Key indices of glycaemic variability for application in diabetes clinical practice

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Highlights

- Coefficients of variation (CVs) for glucose and HbA1c are key metrics for assessing short- and long-term variability in glucose homeostasis

- A threshold of 36% for the $CV_{glucose}$ is recommended to separate stable from labile diabetes

- A $CV_{glucose}$ value of < 27% reduces the risk for hypoglycaemia to a minimal level

- A CV_{HbA1c} of < 5% for the is proposed as a suitable approach to guarantee a long-term stability of glucose homeostasis

Abstract (149 words)

Near normal glycaemic control in diabetes consists to target daily glucose fluctuations and quarterly HbA1c oscillations in addition to overall glucose exposure. Consequently, the prerequisite is to define simple, and mathematically undisputable key metrics for the short- and long-term variability in glucose homeostasis. As the standard deviations (SD) of either glucose or HbA1c are dependent on their means, the coefficient of variation (CV = SD/mean) should be applied instead as it that avoids the correlation between the SD and mean values, A $CV_{glucose}$ of 36% is the most appropriate threshold between those with stable versus labile glucose homeostasis. However, when near normal mean glucose concentrations are achieved a lower CV threshold of <27% is necessary for reducing the risk for hypoglycaemia to a minimal rate. For the long-term variability in glucose homeostasis, a CV_{HbA1c} < 5% seems to be a relevant recommendation for preventing adverse clinical outcomes.

Key words: glycaemic variability; key metrics; diabetes

Abbreviations

CGM : Continuous Glucose Monitoring

$CV_{glucose}$: Coefficient of variation for glucose

CV_{HbA1c} : Coefficient of variation for HbA1c

Search strategy and selection criteria

References for this review were identified through searches of PubMed and Google Scholar for articles published in English from database inception to July 31, 2023, by use of the terms “metrics of glycaemic variability”, “glycaemic control continuous glucose monitoring metrics”, “metrics of HbA1c variability in diabetes”, “HbA1c variability glycaemic targets”, “metrics of long-term glycaemic variability”, “glycaemic variability and hypoglycaemia”, “variability independent of the mean”. We reviewed and selected retrieved references on the basis of their relevance. We gave priority to those published from 2010 onwards, even though key older references are also cited

Introduction

In the early 1970s certain pioneers of continuous monitoring of blood glucose [1-3] reported that persons with diabetes especially those with type 1 diabetes treated with insulins possessing poor pharmacokinetic and pharmacodynamic reproducibility were subject to large daily glucose fluctuations from peaks to nadirs [4-7]. It was at this time the first metrics for assessing the short-term within- and between-day glucose variability, such as the MAGE (Mean Amplitude of Glycaemic Excursions) and MODD (Mean Of Daily Differences) respectively, were proposed [2,3]. More than 3 decades later, in the early 2000s, the advent of the revolutionary technology of continuous glucose monitoring (CGM) on an ambulatory basis [8-10] has greatly facilitated the analysis of patterns of daily glucose fluctuations [9,11,12] over increasingly prolonged periods of time using less and less invasive devices based on the insertion of tiny glucose sensors into the subcutaneous tissue. These new tools have also led to a better approach to treatment of type 1 diabetes, when coupled with different regimens of insulin delivery [13-16], together with the application of new metrics of glucose variability aimed at reducing the risk of adverse outcomes [17-25]. Despite progress being made with the introduction of more sophisticated basal and prandial biosynthetic insulin preparations [26-30] and the development of more physiological insulin delivery systems [13,14], the objective of achieving near normal control of diurnal glucose variability remains insufficiently achieved even when the overall glucose exposure is significantly improved [15,16,31,32]. It is therefore somewhat surprising that recommending thresholds for key indices of glycaemic variability remains relatively ignored in routine clinical practice despite healthcare professionals having at their disposal an extensive panel of metrics for evaluating overall glucose exposure (ambient hyperglycaemia) [12,33] and grading the severity of hypoglycaemic episodes in people with diabetes [10,33,34]. Fifteen years have elapsed from the discovery of HbA1c in the late 1950s [35,36] and to the description of its physiological meaning [37]. Moreover, it was only in the late 1990s that a value of ≤ 7.0% was universally recommended as a goal [38] after the results of the DCCT (Diabetes Control and Complications Trial) had been taken into account [39]. Limiting or minimizing the overall exposure to glucose is unanimously acknowledged as the first tier in the management of diabetes [39-42]. The need to normalize the fluctuations (upwards and downwards) of glucose homeostasis has more recently emerged as an additional objective because people displaying acute glucose excessive oscillations from peaks to nadirs are at increased risk for hypoglycaemia [18,20,43-46] and potential adverse cardiovascular outcomes [47-49]. In addition, the long-term variability in HbA1c is now recognized to be associated with all-cause mortality and to be a predictor of cardiovascular events [50-52] and possibly microvascular complications [53-56]. Consequently, markers of glycaemic variability should be used to ensure

