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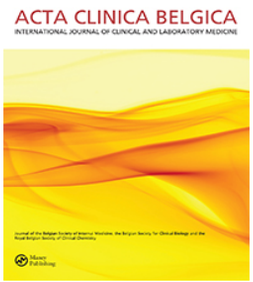

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"Mind the gap please…": estimated vs. measured A_{1c} from continuous measurement of interstitial glucose over a 3-month period in patients with type 1 diabetes

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ABSTRACT

Introduction: Glycated hemoglobin (A_{1c}) is the measurement of choice to estimate the glycemic exposure over the last 3 months prior to sampling. The Free Style Libre® is a continuous glucose monitoring device which provides an estimated A_{1c} (eA1c) from average interstitial glucose using Nathan's ADAG equation. The objective of this study was to compare eA1c and A_{1c} in type 1 diabetes patients (T1D) over a period of 3 months.

Materials and methods: Data were collected from patient charts between July 2016 and October 2017. 3-months recordings with >70% of data available were analyzed. eA1c was recorded at each visit and the corresponding A_{1c} value measured by high performance liquid chromatography in a single reference lab.

Results: A total of 344 reports from 170 T1D were studied, 3 categories were identified: eA1c = A_{1c}: 13% of reports. eA1c > A_{1c}: 57% of reports, positive difference (eA1c – A_{1c}) of +0.74 ± 0.5% ($P < 0.0001$). eA1c < A_{1c}: 30% of reports, negative difference (eA1c – A_{1c}) of −0.5 ± 0.3% ($P < 0.0001$).

Conclusion: eA1c value was generally overestimated compared to measured A_{1c} in this T1D cohort. This lesser concordance may result from differences in measured glucose source and/or frequency to calculate eA1c compared to ADAG, but also from using the reverse equation which is a source of potential bias. Another explanation could be a different rate of hypoglycemia between groups, or an asymmetric distribution of A1c patients' phenotypes with differential hyper- or hypoglycation intrinsic propensity.

KEYWORDS
Type 1 diabetes; HbA_{1c}; eA1c; GMI; CGM; FreeStyle Libre (FSL)

Introduction

The landmark *Diabetes Control and Complications Trial* (DCCT) in patients with type 1 diabetes (T1D) confirmed the close relationship between hyperglycemia, glycated hemoglobin A1c (HbA_{1c}) as marker of glycemic control and incident microvascular complications [1]. HbA_{1c} became the 'Gold Standard' for following-up of metabolic control in diabetes patients, as it reflects the average of blood glucose levels over the past 3 months preceding sampling and predicts the risk of incident vascular complications over time, in particular microangiopathy [2]. Recently, continuous glucose monitoring (CGM) using FreeStyle Libre (FSL) Flash Glucose Monitoring System (Abbott Diabetes Care, Alameda, CA, USA) was made available to individuals with diabetes from many European countries. With an adequate frequency of scans, the FSL software (version 1.0) provides an estimate of HbA_{1c} (eA1c) for a maximum retrospective period of 3 months, based on a linear equation connecting average glucose (AG) and HbA_{1c} published by Nathan et al. [3].

The objective of this study was to compare the concordance between eA1c calculated from FSL over 3 months and measured HbA_{1c} over the same period in T1D patients.

Materials and methods

This was an observational, retrospective, non-interventional study performed in accordance with the Helsinki Declaration [4] among T1D patients treated by basal-bolus insulin regimen or continuous subcutaneous insulin infusion. Patients were recruited from the diabetes clinic at the Hospital of Mouscron (Belgium). Diagnosis of T1D was based on low/nil C-peptide levels and/or positive GAD_{65} antibodies. All investigations were routinely performed in the same diabetic clinic. Data were collected from patient charts over approximately 15 months between July 2016 and October 2017. Patients attended the outpatient clinic approximately every 3 months over that period.

Measures of glycemia and eA1c

All patients underwent ambulatory FSL for 90 consecutive days, with sensors inserted in the upper arms,

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replaced every 14 days (or earlier in case of detachment or non-operation). Sensors had to be scanned at least every 8 h per day to gather 24 h of continuous interstitial glucose measurement. Each report edited by FSL software provides an average of interstitial glucose (AIG; mg/dl), number and duration of low glucose measurements (<70 mg/dl or 3.9 mmol/L), percentage of data captured by the reader during the study period, and an eA1c value estimated by Nathan's equation [$AG_{mg/dl}$ = 28.7 × A1C −46.7 or $AG_{mmol/l}$ = 1.59 × A1C- 2.59)] [3].

