Hemoglobin $A_1c$ (Hb $A_1c$) is the analyte most commonly measured in clinical laboratories for patients with diabetes mellitus. Physicians use Hb $A_1c$ to monitor long-term glycemic control, adjust therapy, and predict complications of diabetes. Recently, Hb $A_1c$ was added as a criterion for the diagnosis of diabetes. Unlike most analytes, many patients with diabetes know their Hb $A_1c$ value and are familiar with the target value they need to attain for good glycemic control.

Glycation of proteins was recognized over 100 years ago. Hb $A_1c$ was first isolated (by chromatography) in 1958 (1) and was identified 8 years later as a Schiff base between hemoglobin and a ketone or aldehyde (2). Early commercial assays for Hb $A_1c$ were limited by the absence of standardization. For example, a comparison of 7 methods in 1992 revealed very large differences (>200%) in Hb $A_1c$ values among methods (3). Standardization programs were developed soon thereafter (in 1993), when the Diabetes Control and Complications Trial (DCCT) documented the clinical values of Hb $A_1c$ for patients with type 1 diabetes (4).

The publication 5 years later of results for the UK Prospective Diabetes Study (UKPDS), which revealed that decreasing Hb $A_1c$ in patients with type 2 diabetes reduced complications (5), further emphasized the essential contribution of Hb $A_1c$ monitoring to patient care. Importantly, the Hb $A_1c$ results obtained in the UKPDS were in accord with those in the DCCT. Therefore, appropriate patient management requires that an individual’s Hb $A_1c$ value be traceable to DCCT/UKPDS values.

The National Glycohemoglobin Standardization Program (NGSP) was formed to achieve this objective. The NGSP laboratory network assists manufacturers of Hb $A_1c$ assays in calibrating their methods so that patient values correlate with those of the DCCT and the UKPDS (6). Analogous to the clinical-outcomes trials, Hb $A_1c$ is reported as a percentage of the total hemoglobin. The NGSP has markedly improved Hb $A_1c$ standardization (6), and numerous countries have adopted it. A few years after the establishment of the NGSP, the IFCC developed a higher-order reference method for Hb $A_1c$. A comparison of the NGSP and IFCC networks revealed a linear relationship, but IFCC values were approximately 1.5% to 2% lower (7). A subsequently influential decision was made to report IFCC results in SI units [millimoles of Hb $A_1c$ per mole of Hb $A_0$ (8)] and several countries, predominantly in Europe and the Antipodes, have adopted SI units for Hb $A_1c$ (9). One of the motivations for the use of SI units was that the large difference in results (e.g., an Hb $A_1c$ value of 6.5% is equivalent to 48 mmol/mol) would eliminate confusion regarding the reporting schemes, but no evidence to support this premise has previously been published.

The study reported by Kilpatrick et al. (10) in this issue of Clinical Chemistry has addressed this topic by evaluating the effect on glycemic control of changing Hb $A_1c$ reporting from DCCT/NGSP units (a percentage) to SI units (millimoles per mole). Data were derived from all the patients on the diabetes register in Hull and East Yorkshire, UK. In the UK, Hb $A_1c$ was reported exclusively as a percentage until June 1, 2009, when “dual reporting” of both DCCT/NGSP units and the new units was instituted. Beginning October 1, 2011, Hb $A_1c$ results were reported only in SI units. Kilpatrick et al. (10) compared Hb $A_1c$ values during the last year of dual reporting (October 1, 2010, to September 30, 2011) to those obtained during the first year after DCCT/NGSP units were eliminated (October 1, 2011, to September 30, 2012). The authors have drawn 2 general conclusions from their data analysis: (a) There was no difference in the overall glycemic control of the entire population before and after the units were changed, and (b) the change in Hb $A_1c$ in the patients who had poor glycemic control (defined in their study as an Hb $A_1c$ value >8%) was not altered by the units used for reporting.