more stringent management of short-term fluctuations and long-term oscillations of glucose homeostasis.

Addressing the general concept of glucose variability

For many healthcare professionals the glucose variability still remains misunderstood and therefore poorly integrated as a component of glucose homeostasis. As the assessment of glucose variability should circumvent the multiple issues with CGM data, the quest for its most appropriate quantification in clinical practice should firstly consider its relevance, ease of measurability and interpretation [20,57]. The assessment of the variability of glucose homeostasis consists of calculating the data distribution of glucose or HbA1c for short-or long-term variability, respectively. The computation of Standard Deviation (SD) around their mean values is unfortunately dependent on the magnitude of data and therefore any increment or decrement in the mean of the data is inevitably associated with parallel increased or decreased changes in the SD [58]. Consequently, when a glucose-lowering agent is initiated in people with diabetes, it is mandatory to separate the real biological decrement in the SD for glucose from the inescapable mathematical decrement associated to the improvement in the mean glucose concentration. This can be done by the following simple formula to adjust the SD on the mean: [$SD_{glucose}$/mean glucose] x 100 deriving the % (coefficient of variation for glucose, CV). Therefore the CV is a measure of the relative variability that represents irrespective of the magnitudes (mean) of data a meaningful matrix for comparing data dispersions between data sets involving different persons with diabetes (inter-individual glucose variability), the same individual at different times (intra-individual glucose variability), in groups of persons with diabetes treated with different glucose lowering agents (between-group glucose variability) or within one group before and after the initiation of a new antidiabetic treatment (within- group glucose variability) . Therefore, importantly the CV permits to obviate the differences due to means [58].

To illustrate the importance of using the CV rather than the SD, an example can be provided by the comparison between mean body weights and its within-group variability in families of mice versus elephants. As body weights of elephants (4 tons by average) are 200,000 times greater than those of mice (20 grams by average) the SD for body weight in these two populations of animals should differ in a similar ratio and therefore any comparison of the within-group variability in body weights must be estimated according to the coefficient of variation likely to be within the same range in mice and elephants.

The coefficient of variation for glucose

Although the $CV_{glucose}$ is used as a metric of the short-term within-day variability obtained by averaging each daily CV on several consecutive days [10], there are many other metrics

which have been proposed for evaluating the short-term glucose variability on timescales ranging from minutes to days such as the MAGE (Mean Amplitude of Glycaemic Excursions) [2], MODD (Mean Of Daily Differences) [3], CONGA (Continuous Overlapping Net Glycaemic Action), GVP (Glycaemic Variability Percentages), ADRR (Average Daily Risk Range), MAG (Mean Absolute Glucose variation), LBGI (Low Blood Glucose Index), HBGI (High Blood Glucose Index), IQR of AGP (Inter Quartile Range of Ambulatory Glycaemic Profiles) [20,22,57,59-63]. However most are not directly accessible to the vast majority of healthcare professionals and, secondly, none of them fulfills the 3 main conditions for defining an "ideal" metric of glycaemic variability, which should assess in a composite manner its magnitude and temporal component, whilst remaining independent on the mean glucose value.