The standard deviation (SD) of AIG was obtained by DIABASS® Pro software (Version: 15.12.0.1) and the percentage coefficient of variation of glucose was calculated as %CV = (SD of AIG)/(mean AIG)]x 100) [5].

In each patient, HbA_{1c} was measured on a venous blood sample by high performance liquid chromatography (HPLC) on a Tosoh G8 instrument in the hospital laboratory, with a coefficient of variation for HbA_{1c} ($CVHbA_{1c}$) < 1% of value (ex: HbA1c measured at 7.39%, $CVHbA_{1c}$ = 0.42% whether ± 0.03 around of HbA_{1c} value). Tosoh G8 dosages are not interfered with by the presence of hemoglobin HbC, HbS, HbD, nor by that of HbE [6].

Study criteria

Inclusion criteria: T1D patient, age >18 years, and continuous interstitial glucose data available >70% over the study period of 90 days [7]. *Exclusion criteria*: pregnancy, patients with glomerular filtration rate (GFR) <30 ml/min/1.73 m^2 and/or undergoing dialysis, recent blood transfusion or recent or chronic bleeding. Patients with type 2 diabetes, maturity-onset diabetes of the young, or secondary types of diabetes were excluded from the study. Patients with hereditary conditions affecting hemoglobin structure or function were also excluded, as were patients with splenectomy or other acquired or hereditary conditions affecting erythrocytes' lifespans.

Outcomes

To compare eA1c and HbA_{1c}, the previous 90 days of AIG values and eA1c were recorded for all patients at each visit and the corresponding HbA_{1c} value was measured in the lab.

The difference (Δ) between eA1c and HbA1c expressed in % was calculated by their absolute values in each patient. Reports were divided into three categories based on the difference (Δ) between eA1c and HbA_{1c}, and defined as:

- Category I: Δ (eA1c − HbA_{1c}) ranging from −0.099% to 0.099%; such Δ arbitrarily classified as without (or of negligible) clinical significance.
- Category II: Δ (eA1c − HbA_{1c}) ≥ +0.1%; positive difference considered present.
- Category III: Δ (eA1c − HbA_{1c}) ≤ −0.1%; negative difference considered present.

Statistics

The data were expressed as means ± standard deviation (SD), categorical variables were presented as numbers and percentages. The data were analyzed using Student's T-test or ANOVA, *P* values <0.05 considered statistically significant. The relationship between HbA_{1c} *in %* and eA1c *in %* was analyzed using simple linear regression and the Bland-Altman analysis of agreement method was used to compare eA1c and HbA1c measurements. All analyses were implemented using GraphPad Prism Software 7.04 (2017).

To assess the accuracy of eA1c tracking over time, the trends between eA1c and HbA1c were compared using an error grid plot (eA1c values versus reference HbA1c), and all data were implemented using SAS Software System v 9.3 (Canchola JA, Canchola CM (2013)). 'Using SAS for Error Grid Analysis (EGA) of Glycated Hemoglobin A1c (HbA1c)'. Proceedings of the Twenty First Western Users of SAS Software Conference, San Diego; Cary, North Carolina, SAS Institute.

- Region A: contains eA1c values that are approximately within 20% as compared to reference HbA1c measured and are considered 'clinically accurate';
- Region B contains eA1c values that are approximately greater than 20% of the reference HbA1c values but would 'not lead to inappropriate treatment';
- Region C contains values that would 'confuse treatment decision for diabetes'.

Results

A total of 170 patients (98 males and 72 females) met the inclusion criteria. The cohort included 159 Caucasian patients, 7 patients from the Maghreb and four patients from sub-Saharan Africa. Their clinical characteristics are shown in Table 1.

A total of 344 CGM reports covering 90 days of continuous FSL were thenceforward studied and compared with the 344 corresponding values of HbA_{1c}. After comparing measured HbA_{1c} and predicted eA1c, the reports were categorized into three types (Table 2). All reports contained >70% of data scanned [7] by FSL reader (Table 2), corresponding to approximately 7000–8000 measures of interstitial glucose per day. Figure 1. shows the linear regression between eA1c and HbA_{1c}.