This concise—and timely—report, which provides valuable information, exhibits several positive attributes. The population was large, with 44 721 Hb $A_1c$ measurements (21 880 in the first year and 22 841 in the second year) obtained from 13 197 patients, all of
whom have diabetes. All samples were analyzed in a single laboratory using a single method. This strategy minimized any potential effect of interlaboratory imprecision or bias on the data. The analytical performance was excellent, with interassay CVs of 1.6% and 1.3% at Hb A1c concentrations of 5.4% (36 mmol/mol) and 9.3% (80 mmol/mol), respectively. These results met the recommended intralaboratory imprecision of <2% (11). The data demonstrate that the conversion of units for reporting Hb A1c in the UK did not lead to any deterioration in glycemic control during the period of the analysis.

Like all good studies, this report elicits numerous questions. One is eager to know more about the patients. What was the breakdown between patients with type 1 diabetes and those with type 2 diabetes? Were there any differences between the 2 groups? Were the findings for children and adults with type 1 diabetes identical? Was there any difference between patients who were managed by diabetologists and those treated by general practitioners? Were DCCT/NGSP values made available to some physicians and/or patients when only SI units were on the printed reports? If so, did this information influence patients’ Hb A1c concentrations? Other factors, such as the introduction of new oral agents or insulins and changes in patient demographics (e.g., deaths or new individuals diagnosed with diabetes), may have influenced the findings. The most pertinent limitation of the study is the short period of analysis. The authors present no data regarding Hb A1c values for the patients in the year preceding the institution of dual reporting. More importantly, the brief follow-up period does not guarantee that long-term glycemic control will remain unchanged. A prior study in Sweden evaluated the consequences of altering the scale of Hb A1c results when methods were changed (12). Analogous to the present work, glycemic control in the first year was essentially the same as before the change; however, glycemic control in the Swedish patients deteriorated approximately 1 year after the reference interval was lowered. Long-term follow-up of the patients evaluated by Kilpatrick et al. is required to address this possible concern.

Perhaps the most consequential question that arises from this report is whether these findings can be extrapolated to other countries. Several factors need to be considered. The study was conducted in the UK, a very wealthy country that devotes considerable resources (approximately 10% of gross domestic product in 2010) to healthcare (13). A highly coordinated, well-thought-out campaign was undertaken to educate healthcare professionals and patients. Dual reporting was carried out for 28 months, and all laboratories in the UK converted to SI units on the same day, thereby minimizing the potential for confusion. That the standard of care was high is exemplified by the observation that the mean number of days between successive Hb A1c analyses for patients with poor glycemic control (Hb A1c >8%) was 99 days. This finding is consistent with guidelines that recommend testing Hb A1c every 3 months for patients who are not meeting treatment goals (11). I look forward to publications of glycemic control from other countries that have changed Hb A1c units.

The same data could have a different interpretation. All the effort invested to switch units failed to produce any improvement in the glycemic control of patients with diabetes. Some might be tempted to use the data to invoke the counterargument that there is no evidence for promoting a change of units. Many countries lack both Hb A1c standardization and the proficiency testing necessary to ensure that clinical laboratories measure Hb A1c accurately. Some diabetologists from these countries have voiced the opinion that the limited resources available should be used to enhance the quality of Hb A1c analysis, not change the units for reporting. The units used for reporting Hb A1c remains a highly contentious topic, and the hope previously expressed “that the same Hb A1c values should be reported globally” (14) will, unfortunately, not be realized.

Notwithstanding these issues, the report by Kilpatrick et al. (10) makes a valuable contribution. It allays (at least in the short term) the anxieties of those caring for patients with diabetes in countries that have adopted SI units. For countries that plan to convert from DCCT/NGSP units to SI units, it is vital that an organized strategy with adequate education be adopted. In diabetes, patient self-management is critical for improving treatment outcomes (15). Several influential organizations, including the American Diabetes Association, the American College of Physicians, and the NIH, have encouraged patients to “know your ABCs” (where “A” represents Hb A1c). Therefore, any change in reporting needs to be unambiguously communicated to patients. It is vital for countries that convert to SI units to avoid jeopardizing the health of patients, and the well-known adage primum non nocere (first do no harm) should not be forgotten.

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