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Real world hypoglycaemia related to glucose variability and Flash glucose scan frequency assessed from global FreeStyle Libre data

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Abstract

Aim: Flash glucose monitoring provides a range of glucose metrics. In the current study, we aim to identify those that indicate that glycaemic targets can be consistently met and contrast the total (t-CV) and within-day coefficient of variation (wd-CV) to guide the assessment of glucose variability and hypoglycaemia exposure.

Methods: De-identified data from Flash readers were collected. The readers were sorted into 10 equally sized groups of scan frequency followed by quartiles of estimated A1c (eA1c). A similar grouping was performed for the total coefficient of variation (t-CV) and within-day coefficient of variation (wd-CV). In addition, analysis of the association of time below 54 mg/dl and glucose variability measured by t-CV and wd-CV was performed.

Results: The dataset included 1 002 946 readers. Readers sorted by 10 equal groups of scan rate and quartiles by eA1c, t-CV and wd-CV represented 25 074 readers per group. The association of lower eA1c with higher time in range and reduced time above range was clear. The correlation of eA1c quartiles and time below range was not consistent. An association between glucose variability and hypoglycaemia was found. Both wd-CV and t-CV were associated with time below range. For achieving the consensus target of <1% time below 54 mg/dl, the associated wd-CV and t-CV values were 33.5% and 39.5%, respectively.

Conclusions: The type of CV reported by the different continuous glucose monitoring systems should be acknowledged. CV <36% might not be adequate to ensure low hypoglycaemia exposure. To our knowledge, the majority of continuous glucose monitoring reports the t-CV. Appropriate thresholds should be used to identify patients that would probably meet time below range targets (t-CV <40% or wd-CV <34%).

KEYWORDS
blood glucose monitoring, diabetes, FreeStyle Libre, glucose variability, real life data

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1 | INTRODUCTION

Continuous glucose monitoring (CGM), which includes both traditional CGM and Flash CGM (Flash) is an important part of diabetes management. The use of CGM helps patients to achieve better glycaemic management[1,2] with an increased time within the target range[3] and reduced time spent in hypoglycaemia.[3-6] Recently, it has been shown that use of Flash decreases the incidence of hospital admissions for diabetic ketoacidosis and for diabetes-related coma in type 1 and type 2 diabetes.[7]

CGM data are used by patients on a daily basis to make key decisions regarding their treatment and their lifestyle to limit the risk and exposure to hypo- and hyperglycaemia. Retrospective analysis of CGM data allows patients and their clinicians to identify glycaemic patterns to make shared treatment decisions. As CGM provides a large amount of information, a systematic approach with key CGM metrics[8] as well as clinical targets was proposed by a consensus panel[9] and endorsed by several diabetes associations. The use of these metrics enables assessing the overall glycaemic control, identifying glycaemic variability and exposure to hypoglycaemic or hyperglycaemic events, and allows patients and their clinicians to optimize treatment decisions. Among these CGM metrics, the percentage coefficient of variation (%CV) is used to evaluate glucose variability and helps to identify patients with higher risk of hypoglycaemic events as several publications suggest that glucose variability is a consistent predictor of hypoglycaemia.[10,11] Stable glucose levels are defined as a CV <36%, and unstable glucose levels are defined as CV ≥36%.[8,12] The threshold for excess glucose variability was defined in a study[12] that calculated the within-day CV (wd-CV). However, our understanding is that CGM devices provide the total CV (t-CV). Another recent study, including data from type 1 patients using Flash, assessed whether wd-CV and t-CV have the same relevance to identify patients with a higher risk of hypoglycaemia.[13] This study showed that whatever the method of calculation, %CV was positively correlated with time below range (TBR). However, thresholds to predict severe hypoglycaemia risk seem to be different between t-CV and wd-CV and should be assessed in a larger study.

The objective of the study described is to identify, among the existing metrics, those that indicate that glycaemic goals can be consistently achieved, how these parameters are impacted by the scan frequency, and to contrast the total and within-day coefficient of variation for glucose (CV) thresholds to guide clinical assessment of glucose variability and hypoglycaemic exposure. Based on anonymized information, the correlation between estimated (eA1c), CV (both wd-CV and t-CV), scan frequency, hypoglycaemic exposure and time within glycaemic targets was assessed using data collected from 1 million Flash users.