Table 1. Baseline characteristics.

Type 1 diabetes subjects	170			
Age (years)	53.0	±	15.0	
Male/Female (n)	98	/	72	
Race (% white)		93		
Duration of diabetes (years)	20	±	11	
BMI (kg/m^2)	27	±	4	
HbA1c (%)	7.8	±	1	*(7.7 to 7.9)*
eA1c (%)	8.0	±	1.1	*(7.9 to 8.2)*
C peptide(0.28–1.42 nmol/l)	0.09	±	0.1	
Average of sensor control/day/patient	7.2	±	3	
Treatment				
MDI (n) (%)	146		(86)	
External pump (n) (%)	24		(14)	

BMI: body mass index; HbA1c: glycated hemoglobin; eAC: estimated A1c. MDI: Multiple daily injections
Results are expressed mean ±SD. Data in parentheses are 95% Cis.

Table 2. Data characteristics of 344 estimated A1c over 90 days compared with 344 corresponding HbA1c values.

	I	II	III
Categories	eA1c = HbA1c	eA1c > HbA1c	eA1c < HbA1c
Reports CGM	*45 (13)*	*195 (57)*	*104 (30)*
Glycemia recorded by scan (%)	*87 ± 12*	*89 ± 10*	*89.6 ± 12 (ns)*
Hypoglycemia	*55 ± 35*	*50 ± 33*	*73 ± 42****
Duration of hypoglycemia (mn)	*118 ± 32*	*113 ± 34.5*	*123 ± 36 (ns)*
%CV (%)	*42.0 ± 6.0*	*42.4 ± 6.2*	*42.0 ± 7.3 (ns)*
eA1C (%)	*7.7 ± 0,8*	*8.5 ± 1.0*	*7.3 ± 0.8*
HbA1c (%)	*7.7 ± 0.8*	*7.8 ± 0.8*	*7.8 ± 0.8*
Δ (%)	*0 (−0.02 to 0.02)*	*+0.74 ± 0.5*** (+0.81 to +0.66)*	*−0.5 ± 0.3*** (−0.44 to −0.56)*

CGM: Continous Monitoring Glucose; %CV: Coefficient of Variation; eA1c: estimated A1c; Δ: difference between eA1c and HbA1c.
Data are expressed n (%) or means ± SD; Data in parentheses are 95% Cis;
*** P < 0.0001.

Category I

Minimal or no Δ between eA1c and HbA_{1c}.This concerned 45 (13%) reports, of which 87 ± 12% of sensor data were scanned over 90 days, and whose HbA_{1c} and eA1c both averaged 7.7 ± 0.8% (ns), with mean number of hypoglycemia 55 ± 35, mean duration of hypoglycemia: 118 ± 32 min, and %CV at 42.0 ± 6.0%.

Category II

Δ eA1c > HbA_{1c} (overestimation of eA1c). This was the case for 195 (57%) reports, of which 89 ± 10% of sensor data were scanned over 90 days, and whose mean eA1c was 8.5 ± 1.0%, mean HbA_{1c} 7.8 ± 0.8%, average Δ between eA1c and HbA_{1c} positive at +0.74 ± 0.5% ($p < 0.0001$), with mean number of hypoglycemia 50 ± 33, mean duration of hypoglycemia 113 ± 34.5 min, and %CV at 42.4 ± 6.2%.

Category III

Δ eA1c < HbA_{1c} (underestimation of eA1c). This was the case for 104 (30%) reports, of which 89.6 ± 12% of sensor data were scanned over 90 days, and whose mean eA1c was 7.3 ± 0.8%, mean HbA_{1c} 7.8 ± 0.8%, average of the Δ between eA1c and HbA_{1c} negative at − 0.5 ± 0.3% ($p < 0.0001$), with mean number of hypoglycemia 73 ± 42, mean duration of hypoglycemia 123 ± 36 min, and %CV at 42.0 ± 7.3%.

The differences between eA1c and HbA_{1c} in category II and III could not be ascribed to differences in coefficients of variation of glucose (*ns*) or number of sensor scanning (*ns*).