Reverting to the $CV_{glucose}$ and its computation, additional comments are needed because its clinical relevance is not as simple as it looks at first glance. One of the main pitfalls is that the coefficient of variation for glucose encompasses a "cluster" of metrics each having different meaning as mentioned above. The most popular is the "averaged $CV_{glucose}$ " derived from the daily determination of the SD and the mean glucose concentration usually measured from midnight to midnight over a period of several consecutive days and further calculated using the simple arithmetic average of each daily CV. Other computations are also possible, for instance, the CV could be calculated from the average variability of the Ambulatory Glycaemic Profile (AGP) [64]. This CV is referred to as the "CV by average" and should not be mistaken for the "averaged CV" mentioned above. It suffers from many disadvantages such as underestimation of glucose variability when daily patterns of glucose are subjects to large day-to-day variations with the under-assessment steadily increasing when the asynchronism between 24-h glucose patterns becomes more and more marked [64]. Therefore, at the end of this paragraph among the main messages a particular attention should be paid at two of them: firstly, to adopt the "averaged CV" rather than the "CV by average" as an index for quantifying the short-term within-day glucose variability and, secondly, to use the IQRs at different time points as a surrogate for a qualitative rather than for a quantitative assessment of the short-term between-day variability [61].

The coefficient of variation for HbA1c

The concept of the coefficient of variation can be extrapolated to the assessment of the long-term variability of glucose homeostasis by using in a given individual the determination of quarterly HbA1c fluctuations [50-52,65]. However, the calculation of the CV for HbA1c (CV_{HbA1c}= 100 x [HbA1c SD]/[HbA1c mean]%) is subject to limitations due to the fact that in clinical practice it is difficult to obtain within reasonable delays a sufficient number of consecutive HbA1c measurements from routine quarterly readings [39,66]. To circumvent the

inconvenience of HbA1c skewed distributions and HbA1c SD dependence on its mean [55], it has been proposed to assess the visit-to-visit variability of HbA1c from the calculation of the VIM (Variability-Independent of the Mean), which is being used by cardiologists for assessing the visit-to-visit variability of blood pressure [67-70]. The VIM is calculated as the SD divided by the mean, the latter being elevated to the power β. Consequently, the VIM for HbA1c is represented by the following equation: HbA1c VIM = 100 x [HbA1c SD]/[HbA1c mean] $^{\beta}$, where β is the regression coefficient obtained when natural logarithms of the SD are plotted against the natural logarithms of the mean [50,71]. As established for blood pressure variability, the regression coefficient β is intended to remove any residual correlation between the HbA1c variability and its mean value, but studies have shown that, in most situations, VIM and CV are strongly intercorrelated [67,68], Therefore, in clinical practice the easy computation and interpretation of the CV_{HbA1c} render its application more appropriate than that of the VIM. Other metrics have been proposed to estimate the long-term variability of clinical or biological parameters such as blood pressure or markers of glycaemic control [72,73]. Such metrics that are referred to as either the Average Real Variability (ARV) or the Average Successive Variability (ASV) are based on the measurements of absolute differences between successive values in a serial set of data provided that the number of data is sufficiently large. The variability score described by Forbes et al [73] is a variant of methods used for estimating the long-term variability of HbA1c. Its calculation consists of counting the number of times successive readings of HbA1c differ by 0.5% or more. Despite its relative simplicity, the variability score is based on the arbitrary hypothesis that the threshold of HbA1c for abnormally large successive increments or decrements in HbA1c is of 0.5%. Secondly the variability score depends on the absolute HbA1c levels collected at the time of readings, i.e. in other words on the mean of HbA1c, a remark also applicable to the ARV and ASV.

At the end of this preliminary overview of the key metrics used for the determinations at individual levels of the short- and long-term glucose variability the general conclusion can be worded as follows: “The most clinically applicable index of glycaemic variability appears to be the CV for either glucose or HbA1c whether the timescales of variability is based on minutes or months. This well acknowledged mathematical index has the main advantage of being simple to calculate, easily understandable and not dependent on mean values of either glucose or HbA1c levels”.

