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Glycaemic variabilities: Key questions in pursuit of clarity

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Glycaemic variabilities: Key questions in pursuit of clarity

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Abstract

After years of intensive investigation, the definition of glycaemic variability remains unclear and the term variability in glucose homoeostasis might be more appropriate covering both short and long-term glycaemic variability. For the latter, we remain in the search of an accurate definition and related targets. Recent work leads us to consider that the within-subject variability of HbA1c calculated from consecutive determinations of HbA1c at regular time-intervals could be the most relevant index for assessing the long-term variability with a threshold value of 5% (%CV = SD of HbA1c/mean HbA1c) to separate stability from lability of HbA1c. Presently, no one can deny that short- and long-term glucose variability should be maintained within their lower ranges to limit the incidence of hypoglycaemia. Usually, therapeutic strategies aimed at reducing post-meal glucose excursions, i.e. the major contributor to daily glucose fluctuations, exert a beneficial effect on the short-term glucose variability. This explains the effectiveness of adjunct therapies with either GLP-receptor agonists or SGLT inhibitors in type 2 diabetes. In type 1 diabetes, the application of a CGM device alone reduces the short-term glycaemic variability. In contrast, sophisticated insulin delivery does not necessarily lead to such reductions despite marked downward shifts of 24-hour glycaemic profiles. Such contrasting observations raise the question as to whether the prolonged wear of CGM devices is or not the major causative factor for improvement in glucose variability among intensively insulin-treated persons with type 1 diabetes.

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Glycaemic variability is a heterogeneous cluster of metabolic dysregulation that covers several entities with a common denominator defined as either short or long-term fluctuations of glucose homoeostasis [1-6]. The short-term within-day glucose variability corresponds to daily upward or downward glucose excursions [1,2]. Even though the percentage of time above or below range (TAR or TBR) reflects glucose excursion [7], these two metrics do not provide a full and accurate assessment of the intra-day variability [8]. These indices represent the non-arithmetic sum of post-prandial glucose increments above pre-meal values, decrements below the 24-h mean glucose concentration and glucose fluctuations during inter-prandial periods. The coefficient of variation for glucose (%CV = [SD around the 24-h mean glucose /24-h mean glucose] x 100), expressed as percentage) is the easiest and most comprehensive metrics for quantifying daily glucose fluctuations and a %CV of 36% is presently consensually acknowledged as the cut-off value that separates stable from labile diabetes [9,10]. Its assessment requires the use of a continuous glucose monitoring (CGM). However the analysis of 24-h glucose profiles, especially in type 1 diabetes indicates that a poor day-to-day synchronism exists in upward and downward glucose fluctuations [11]. Consequently, a full assessment of the short-term glucose variability should integrate its between-day component [2]. Despite many attempts to find an ideal index that integrates the temporal component of glycemic variability [12,13], it seems that the Mean Of Daily Differences (i.e. the MODD) defined by Service and Molnar several decades ago [14], remains the most efficient metrics for assessing the inter-day variability. A value less than 60 mg/dL is probably an indicator of an acceptable between-day variability [2], but surprisingly this metrics and its cut-off value are not currently adopted as a reference. More surprising is the absence of any reference in terms of long-term variability in glucose homoeostasis, even though visit-to-visit fluctuations of fasting glucose or HbA1c levels at weekly, monthly or quarterly time-intervals for the latter have been associated with the incidence of long-term harmful clinical outcomes such as adverse cardiovascular events [15]. Reverting to the short-term glycaemic variability, its reduction should be the major objective of healthcare professionals when they plan to limit the intensity of post-meal glucose increments and the incidence of hypoglycaemia. Such a goal cannot be attained merely from downward translation of 24-h glycaemic profiles. The typical example is provided by the use of basal insulin regimens alone for the management of insulin requiring type 2 diabetes with secondary failure to treatments with maximal tolerated doses of non-insulin antidiabetic agents. Such treatments reduce the overall glucose exposure, but usually fail to improve the short-term glycaemic variability [16,17]. Considering that the latter glycaemic disorder can potentially be at risk for diabetic complications [5], augmented-managements of diabetes should be aimed at searching for strategies such as initiations of either GLP-1 receptor agonists or SGLT2 inhibitors [18-21], implementations of new modalities of insulin delivery [22-28] or simply the wear of new rtCGM or isCGM devices [29-34]. All these

strategies are potentially able to reduce both the ambient hyperglycaemia and acute or chronic glucose fluctuations. These considerations can be applied to both type 1 and type 2 diabetes and raise three main questions that can be summarized as follows:

(1) Do we need a target value for long-term glycaemic variability?