2 | MATERIALS AND METHODS

2.1 | Sensors and readers

The FreeStyle Libre system, manufactured by Abbott Diabetes Care (Witney, UK), has a glucose sensor placed on the back of the upper arm using an applicator. A 5 mm filament of the sensor is inserted in to the subcutaneous tissue. The sensor is factory-calibrated and has a wear time of up to 14 days without any user calibration; it measures glucose levels in the interstitial fluid every minute and stores glucose data automatically every 15 min. The glucose data are transmitted wirelessly to a dedicated reader or smartphone each time that they are used to scan the glucose sensor. The user gets the current glucose, glucose trend and historic glucose up to 8 h from scanning the sensor.

2.2 | Analysed data

2.2.1 | Data collection

This study only included data collected via the dedicated reader. The software interface, when connected to an active internet connection, was used to upload the de-identified data from the reader's 90-day memory glucose readings into an anonymized database of users of the Flash system (FigureS1). The processing of these data is detailed in the software privacy policy and is in accordance with terms of the General Data Protection Regulation (GDPR).

2.2.2 | Analyses of the data

The sensors included in the analysis had at least 120 h of automatically stored readings. Data from all sensors belonging to the same reader were combined. The scanning frequency for each sensor was calculated by the number of scans divided by the duration of sensor use. To investigate the relationship of daily scan frequency and different quartiles of eA1c with glucose metrics, the readers were grouped by 10 equal bins of scan frequency followed by quartiles of eA1c into equal size groups of 25 074 readers. Similarly, to assess the correlation of scanning frequency and glucose metrics the readers were grouped by 10 equally sized bins of scan frequency followed by quartiles of t-CV and, a similar grouping was performed for the wd-CV with groups of 25 074 readers. Furthermore, taking those equal-size groups by t-CV and wd-CV quartiles, the correlation of glucose variability and hypoglycaemia was examined in more detail, with an analysis of the association of time below 54 mg/dl and glucose variability measured by t-CV and wd-CV. A receiver operating characteristic (ROC) curve analysis was performed to assess the ability of both t-CV and wd-CV to identify patients with higher risk of hypoglycaemic exposure.

2.3 | Statistical analysis

The different groups defined by the frequency of scans were compared by a univariate analysis of variance test. The range of glucose parameters and relative variations were established for the patient groups from those scanning least to those scanning most frequently.

The database was analysed in a structured query language, described in more detail at www.knime.org and by the statistical software package R (www.r-project.org). The large sample size and multiple comparisons resulted in $p < .01$ as statistically significant. Confidence intervals were calculated for each scan frequency group by least-squares mean and comparisons were made between these different groups.
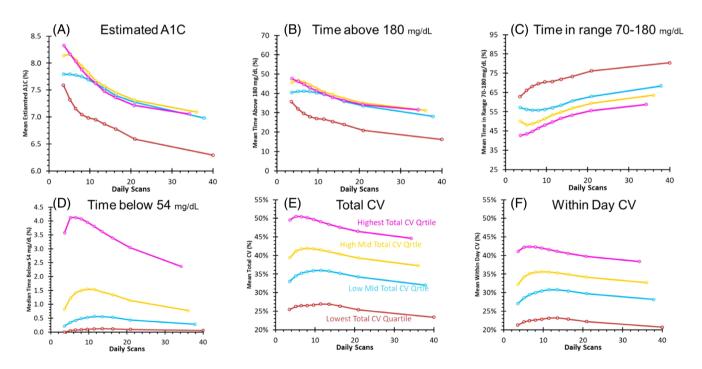
3 | RESULTS

