	0.74–0.86	0.86
Variant II Turbo A1C Program	8	0.37–0.56	0.43	0.73–0.84	0.77
Arkray/Menarini (HPLC)					
HA-8140 DM	11	0.21–1.14	0.45	0.66–1.30	0.79
HA-8160 TP	6	0.29–0.91	0.49	0.69–1.11	0.82
HA-8160 VP	98	0.22–1.50	0.36	0.67–1.63	0.74
Roche (immunoassay)					
Cobas (501 – 311-111)*	10	0.38–0.89	0.62	0.74–1.09	0.89
Integra 400/800	14	0.24–2.87	0.68	0.67–2.94	0.97
Tosoh (HPLC)					
G7	20	0.23–1.06	0.37	0.67–1.24	0.74
G8	17	0.21–0.37	0.28	0.66–0.73	0.69
Others [†]	12	0.29–1.20	0.63	0.69–1.35	0.91

For clarity of presentation, only Diabetes Control and Complications Trial (DCCT) values are shown. Bio-Rad, Hercules, CA; Arkray/Menarini, Kyoto, Japan and Florence, Italy, respectively; Roche, Basel, Switzerland; Tosoh, Tokyo, Japan.

*Whole blood and hemolysate mode.

[†]Beckman Coulter (Brea, CA) Synchron LX, Beckman Unicel DxC, Siemens (Munich, Germany) Dimension RxL, Vitros[®] 5,1 FS (Johnson & Johnson, Raritan, NJ), Trinity Biotech (Bray, County Wicklow, Ireland) Ultra² HPLC and PDQPlus, Roche Hitachi (902-911-912-Modular) Tina-quant.

CV, coefficient of variation; CV_w, intra-individual biological CV; HPLC, high-performance liquid chromatography; RCV, reference change value.

twice a year. Results are presented per method, number of laboratories applying that method, mean bias, and inter-method/laboratory CV. The current CAP acceptance limit is 8% but will be tightened to 6% in the future.¹² The design of the Dutch SKML/Belgian WIV scheme is based on 24 lyophilized inter-connected samples. The advantage of lyophilized samples is the long-term stability; therefore, analytical variation can be determined over a longer period of time. However, the best way to assess the RCV is with controls, based on patient material, analyzed daily on the HbA_{1c} instrument. The results of the two pooled fresh whole blood samples showed sufficient analytical performance of almost every method used in a laboratory based on a TE_a of 6%. Although a CV_a of 3% is a realistic goal, a value of less than 2% is definitely desirable.¹⁴⁻¹⁶ Indeed, our results suggest that a value of less than 2.4% should be implemented in order to be able to detect changes in HbA_{1c} levels of 5.0 mmol/mol (0.5%-DCCT).

We chose to use a CV_w of 1% to calculate the RCV. On the Westgard website¹⁰ Ricos et al. presented a CV_w of 3.4%. Applying a CV_w of 3.4% results in an absolute RCV of 6.6 mmol/mol (0.66%-DCCT) at a medical decision point of 53 mmol/mol (7.0%-DCCT) without taking into account analytical variation. Rohlfling et al.⁹ suggested a CV_w of <1%, which seems more appropriate and was also supported by our own data (E.L.-W., unpublished data). Hence, a CV_w of 3.4% implies that the CV_a could not have a significant impact on the RCV, and therefore changes in serial HbA_{1c} would mostly rely on biological variation, which seems unlikely.

Conclusions

Thus, the analytical performance of some HbA_{1c} methods is not accurate enough to sufficiently support treatment decisions in the management of patients with diabetes when differences in serial HbA_{1c} measurements amount to 5 mmol/mol (0.5%-DCCT) or less. ADA guidelines for treatment of patients with diabetes may assume higher-quality laboratory testing than might be available in the real world. Laboratories using methods with a CV_a >2.4% should consider changing to a method with better precision. In our opinion, the laboratory-specific RCV should be provided to the healthcare professional in order to make this professional aware of the fact that changes in serial HbA_{1c} results might not be caused by true changes in the degree of glucose control, but also may be due to the variability of the method used to measure HbA_{1c} in a specific laboratory.

Acknowledgments

This manuscript could not have been written without having the results of the Dutch SKML and Belgian WIV. We thank the SKML and WIV for sharing these results with us.

Author Disclosure Statement

No competing financial interests exist.

References

- Standards of medical care in diabetes—2010. *Diabetes Care* 2010;33(Suppl 1):S11–S61.
- Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:837–853.
- The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993;329:977–986.
- Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B; American Diabetes Association; European Association for Study of Diabetes: Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2009;32:193–203.
- Omar F, van der Watt GF, Pillay TS: Reference change values: how useful are they? *J Clin Pathol* 2008;61:426–427.
- Ricos C, Cava F, Garcia-Lario JV, Hernandez A, Iglesias N, Jimenez CV, Minchinela J, Perich C, Simon M, Domenech MV, Alvarez V: The reference change value: a proposal to interpret laboratory reports in serial testing based on biological variation. *Scand J Clin Lab Invest* 2004;64:175–184.
- College of American Pathologists (CAP) GH2 Survey Data. www.ngsp.org/CAPdata.asp (accessed July 2010).
- European Reference Laboratory for Glycohemoglobin. Dutch External Quality Scheme, SKML. www.euroreflab.com (accessed July 2010).
- Rohlfling C, Wiedmeyer HM, Little R, Grotz VL, Tennill A, England J, Madsen R, Goldstein D: Biological variation of glycohemoglobin. *Clin Chem* 2002;48:1116–1118.
- Desirable Specifications for Total Error, Imprecision, and Bias, Derived from Intra- and Inter-Individual Biologic Variation. www.westgard.com/biodatabase1.htm (accessed July 2010).
- Approved laboratories of the IFCC Network Laboratories for HbA_{1c}. www.ifcchba1c.net/IFCC_01.asp?type=N (accessed July 2010).
- Future Changes in CAP GH2 HbA_{1c} Survey Grading. www.ngsp.org/news.asp (accessed July 2010).
- IDF Clinical Guideline Task Force: Global Guideline for Type 2 Diabetes. Brussels: International Diabetes Federation, 2005.
- Bruns DE, Boyd JC: Few point-of-care hemoglobin A_{1c} assay methods meet clinical needs. *Clin Chem* 2010;56:4–6.
- GLAD Working Group: Recommendations for the implementation of international standardization of glycated hemoglobin in Italy. *Clin Chem Lab Med* 2010;48:623–626.
- Lenters-Westra E, Slingerland RJ: Six of eight hemoglobin A_{1c} point-of-care instruments do not meet the general accepted performance criteria. *Clin Chem* 2010;56:44–52.

Address correspondence to:

Erna Lenters-Westra, B.Sc.

Department of Clinical Chemistry

Isala Klinieken

Groot Wezenland 20

8011 JW Zwolle, The Netherlands

E-mail: w.b.lenters@isala.nl