(2) Is it important to reduce the glycaemic variability and how to do it?

(3) The missing link: Does improvement in glycaemic variability contribute to the additional cardiovascular benefits observed with GLP-1 receptor agonists and SGLT inhibitors?

Attempting to shed light on these pending poorly documented questions should open new road maps for treating and controlling glycaemic variability.

1. Do we need a target value for long-term glycaemic variabiity?

In a systematic review and retrospective analysis and meta-analysis of 20 studies (7 in type 1 and 13 in type 2 diabetes) Gorst et al [15] reported that HbA1c variability is positively associated with micro- and macrovascular complications and all-cause mortality, independently of HbA1c levels. Most studies included in this meta-analysis were conducted in large populations, the total numbers of participants being 44,021 and 43,620 for the studies that were conducted in type 1 and type 2 diabetes, respectively. Despite the statistical significance of the results the authors pointed out the absence of consistency in definitions of HbA1c variability that was either given as standard deviation (SD) around a mean HbA1c level or as coefficient of variation (%CV= [SD/mean HbA1c] x 100). In addition, the number of HbA1c measurements used for calculating the SD or CV differed from one study to another and ranged from a median as large as 3 to 79 per patient. This observation raises two questions: what should firstly be the minimal number of HbA1c measurements collected to consider that the HbA1c variability is correctly assessed and secondly the minimal duration of the follow-up periods. In many studies the visit-to-visit fasting blood glucose variability is used as a substitute for the quarterly HbA1c variability, but there is no consensus on the frequency of glucose testing, whilst quarterly assessments are generally recommended when the HbA1c testing is used. An additional argument that favors the use of the visit-to-visit HbA1c variability rather than that of its seemingly equivalent the visit-to-visit fasting blood glucose (FBG) variability is simply relying on the fact that careful evaluations over several consecutive days have shown that within-subject CVs for FBG in healthy individuals range from 4.8 to 6.1%, whereas intra-individual CVs for HbA1c are much smaller at 2-3% [35]. For obvious reasons it is recommended that spontaneous intra-individual variations of any biological metrics in healthy persons should remain as small as possible when compared with the temporal fluctuations observed in those who suffer from diseases that affect such

metrics. A few examples can be given [36-38]. For the within-subject variability of FBG in type 2 diabetes, Lin et al [36] reported values ≤14.1% and > 42% in the lowest and highest quartiles, respectively. In the ALLHAT study [37], the values reported for this metric were found to be somewhat different: 0 to 5.6% and 19.7 to 94.6% in the lowest and highest quartiles mainly represented by persons without and with diabetes, respectively. After separating into quartiles the data collected In a large primary cohort of 58,832 persons with type 2 diabetes Critchley et al [38] have considered that low and high variability in HbA1c can be defined according to whether the within-subject variability (%CV) for HbA1c was ≤ 4.71% or > 11.4%, respectively. Bringing all these data together, the dispersion of visit-to-visit fluctuations of HbA1c seems to be less erratic than those of FBG. This latter observation combined with the fact that it is easier to define appropriate quarterly time-intervals for serial measurements of HbA1c [38-43] rather than daily, weekly, monthly or quarterly intermittent visit-to-visit laboratory testing or self-monitoring of FBG and/or other additional spot glucose values [37, 44-46], claims for the preferential utilization of %CVs for HbA1c to assess the within-subject long-term glucose variability also referred to as “long-term variability of glucose homoeostasis”. This wording probably better encompasses all features of long-term fluctuations of glycaemic disorders. The relevance of the HbA1c variability as marker of quality of the diabetic control has been recently reinforced by two post-hoc analyses of the ACCORD trial [41,42]. These two analyses have included participants in the intensive and standard glycemic control arms of the ACCORD trial [47] that was initially designed for testing the effects on cardiovascular outcomes and all-cause mortality of an intensive therapy aimed at reducing HbA1c levels below 6.0% versus a standard therapy targeting HbA1c levels between 7.0 and 7.9%. Unfortunately, this trial was discontinued because after a mean treatment period of 3.7 years the intensively treated group showed an increased mortality without any reduction in the incidence rate of major cardiovascular events. Such disappointing and unexpected results have never been clearly explained but there is suggestive evidence that the increased frequency of hypoglycaemic episodes in the intensive-therapy arm could have substantially increased the risk of deaths [48]. Nevertheless there remains that the ACCORD trial represents an excellent basis for retrospective analyses of the role of HbA1c variability on adverse clinical outcomes because HbA1c measurements were performed every 4 months in both groups over a mean period of several years [47]. In one of this post-hoc analysis [41] the authors demonstrated that the proportion of patients with incident heart failure increased steadily with worsening HbA1c variability. In another post-hoc analysis of the ACCORD trial data sets it was observed that the long-term HbA1c variability was a strong predictor of all-cause mortality both in the intensive and standard- therapy groups [42] and that this disorder conferred an increased risk in combination with HbA1c mean especially when patients were intensively treated. In this study the visit-to-visit HbA1c variability was quantified using both the coefficient of variation for HbA1c (%CV =