In total, 1 002 946 readers were available for analysis, with a median of 84 days of sensor data (95% had more than 10 days of data). Over the total of 3.4 billion hours of monitoring, the average (SD) daily scans was 13.2 (10.8), t-CV 37.5% (9.0%), wd-CV 31.9% (8.0%), eA1c 7.5% (1.5%), time in range 58.2% (20.3%), time above 180 mg/dl 36.4% (21.3%) and time below 54 mg/dl 1.9% (3.0%) (TableS1). The readers were grouped by 10 equal-sized bins of daily scans and eA1c quartiles shown in Figure S2A. As expected, there is a clear association of lower eA1c with reduced time above range (TAR; Figure S2B) and higher time in range (TIR; Figure S2C), and these trends improve as scan frequency increases. Conversely, as expected, the lowest A1C groups have a higher hypoglycaemia exposure [time below range (TBR); Figure S2D], presenting more than 1.0% of time below 54 mg/dl than the ones with higher eA1c. However, this association is not consistent and in the three other eA1c quartiles TBR seems quite similar. Therefore, eA1c cannot be used as a selective indicator of hypoglycaemia risk.

The quartile groups by scan frequency and glucose variability are shown in Figures 1 and S3, for total CV ('t-CV') and within-day CV

('wd-CV'), respectively. The observed associations were found to be consistent for both measures of glucose variability and the CV quartiles can easily discriminate different categories of patients with a distinct risk of hypoglycaemia.

For t-CV, those in the lowest quartile group (t-CV ranging from 23% to 27%) never reach more than 1% of clinically significant hypoglycaemia (Figure 1D). Those performing more than 16 scans per day (16.3 scans) met all recommended glycaemic targets of eA1c, hyperglycaemia time above 180 mg/dl <25%, time in range 70-180 mg/dl >70% and hypoglycaemia time below 54 mg/dl <1%. Between 9.6 and 16.3 scans per day, patients in that group can achieve the targets for eA1c (6.98%), TIR (70.4%) and time below 54 mg/dl (0.1%), but did not reach the target of TAR, as shown in Table 1. Below this frequency of scans, TIR, eA1c and TAR are not reached anymore, even in these patients with very low variability.

The highest t-CV quartile group (ranging 45%-51%) never met the recommended thresholds and had by far the highest risk of clinically significant hypoglycaemia, all ranging from 2.4% to 4.1% of time below 54 mg/dl, which was substantially above the recommended target of less than 1%. Noteworthy, this CV quartile had greater improvement of meeting targets as the frequency of scans increased. The association of lower TBR with increased daily scans was strongest in this group, those with 6.5 scans per day had 4.1% time below 54 mg/dl as opposed to those with 34 scans per day had 2.4% time below 54 mg/dl, showing a meaningful improvement in clinically-significant hypoglycaemia exposure as scan frequency increased, from 1 h spent in hypoglycaemia to 34 min per day (Table S2). The remaining two quartile groups of t-CV are shown in Tables S3 and S4.

FIGURE 1 Relationship of daily scan frequency with glucose metrics when grouped by 10 equal bins of scan frequency followed by quartiles of total CV. N = 1 002 946 readers, each point is 25 074 readers. Glucose metrics presented are: A, estimated A1c; B, time above 180 mg/dl; C, time in range 70-180 mg/dl; D, time below 54 mg/dl; E, total CV, F, within day CV. CV, coefficient of variation

TABLE 1 Glycaemic metrics for the lowest total CV quartile group

Daily scans	Total CV (%)	Within-day CV (%)	eA1c (%)	TA180 (%)	TIR (%)	TB54 (%)
3.5	25.4%	21.3%	7.59	35.7	62.8	0.00
5.1	26.3%	22.1%	7.32	32.0	66.0	0.05
6.5	26.5%	22.5%	7.15	29.6	68.2	0.07
8.0	26.5%	22.6%	7.04	28.0	69.6	0.09
9.6	26.7%	22.8%	6.98	27.0	70.4	0.10
11.4	26.9%	23.1%	6.95	26.7	70.7	0.11
13.5	26.9%	23.2%	6.87	25.5	71.9	0.12
16.3	26.4%	22.9%	6.78	23.9	73.4	0.11
21.0	25.4%	22.2%	6.59	20.9	76.2	0.10
40.0	23.4%	20.7%	6.29	16.2	80.4	0.05