Key metrics for glycaemic variability

It is well acknowledged that diabetes is characterized by a loss of “tranquility” in glucose homeostasis, a feature more proeminent according to whether the persons have type 1 or type 2 diabetes [9,10,18,20,24,43,57,59,60,64]. People with type 1 diabetes experience hard-to control blood glucose swings from peaks to nadirs more often than those with type 2 diabetes [74,75]. In its more harmful presentation characterized by extreme hyperglycaemic surges and recurrent hypoglycaemia unawareness, sometimes associated to cognitive impairment and the rapid development of ketoacidosis. This condition was termed as “brittle diabetes” by Woodyatt in the 1930s [76], albeit it seems more appropriate to use the wording “unstable” or “labile” diabetes [77]. It is always difficult to delineate the boundary between stable and labile diabetes due to a continuum between the two conditions. Despite such difficulties, there remains the need to providing recommendations to those who experience such instability and in whom intensification of their management is necessary. Such interventions can range from highly sophisticated approaches such as islet-cell transplantations [78,79], implementations of either fully or hybrid automated insulin deliveries [14-16,80], to more conventional therapeutic strategies such as continuous subcutaneous insulin (CSII) therapy [80] or multiple insulin injections paired with real time continuous glucose monitoring [13,81]. Consequently, an individualized intensification of therapy strategy should take into consideration the variability in glucose homeostasis, be it graded into severe, intermediate or low level. It is mandatory to keep in mind that any recommendation should be as simple as possible in order to facilitate the physician’s decision making in routine clinical practice.

The $CV_{glucose}$ of 36% to separate stable from unstable diabetes

This value appears to be the most appropriate threshold above which the individual can be regarded as experiencing a state of labile glycaemic control [10]. The validation of this threshold is based on the analysis of CGM data collected from two subsets of persons with type 2 diabetes only treated with antidiabetic agents theoretically devoid of any risk of hypoglycaemia (insulin sensitizers and DPP-4 inhibitors) and considered to have stable diabetes [75]. The upper limits of the distribution of $CV_{glucose}$ levels in these two groups were identical at 36% (figure 1). In contrast, as soon as treatment was instigated with sulphonylureas or insulin, thus posing a risk of hypoglycaemia, the $CV_{glucose}$ exceeded 36%. In those requiring more intensified treatment with either sulphonylureas or insulin in type 2 diabetes and basal-bolus insulin regimens delivered as multiple injections or by continuous insulin infusions in type 1 diabetes, the $CV_{glucose}$ was further increased to proportions of 12.3%, 19.0% and 55.7%, respectively [75]. Similar findings have also been observed by other authors [82,83], and consequently members of the International Consensus on the Use of Continuous Glucose Monitoring adopted 36% $CV_{glucose}$ as the primary glycaemic index of

variability to separate people with stable from those with unstable control of glucose homeostasis [10]. In those treated with closed-loop or sensor-augmented systems despite improvements in metrics assessing the total glucose exposure (such as the TIR for instance) the $CV_{glucose}$ can remain elevated. The apparent discordance between the lacks of improvement in the $CV_{glucose}$ and the significant reductions in the standard deviation [15, 31] emphasizes that any change in the means of a data set is mathematically associated with a parallel change in the SD [58]. Therefore, it is important to recognize that improvements restricted solely to the SD of glucose around a mean glucose concentration should be regarded skeptically in the absence of a parallel improvement in the $CV_{glucose}$.

A $CV_{glucose}$ below 27%, is it suitable to avoid hypoglycaemia?