[SD/mean HbA1c] x 100) and the variability independent of the mean (VIM of HbA1c). The %CV, which is the ratio of the SD to the mean expresses the sample variability to the mean of the sample and corrects the inconvenience of the SD calculation alone because it should be noted that unfortunately the SD proportionally increases with increasing mean [49]. In order to eradicate the problems encountered between the visit-to-visit HbA1c variability computed from the %CV for HbA1c and the HbA1c mean, it can be useful to measure the variability after raising the mean denominator, which appears in the CV = SD/mean, to a certain power β [37,50-52]. This number β is theoretically intended to remove any correlation between the HbA1c variability and its mean value. Consequently, the VIM is computed from the following equation: VIM = SD/mean$^{\beta}$, where β is the regression coefficient of the linear relationship obtained when the natural logarithms of SD are plotted against the natural logarithm of mean. In most situations VIM units are essentially similar or proportional to CV units after adjustment for mathematical expression. For instance, cardiologists were the first ones to use the VIM for studying the effects of visit-to-visit blood pressure variability on the incidence rate of cardiovascular events [50-54]. Such studies have shown that the CV and VIM for blood pressure are strongly inter-correlated with a Pearson's correlation value as high as 0.99 [54]. Despite the lack of any comparative data between CV and VIM for HbA1c, there is no reason to think that such highly significant correlations cannot be extrapolated to HbA1c and as a consequence it seems that the easily understandable %CV metrics used for HbA1c should be also the most appropriate index for assessing the long-term variability of glucose homoeostasis provided that a sufficient number of HbA1c measurements be recorded, for instance every 3 months throughout a period of at least 3 years.

Presently, the definition of a target value for the HbA1c variability has never been clearly formulated and therefore it remains difficult to know which cut-off threshold could distinguish labile from stable diabetes in terms of long-term variability. However the study of Critchley et al [38] can provide at least a starting point for addressing this issue. By using the data sets of the Clinical Practice Datalink that include 58,832 persons with type 2 diabetes, these investigators have evaluated the incidence rate of several primary outcomes and more specifically of all-cause mortality during 2010-2015 after having measured the CV for HbA1c during the run-in period of this study from 2005 to 2009. After stratifying the participants into two groups according to whether HbA1c averages were found to be low (≤6.5%) or high (> 7.91%), the authors have measured the effect of the long-term HbA1c variability (%CV for HbA1c) on the incidence rate of deaths. As illustrated in figure 1, the results indicate that in the group of patients who exhibited satisfactory overall glycaemic control, the adjusted mean Hazard Ratio for the risk of all-cause mortality compared with the subset of patients taken as reference was significantly lower than 1.5 as long as the %CV for HbA1c remained below

4.71%. In contrast in the participants who had unsatisfactory overall glycaemic control no conclusion can be drawn because the 95% confidence intervals of Hazard Ratios were too large. By only retaining the results observed in the well-controlled group, it seems reasonable to think that a HbA1c-%CV of 5%, approximately, might be an appropriate cut-off value for deciphering type 2 patients with and without excessive long-term variability of glucose homoeostasis. In addition it should be noted that this threshold of 5% is compatible with the following prerequisite of a level significantly higher than that observed for the spontaneous intra-individual HbA1c CV in healthy individuals (2 to 3% as mentioned above) [35].