Red = not meeting recommended target, green = meeting recommended target.
Abbreviations: CV, coefficient of variation; TA180, time above 180 mg/dl; TB54, time below 54 mg/dl; TIR, time in range.
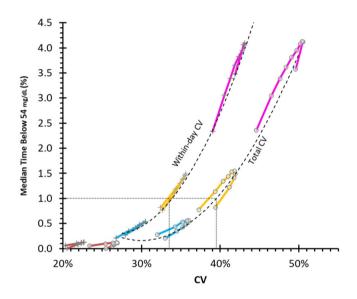

FIGURE 2 Association of glucose time below 54 mg/dl and glucose variability measured by total CV and within-day CV. CV, coefficient of variation

TABLE 2 Recommended criteria for glucose variability measures

Clinical goal	Glucose variability measure	Criteria (cut-off)
Identify acceptable glucose variability to achieve goal of minimal hypoglycaemia exposure (TB54 <1%)	t-CV	t-CV <39.5%
	wd-CV	wd-CV <33.5%

Abbreviations: CV, coefficient of variation; TB54, time below 54 mg/dl; t-CV, total coefficient of variation; wd-CV, within-day coefficient of variation.

below 54mg/dl, TB70 <4% time below 70mg/dl, TAR 180 mg/dl <25% and TAR 250 mg/dl <5%. The accuracy for identifying patients with a high risk of hypoglycaemia was similar for t-CV and wd-CV, albeit at different thresholds (Table S5).

As for wd-CV groups, the highest wd-CV quartile group (wd-CV ranging 39%-43%) had the most exposure to hypoglycaemia, with a clear correlation between TBR and scan frequency (Figure S3D).

The association of glucose variability, measured by t-CV and wd-CV, and hypoglycaemia was examined in more detail, as shown in Figure 2. As expected, the wd-CV is always less than the t-CV at any given level of hypoglycaemia exposure. Both wd-CV and t-CV presents a correlation with time below 54 mg/dl. To achieve the target of <1% time below 54 mg/dl, the associated wd-CV and t-CV values are 33.5% and 39.5%, respectively. These thresholds are summarized in Table 2.

The ROC curves (Figure S4) performed to assess the value of both t-CV and wd-CV as predictors of key glycaemic metric target values confirmed that both parameters are similarly valuable predictors. The ROC curve shows the equivalent performance of t-CV and wd-CV as predictors of TIR 70-180 mg/dl >70%, TB54 <1% time

4 | DISCUSSION

This real-world observational analysis shows that if glycaemic control is defined by eA1c, a clear association with TIR and TAR can be found, but no threshold is available to predict the hypoglycaemia risk. Alternatively, if we define target glycaemic management by glucose variability expressed as either wd-CV or t-CV, then there are levels at which all glycaemic targets can be consistently met with noteworthy discrimination on hypoglycaemia risk and target TAR achieved when scan frequency is greater than 16 times per day. Either CV measures are found to be acceptable to guide clinical care assessments; however, care must be taken to apply the correct evaluation criteria. The threshold of 36% given in the recommendations has been calculated on wd-CV.[6] The value given by the CGMs recording is a t-CV. One of our findings suggests that t-CV and wd-CV are equally good for

clinical care decision guidance, one is not better than the other is. Finally, regardless of the TIR and eA1c, the key clinical scenario is to identify patients with acceptable glucose variability to achieve goals of minimal hypoglycaemia exposure. For identifying those with acceptable glucose variability to meet the time below 54 mg/dl recommended targets, t-CV and wd-CV of <40% and <34%, respectively, are suggested. In clinical practice, CGM systems provide the t-CV, and this is the most convenient CV calculation.[13]

An alternative CV measure of between-day CV was evaluated, but the approach has challenges and is not recommended to guide clinical decision making. Key limitations are that the between-day CV is not sensitive to postprandial excursions, it can be greatly impacted by individual behaviour consistency rather than the aspects of day-to-day treatment, and is dependent on the time period used to define 'day', for example, using midnight-midnight or noon-noon.