Hypoglycaemias are stratified into several categories according to whether blood glucose concentrations are below an alert value of 70 mg/dL (3.9 mmol/L) with or without clinical symptoms or below 54 mg/dL (3 mmol/L) [10,33,34,84]. In recent years, the extended use of CGM technology has permitted the frequency, duration and magnitude of hypoglycaemic episodes to be accurately quantified [12]. One of the metrics currently utilized for this purpose is the Time Below Range (TBR), i.e. the percentage of time spent below either 70 or 54 mg/dL (3.9 or 3.0 mmol/L), i.e. levels 1 and 2, respectively. From the analysis of 200 24-h continuous glycaemic profiles in 100 persons with type 1 diabetes by plotting the TBR < 54 mg/dL (dependent variable on the Y axis) against the $CV_{glucose}$ (independent variable on the X axis), we have demonstrated a simple increasing exponential relationship: $y = 0.93\ e^{0.043}$ ($r = 0.509$, $p < 0.001$) [43]. More interesting, a complementary analysis of the scatter plot of these two variables shows that among the 31 daily glycaemic profiles that display a $CV_{glucose}$ < 27%, only 1 (3.2%) had a TBR < 54 mg/dL (3.0 mmol/L) in comparison to 71 out of 169 (42.0%) exhibiting a $CV_{glucose} \geq 27\%$ ($p < 0.0001$) [43]. As a consequence, there existed a 13.1-fold increased risk of level 2 hypoglycaemia when people with a $CV_{glucose} \geq 27\%$ are compared with those < 27%, leading to the conclusion that the risk of hypoglycaemia becomes minimal when the $CV_{glucose}$ is < 27%. However, maintaining the %CV below this threshold does not guarantee the unexpected occurrence of hypoglycaemic events. The proposal of 27% as threshold for minimizing the risk for hypoglycaemia is supported by other findings. In people with type 1 and type 2 diabetes after normalizing the glucose values, Rodbard reported a positive correlation between the $CV_{glucose}$ and the risk for hypoglycaemia when assessed from TBR < 50 mg/dL (2.8 mmol/L) [85]. In addition, by extrapolating the regression line to its intercept with the TBR value at 0%, it appears that the corresponding $CV_{glucose}$ is approximately of 27%. Similar results were observed in people with type 2

diabetes treated with oral antidiabetic agents either alone or in combination with insulin. By using a cross tabulation with the number of hypoglycaemic events < 56 mg/dL (3.1 mmol/L) as the dependent variable on the vertical axis and the mean glucose concentration and glycaemic variability (SD) as explanatory variables (figure 2), we have observed that the risk of developing hypoglycaemia was completely absent when the mean glucose concentration and the SD for glucose were concomitantly > 7.8 and < 2.2mol/L, i.e. when the %CV was < 28% [23]. However, this cross tabulation also indicates that a $CV_{glucose}$ < 28% is a necessary but not a sufficient condition. For instance, some patients in the lower tertile of mean glucose concentrations < 7.8 mmol/L keep a significant risk for hypoglycaemia even when their $\%CV_{glucose}$ is < 28% (figure 2).

It is therefore not currently possible to define an accurate threshold below which the risk for hypoglycaemia would be eradicated, because such a threshold is also dependent on the mean glucose concentrations. Nevertheless, it remains that a value of 27% is the upper limit of the $CV_{glucose}$ in healthy individuals with a HbA1c < 5.7% (38.7 mmol/mol) [86]. When investigated on an ambulatory basis with a CGM device for 10 days the mean $CV_{glucose}$ (± SD) was of 17 ± 3%. As these people did not experience any hypoglycaemic episode and considering that the glucose distribution at least in normal individuals is symmetrical, 99.9% of the measurement in such a population should lie within the mean ± (3.29 x SD) [87], i.e., within 17% ± (3.29 x 3%), which equates to an upper limit of the total distribution curve at 27%. It is therefore possible to draw an ordinal scale for the risk of hypoglycaemia as displayed in figure 3. The risk can be stratified as low, medium or high according to whether the $CV_{glucose}$ is below 27%, between 27 to 36% or greater than 36% (labile control). Below 27% the risk for hypoglycaemia is low or very low but as indicated by a question mark in figure 3, it remains impossible to set a %CV below which the hypoglycaemic risk would be eradicated.

A CV_{HbA1c} below 5%, is it relevant to guarantee long-term glucose stability?