In summary at the end of this chapter, assessing the full glycaemic status in diabetes infers the availability of parameters evaluating the ambient hyperglycaemia (the overall glucose exposure) but also the variability of glucose homoeostasis both in the short- and long-term. It is now well acknowledged that in routine clinical practice assessments of the Time in Range and HbA1c combined with the following recommendations (TIR > 70% [7] and HbA1c < 7% [55]) permit to achieve the objectives of quantifying the short-and long-term glucose exposure, respectively. A few years ago, the coefficient of variation for glucose (%CV for glucose) has been adopted as the most appropriate metrics for assessing the short-term glucose variability with a cut-off value of 36% for distinguishing stable from labile diabetes [9,10]. However this series of metrics needs to be completed with a parameter that extends the assessment of the glycaemic variability to its long-term component. The visit-to-visit variability of HbA1c measured at 3-month intervals with a threshold of 5% might be a relevant proposal in order to achieve a broader appraisal of the overall glucose status in persons with diabetes.

2. Is it important to reduce the glycaemic variability and how to do it?

There is a large body of presumption for the roles of short-and long-term glucose variability as risk factors for acute and chronic adverse cardiovascular events [1,5,38,42,56-60], possibly mediated through hypoglycaemic episodes [48,61-63] because it has been established that the greater the glycaemic variability the longer the time spent below a glucose value of 54mg/dL [64]. However many uncertainties still remain in terms of relationship between the variability in glucose homoeostasis and the development of and progression to diabetes complications. This is simply due to the fact that most studies are observational or based on retrospective analyses of interventional trials, not initially designed for studying the effects of glycaemic variability [5]. Consequently, assessing the causative role of glycaemic variability as risk factor for adverse clinical outcomes should require a pre-specified controlled randomized interventional trial (CRT) comparing the incidence rates of major adverse cardiovascular events (MACE) in two groups of subjects with diabetes

differing in terms of glucose variability for several years but exhibiting similar exposure to ambient hyperglycaemia (average HbA1c levels) and many risk factors such as plasma lipids, blood pressure and others throughout a follow-up period of several years. Despite the clarity of the design of this study, its practical implementation would certainly be subject to many difficulties due to the requirement of maintaining a tight and stable control of all parameters with the help of a sustained wear of a CGM device over the entire study period. In addition, in such a study glucose oscillations from peaks to nadirs should be estimated using both the SD around the 24-h mean glucose value and the coefficient of variation for glucose (%CV). Two clinical cases reported in figures 2a and 2b can serve as examples for depicting how antidiabetic treatments can lead to divergent effects on SD and %CV for glucose. The first case (figure 2a) corresponds to a patient with type 2 diabetes in whom the implementation of a new therapy, e.g. the initiation of a basal insulin results in a downward shift of the 24-hour glycaemic profile, i.e. in a reduction of the 24-h mean glucose concentration without any change in the SD value from baseline. As a result the %CV increases with the new treatment. In the second case (figure 2b), the new treatment reduces both the 24-h mean glucose concentration and its SD. According to whether the improvements in SD will be greater, equivalent or smaller than those of the 24-h mean glucose concentrations, the %CV will be reduced, unchanged or augmented when compared with baseline. Consequently, it appears that clear conclusions in terms of changes in glycaemic variability can be only drawn when convergent effects are observed on both SD and %CV and more generally on both metrics of short-term glycaemic variability dependent on the mean (the SD for instance) and those adjusted on the mean (the %CV for instance) or independent on the mean such as the MAGE. The relevance of this latter remark requires additional detailed examples of therapeutic approaches aimed at improving the overall glycaemic control of persons with diabetes. For this purpose we have selected several interventional trials related to the use of: 2.1 single wear of a CGM device without any change in the antidiabetic pharmacotherapy [29-34]; 2.2 add-on treatments with non-insulin glucose-lowering agents [18-21,65-69]; and 2.3 sophisticated insulin delivery systems developed for theoretically providing superior glucose control [22-28].