In contrast, the number of hypoglycemia was higher in category III (eA1c < HbA1c): 73 ± 42 vs. 55 ± 35 in category I and 50 ± 33 in category II ($p < 0.0001$). Finally, the difference in mean duration of hypoglycemia between categories was at the limit of statistical significance ($p = 0.05$).

The results of the Bland-Altman show (Figure 2), on average, that eA1c measurements were 0.26 % higher than measured HbA1c (bias is 0.26 %, SD of differences = 0.71; 95% CI for mean 0.19 to 0.34). The 95% limits of agreement were −1.12 and 1.65 %, respectively.

Concerning the A1c error grid (Figure 3), >99.7% (343/344) of eA1c values were within the A + B zones of the error grid, indicating high accuracy of hemoglobin A1c tracking.

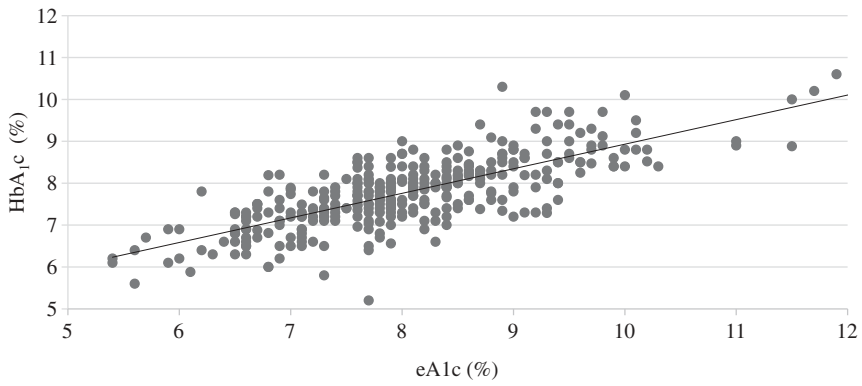

Figure 1. Correlation between eA1C and measured HbA1c (linear regression) during the preceding 3 months. (HbA1c = 0,59 × eA1c + 3,06) ($R^2 = 0.59$, $P < 0.001$).

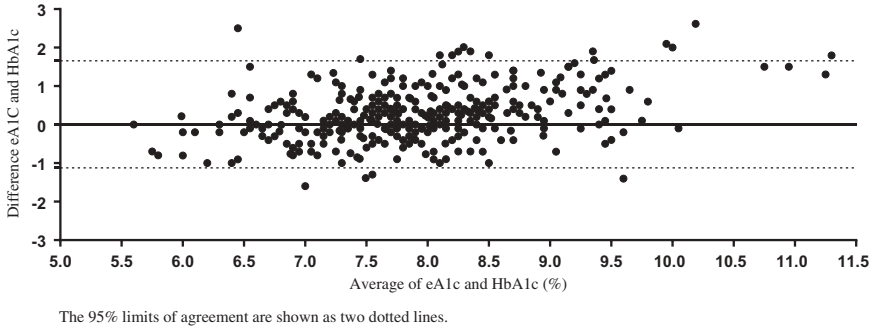

Figure 2. Difference vs. average: Bland-Altman of eA1c and HbA1c (%).