Since the systematic review and meta-analysis published in 2015 by Gorst et al [65] several studies [50-52] and a recent meta-analysis [88] have reported that HbA1c variability quantified as SD or CV is positively associated with vascular complications and mortality independently of HbA1c levels, but the authors did not address the question as to whether there exists or not an upper limit of HbA1c variability that should not be exceeded. However, two of these studies provided data which permitted “labile long-term variability” to be defined [51,52]. In these two retrospective studies, the investigators found that the Hazard Ratio (HR) for all-cause mortality in type 2 diabetes increased progressively and linearly with increasing CV_{HbA1c} and that this HR became significantly greater than the neutral HR of 1 as soon as the

CV_{HbA1c} exceeded a value of 4,71% [51] or 4,13% [52], i.e. approximating 5% [89] to simplify the message delivered from these two epidemiological studies. These data seem to be relevant because the computation of the CV_{HbA1c} has been made from quarterly HbA1c readings throughout periods of 4.7 [51] and 5.5 years [52], respectively, i.e. from approximately 20 consecutive HbA1c measurements. However in clinical practice we have to conciliate the need for a sufficient number of values to validate the calculation of SDs and means for HbA1c, but low enough to render it feasible. One proposal might be simply to only use two successive HbA1c readings at a 3-month interval, designated HbA1c $t_{0(baseline)}$ and $t_{3(3months)}$. The assessment of the upper threshold for the HbA1c variability can be done from the calculation of upward and downward differences between HbA1c levels at t_0 and t_3. To address this issue, it should be reminded that in a normally distributed set of data 95% (the confidence interval, CI) of the data lie within an interval whose upper and lower limits are equal to the mean ± 1.96 SD, i.e. approximately ± 2 SD [87]. By applying this statistical concept to the increments or decrements in HbA1c from baseline (t_0) to the next value measured 3 months later (t_3) the absolute upward or downward differences (ΔHbA1C) between the 2 values should not exceed 2 SD_{HbA1c}. By rearranging the equation of CV_{HbA1c} [SD_{HbA1c}/mean HbA1c] x 100), the absolute value of the 2 SD_{HbA1C} is given by [(2 x CV_{HbA1c})/100] x [mean HbA1c at t_0]. Therefore, for a CV_{HbA1c} of 5% the value of 2 SD_{HbA1c} [(2 x 5)/100] x [mean HbA1c at t_0] means that a HbA1c change (ΔHbA1c) from t_0 to t_3 should not exceed [0.10] x [HbA1c at t_0] to remain within the stable category of glycaemic control [89]. For instance, from a baseline HbA1c value of 7.0% (53 mmol/mol) the next value 3 months later should remain within 7.0 ± 0.7%, i.e. between 6.3% (45 mmol/mol) and 7.7% (61 mmol/mol). Such a calculation displayed in table 1 for baseline HbA1c levels ranging from 7.0 to 10.0% has the main advantage to be simple, to avoid “clinical inertia” when visit-to-visit HbA1c changes exceed such limits, and contrarily to other calculations [88,90], to be adjusted on the baseline HbA1c level.

Conclusion

More attention should be paid to short- and long-term variability in glucose homeostasis is an evidence as it is acknowledged and recommended that the treatment of people living with diabetes must achieve a near normal glycaemic control [20,91]. Independent to the impact of the total glucose exposure as key player of diabetic complications [39-42,92] the risk for adverse clinical outcomes due to the global variability in glucose homeostasis is dependent on 3 explanatory variables: (i) the short-term glucose variability ($CV_{glucose}$), (ii) long-term variability (CV_{HbA1c}) and (iii) hypoglycaemia [93]. These factors are displayed in figure 4

where the global variability in glucose homeostasis is represented by the diagonal arrow of a geometric cube and the short-term $CV_{glucose}$ and long-term CV_{HbA1c} variabilities on the X and Y axis. Hypoglycaemia with an alert threshold of either 70 or 54 mg/dL (3.9 or 3.0 mmol/L) with a $CV_{glucose}$ of < 27% expressed on the Z axis. According to this model, an antidiabetic agent aimed at reducing the risk for adverse clinical events via its action upon glycaemic variability should target the 3 dimensional coordinates (X, Y and Z) by maintaining their values below the following thresholds: (i) 36% at least for the $CV_{glucose}$ in order that patients escape from the diabetic state referred to as “brittle or labile diabetes”; (ii) 5% for the CV_{HbA1c} and (iii) 27% for the $CV_{glucose}$ to eradicate or to reduce the hypoglycaemiac risk. We should however keep in mind difficulties-to achieve these objectives especially the latter in people with type 1 diabetes even when they are treated with sophisticated insulin deliveries [13-16,94]. As final remark, this review also provides an additional piece of evidence for encouraging the assessment of metrics of glucose variability in randomized clinical trials especially in those aimed at comparing different antidiabetic agents or strategies [95].