A previous study performed in a smaller population has identified a wd-CV threshold of 36% to define patients with high glucose variability and found that patients with wd-CV >36% are at higher risk of hypoglycaemic events.[12] In line with previous studies,[7,14] we observed improvement of several CGM metrics with the increase in the number of daily scans such as eA1c, TIR, TAR and TBR. However, measurements of patients with wd-CV <36% are not all in the recommended range. This perfect state seems to be only accessible to low variability patient groups (23-27% t-CV or 20-23% wd-CV) performing more than 16 scans per days. This minority of patients (only 7.5% of recordings) show how our goals may still seem unreachable for most of our patients not treated with closed loop systems. More modestly, if the goal is to avoid clinically significant hypoglycaemia as much as possible, thresholds of 33.5% and 39.5% for wd-CV and t-CV respectively seem to be more appropriate. These thresholds from our big data also confirm the data recently published from a more restricted population in real life showing that a threshold of 34% for the wd-CV is discriminant for the identification of patients at risk of hypoglycaemia <0.54 g/L if their mean glucose is near normal.[15]

Another key finding of our study shows the decrease of CV in parallel with the increased frequency of scans. CGM metrics can be used by patients to discuss therapeutic adjustments with their treating physicians, to support insulin dosing decisions as well as lifestyle modifications, and to improve glucose balance when glycaemic targets are not met. Commonly, the primary goal is to increase TIR while reducing TBR.[9] However, this goal may be challenging in patients with high CV and then higher risk of hypoglycaemic events. In addition, we postulate that therapeutic education to interpret the collected data and act upon them appropriately, combined with optimization of the treatment regimen could positively impact the wd-CV and t-CV in the same way. Nevertheless, in our study, t-CV and wd-CV are impacted by the scan frequency particularly in the highest t-CV and wd-CV quartile group, the group that is more exposed to hypoglycaemia. As a result, one of the first recommendations of the physicians for this kind of patient could be the intensification of scan frequency. The last quartile CV patients with diabetes that can be defined as patients with intrinsic high glucose variability, are potentially those for whom closed-loop insulin administration or islet transplantation could benefit the most.

A key strength of this analysis is that, to our knowledge, this is the largest data analysis performed to evaluate the value and calculation method of a glycaemic variability metric (%CV) as an assessment tool for the different glycaemic parameters. Another strength is that our findings are aligned with a recent publication that analyses and describes wd-CV and t-CV showing that the t-CV was systematically greater than the wd-CV in the analysed dataset and that both calculation methods were significantly correlated with TBR.[13]

As this study only included de-identified data, a notable limitation is the lack of information regarding patient s behaviours. Therefore, we cannot evaluate whether patients used their glucose data to make therapy decisions neither if they use it appropriately, and at the end, whether the therapeutic changes they maybe have done impact their glucose balance and the several CGM metrics.

Another limitation of our study is that the data are anonymous and lacking any other individual characteristics, such as the inability to identify patients with type 1 and type 2 diabetes and analyse their data separately.

5 | CONCLUSIONS

Our analyses highlight that only a minority of patients achieved all the clinical CGM targets as recommended in the 2019 ATTD consensus for most patients with type 1 and type 2 diabetes. Estimated A1c is found to be a good indicator of patients who meet the TAR and the TIR criteria but is not a selective indicator for meeting targets for the control of hypoglycaemia.

In addition to characterizing glucose variability, the CV can be a selective indicator for estimating patients' risk of hypoglycaemia and patients' ability to achieve minimal time in hypoglycaemia. This analysis shows that t-CV and wd-CV are equally valuable in identifying the patients with a higher risk of hypoglycaemia exposure. Notably, the thresholds are different for these two metrics.

Therefore, health care professionals should be aware of the type of CV reported by the different CGM systems. To our knowledge, for all systems, the CV calculated in the CGM reports is the t-CV. Then, appropriate thresholds should be used to identify patients presenting a clinically significant hypoglycaemia exposure above 1%, in our analysis these thresholds are t-CV >39.5% (on most of CGM reports) and a wd-CV >33.5% if detailed analysis is performed. In the future, prospective studies could help examine how CV can be improved and if the CV reduction can positively impact time in hypoglycaemia.

CONFLICT OF INTEREST
J-PR is an expert for the following companies: Sanofi, MSD, Eli Lilly, Novo Nordisk, Abbott and Medtronic; and has received research

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14795.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.