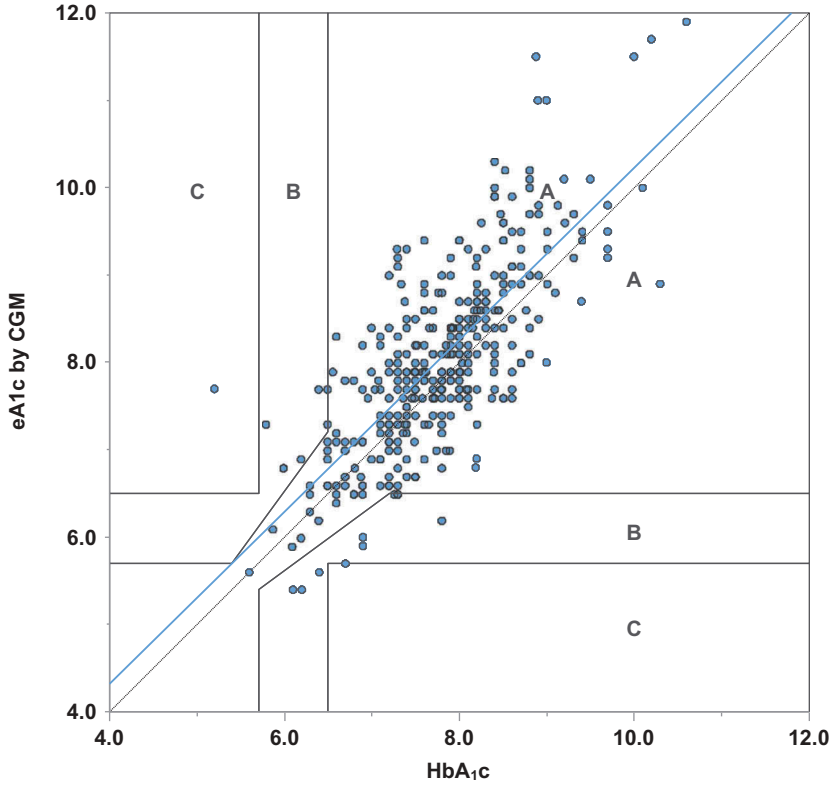

Figure 3. Error grid for eA1c vs. HbA_{1c} (%).

Discussion

The main objective of this study was to compare the concordance between estimated eA1c over 3 months and measured HbA_{1c} over the same period in T1D patients on ambulatory CGM. About measurement of continuous biological variables, it was expected to have a strong and linear correlation between two measurements designed to evaluate a common underlying biological process. Such a concordance is expected to be found concerning the direct measurement of HbA_{1c} on the one hand, and its predicted value (eA1c) based on correctly recorded continuous measurements of interstitial glucose, on the other hand. Yet the results of this study show that this is clearly not the case for a majority of continuous measurements of interstitial glucose. Where could these differences come from?

Fallacy of measured HbA1c?

The hospital laboratory used for this study performs its HbA_{1c} assays using HPLc aligned with DCCT norms, and in accordance with the National Glycohemoglobin Standardization Program (NGSP) [8]. It is well established that substantial intra- and inter- variations in HbA_{1C} do exist [6], and that glucose levels are not the sole biological parameter affecting HbA_{1c}. HbA_{1c} values can be interfered with by anemia or changes in erythrocyte turnover rates, as evidenced by reticulocytosis (bleeding) or following red cells transfusions [3]. Also, chronic renal or liver diseases are associated with lower HbA_{1c} [9]. Normal or diabetic HbA_{1c} ranges are also constitutionally higher in some ethnic groups, including sub-Saharan Africans [10–12]. Such confounders can be ruled out in the present study, due to the inclusion/exclusion

criteria and the patient's characteristics, with modest enrollment of African patients, and exclusion of patients with anemia or renal failure. Overall, a very substantial number of diabetes patients showed discrepancies in measured HbA_{1c}, substantially higher or lower, respectively, than those predicted from their corresponding average plasma glucose [13].

It should also be borne in mind that laboratory HbA1c considers AG and glycation characteristic for all individuals, as well as average red cell production and elimination rates, whereas eA1c is essentially a measure of 'average glucose'.

Calculation method of eA1c?

The performance and reliability of Flash glucose monitoring system was demonstrated by the accuracy of sensor readings and the stability of accurate readings over 14 days of use, making iterative recalibration from capillary blood superfluous, to the great satisfaction of patients. The accuracy of the system is unaffected by subject characteristics, making it suitable in a broad range of patients [14]. Also, the results of FSL cannot be falsified by the patient during normal use, since the device is pre-calibrated at the factory.

The performance of Nathan et al's equation, as formulated in the context of the ADAG program, can on the other hand be questioned. In the ADAG study [3], patients' glucose averages were obtained from two different sources of measurements, namely interstitial glucose from CGM and intermittent self-monitoring of capillary blood glucose, even though separate analyses comparing the relationships between HbA_{1c} and AG from CGM or finger prick capillary measurements found no significant difference between measurements sources.

The present study included only CGM data from interstitial glucose in T1D patients.

Other hypotheses

Some of the observed differences could relate to biological variations between patients, a subset of whom having an intrinsic ability to hyper- or to hypo-glycate target proteins, including Hb.