Authors’ contributions:

L Monnier and D Owens equally contributed to the conceptualization and writing of this review; F Bonnet, C Colette and E Renard participated into its validation and editing. L Monnier has directly accessed and verified the data reported in this research review.

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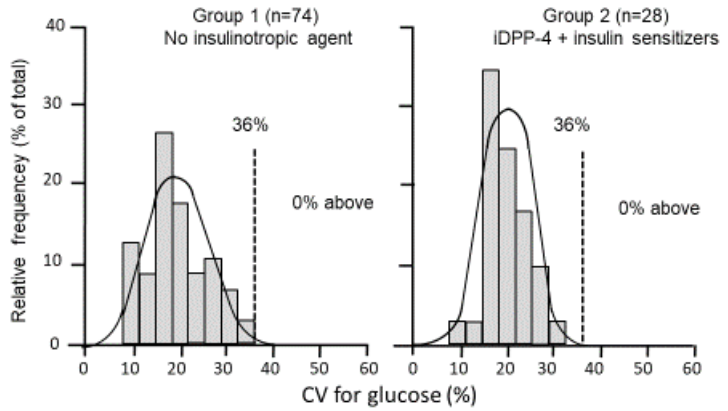
Table 1. Proposal ranges of HbA1c fluctuations between two successive measurements at 3 month-interval

HbA1c at t_0	Expressed as absolute differences (Δ) between t_0 and t_3 month	Expressed as upper and lower limits of HbA1c at t_3 month
7.0%	Δ ≤ 0.7%	6.3 – 7.7%
8.0%	Δ ≤ 0.8%	7.2 – 8.8%
9.0%	Δ ≤ 0.9%	8.1 – 9.9%
10.0%	Δ ≤ 1.0%	9.0 – 11.0%

General rule: The quarterly decrements or increments (Δ) in HbA1c levels from a baseline visit (at t_0) to the next one, 3 months later (at t_3), should not exceed a value equal to: 0.10 x [HbA1c]

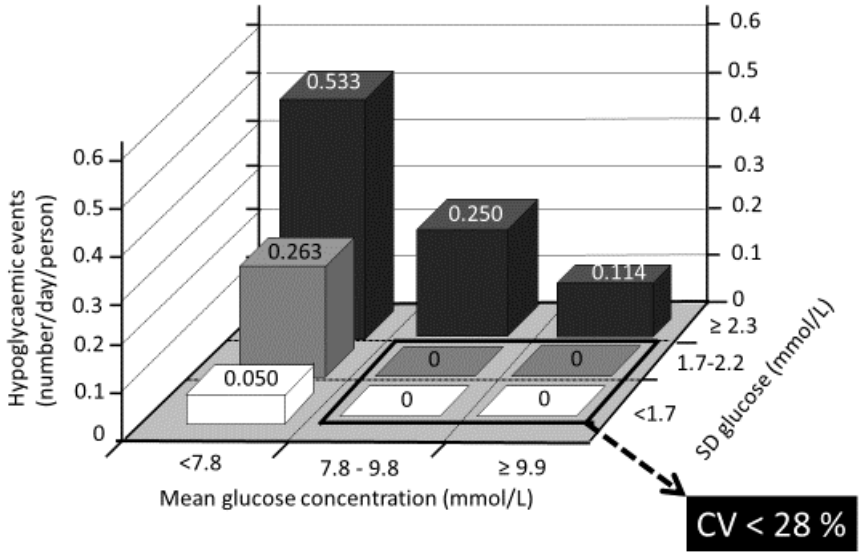
Figure captions

Figure 1 : Histograms of relative frequency distribution of the CV for glucose (CV) in 2 populations of people with type 2 diabetes



The threshold between stable and labile diabetes (CV =36 %) is defined as the upper limit of the frequency distribution in groups of persons with type 2 diabetes who were treated with diet alone or associated with insulin sensitizers (group 1) or with a dual therapy combining insulin sensitizers and DPP-4 inhibitors (group 2), i.e. with antidiabetic agents theoritically devoid of any risk for hypoglycaemia (from reference 75)

Figure 2 : Number of hypoglycaemic events in type 2 diabetes



Cross tabulation analysis as a function of tertiles of mean glucose concentrations and tertiles of SD for glucose (from reference 23).

Figure 3 : Ordinal increasing scale for the risk of hypoglycaemia

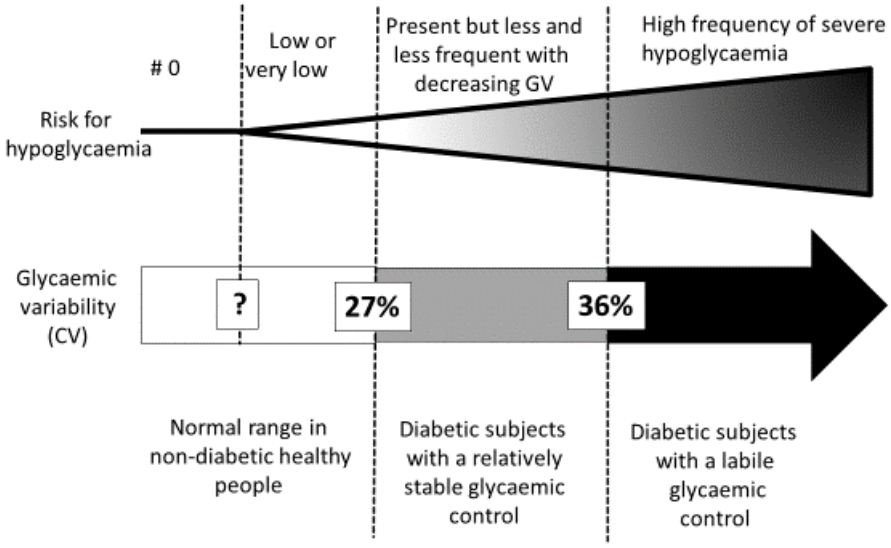
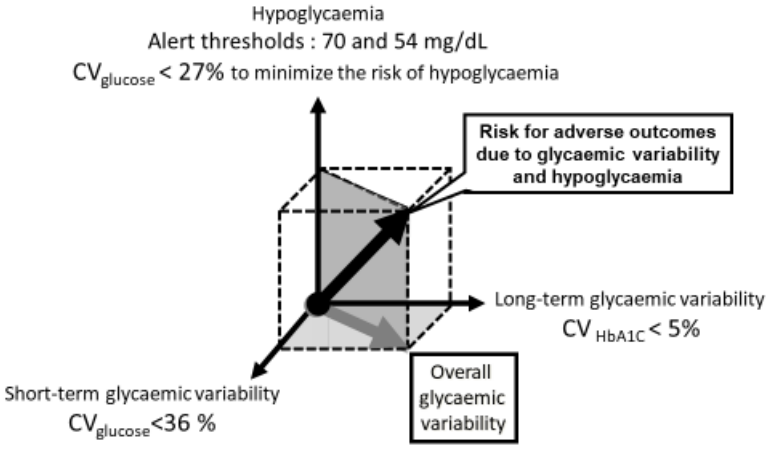


Figure 4 : Targets for the metrics of variability in glucose homeostasis


Hypoglycaemia
Alert thresholds : 70 and 54 mg/dL
$CV_{glucose}$ < 27% to minimize the risk of hypoglycaemia
Risk for adverse outcomes due to glycaemic variability and hypoglycaemia
Long-term glycaemic variability
CV_{HbA1C} < 5%
Overall glycaemic variability
Short-term glycaemic variability
$CV_{glucose}$<36 %