A hyper-glycating subject would exhibit a constantly higher HbA_{1c} for a given corresponding AIG, and *vice-versa* for hypo-glycating subjects [6]. Among explanations put forward to explain such differential tissue glycating capacity are factors influencing membrane influx/egress of glucose, differential hemoglobin binding, and other genetic factors.

Some putative factors involved with variation in HbA_{1c} independent of glycemia are age, sex hormones, visceral fat distribution, other physiologic and genetic factors, and socioeconomic status, including racial and ethnic differences [10,15].

To avoid these confusions, some authors [16,17] propose to use a hemoglobin glycation index (HGi) as a method to quantify biologic variation in HbA_{1c}. HGi is the difference between a patient's measured HbA_{1c} and the predicted HbA_{1c} (eA1c). eA1c was calculated from the patient's MBG using a multiple regression equation that compared HbA_{1c} and MBG for the studied population.

On the other hand, some studies [18,19] showed substantial variability in mean individual glucose concentrations for a given HbA1c, and therefore their authors concluded that trying to transform HbA_{1c} into calculated mean glucose might introduce substantial error.

This study has several major limitations, the methodology used to estimate HbA1c (eA1c) from FSL was based on the equation provided by the A1C-derived average glucose (ADAG) study [3]. Its objective was to estimate, using a mathematical model, individual AG from HbA_{1c} values measured over the previous 3 months. The authors produced a simple linear regression relationship between HbA_{1c} and AG levels in patients with type 1 and 2 diabetes and in non-diabetic subjects. In addition, Nathan et al. arbitrarily chose that 90% of the AG obtained per patient should be within 15% of the average predicted by the equation. Therefore, the estimate AG from HbA_{1c} had a confidence range of 15%, eg: an HbA1c result of 7% equalled 154 (95% CIs: 123–185) mg/dl glucose or 8.6 (95% CIs: 6.8–10.3) mmol/l [3].

In the present study, the FSL software included Nathan's equation but in an inverted way (*eA1c (%) = (average glucose (mg/dL) + 46,7)/28,7*) in order to derive eA1c from AIG in all patients (irrespective of confidence intervals) using CGM-derived AIG. In doing so, the eA1c was provided without including a confidence interval, and using the inverted linear equation can calculates eA1C very different (eg: AIG: 154 mg/dl is equivalent to 7% but for the extremes 123 mg/dl is equivalent to 5.9% and 185 mg/dl equals 8% while these glycaemic values are equivalent to a 7% HbA1c in ADAG). To be perfectly reversible Nathan's equation should have a relationship coefficient (R^2) = 1 instead of 0.84.

Finally, in the ADAG study, the T1D patients studied (n = 268) had a substantially lower average HbA1c (7.3% vs. 7.8%) (Table 1), and their glycemic profiles from CGM were often less brittle [3]; in contrast, glycemic variability was larger in our cohort, as shown by a %CV of 42% (> 36%) [5].

Conclusion

Estimated A1C (eA1C) converts the mean glucose from CGM into an estimate of simultaneously measured laboratory A1C, but confusion arises when the two results do not agree. Caution should be exercised

when eA1C is used for clinical decision purposes in the absence of a contemporary measure of HbA1c [20].

In this study, a majority of eA1C estimated by CGM were overestimated compared to measure HbA_{1c} in patients with T1D, for whom eA1c must be interpreted with care.

Despite studies having confirmed a close relationship between HbA_{1c} and CGM, different linear equations were proposed over the years [21]. Wide prediction intervals in the latter preclude generalized accurate conversion of HbA_{1c} into eA1c at present, as wide prediction intervals of regression would not provide accurate translation of HbA_{1c} to CGM or the opposite. There is an unmet need for establishing an unbiased linear equation between FSL-derived AG and measured HbA_{1c}, and then for providing a more accurate estimate of eA1c from average 3-month interstitial glucose levels obtained by FSL.

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Authors' contributions

PO, MPH conceived and designed this study
PO recruited and followed patients.
PO, MPH drafted the manuscript

Disclosure statement

Dr. Oriot Philippe is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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No conflict of interest with Abbott for this study.

All procedures followed were in accordance with the ethical standards of the responsible committee.

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Ethical standards

All procedures followed were in accordance with the ethical standards of the responsible committee.

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