2.1 Single wear of CGM devices: Impact on glycaemic variability.

Historically, the starting points were the DIAMOND and GOLD trials [29,30]. The DIAMOND randomized clinical trial [29] was conducted in 158 adults with type 1 diabetes treated with multiple daily insulin injections. After a run-in period of 2 weeks with a “blinded” CGM, each participant was randomly assigned for 24 weeks to either “unblinded” CGM or control group. For those allocated to the CGM, individualized recommendations were made by their healthcare professionals to incorporate the data provided by the “unblinded” CGM into their diabetes management. In the control group, the patients were asked to perform a self-blood glucose monitoring (SBGM) at least 4

times a day and a CGM sensor was inserted in a “blinded” mode at 1, 12 and 24- week visits. The main results (table1) showed significant differences between the 2 groups with marked reductions in HbA1c (- 0.6%, 95% CI = - 0.8 to - 0.3, $p < 0.001$), coefficients of variation for glucose (- 4%, 95%CI = - 6 to - 2, $p < 0.001$) and hypoglycemic events (time spent below range = 70 mg/dL) in the CGM group, whereas these parameters remained unchanged in the control group.

In the GOLD study [30], the objective was also to evaluate CGM against conventional monitoring (SMBG alone) but with a slightly different design since patients were submitted to a randomized cross over trial with two sequences of either CGM or SMBG for 25 weeks with a 17-week washout between the two periods. Analyses of the between-sequence differences showed (table 1) that the overall glucose exposure (HbA1c = - 0.43%, 95%CI = - 0.57 to - 0.29, $p < 0.001$) and metrics of glycaemic variability: SD for glucose = - 9.69 mg/dL (95%CI = - 10.76 to - 6.61, $p < 0.001$) and MAGE = - 19.36 mg/dL (95% CI = - 24.26 to - 14.16, $p < 0.001$) were better at the end of the CGM periods when compared with the conventional monitoring.

The GOLD trial was further extended (SILVER study) [31] for an additional period of one year along which all participants benefited from the wear of “unblinded” CGM. The results of comparison from SMBG periods in GOLD to end of the SILVER study showed significant decreases in HbA1c (- 0.345%, $p < 0.0001$), mean glucose concentrations (- 0.53 mmol/L, $p = 0.016$), SD around the 24-h mean glucose value (- 0.62 mmol/L, $p < 0.0001$) and MAGE (- 2.26 mmol/L, $p < 0.0001$) (table 1).

Even though the primary end point of the CONCEPTT trial [32] was to examine the impact of real time CGM on HbA1c and neonatal outcomes in pregnant women, it was also shown that the participants included in the CGM group had slightly reduced their short-term glucose variability: SD for glucose from 3.1 to 2.2 mmol/L and MAGE from 6.0 to 4.2 mmol/L with p values of 0.0359 and 0.0495, respectively, when tested for between-group differences with the group taken as comparator. However it should be noted that in the CONCEPTT trial the changes in %CV for glucose in the control and CGM groups were not significantly different ($p = 0.058$), thus highlighting that due consideration in beneficial effects on glycaemic variability considered as a whole requires that improvements be observed with all metrics irrespective of their dependency or not on mean glucose concentration.

Interesting results were also recently reported in the COMISAIR study [33]. In this trial the effectiveness of real time continuous glucose monitoring (rtCGM) was tested in adults with type 1 diabetes treated with two different insulin regimens according to whether the insulin was delivered as multiple daily insulin injections (MDI) or continuous subcutaneous insulin infusions (CSII). Firstly the results confirmed that the rtCGM was superior to the SMBG in reducing HbA1c levels, mean

glucose concentration and glycaemic variability when patients on MDI were compared for SMBG and rtCGM (table 1). More surprising was the observation that the improvements attributed to the wear of the rtCGM occurred with similar magnitude regardless of the insulin delivery method. For instance, the statistical significances of the reductions in mean glucose concentrations and glycaemic variability were found to be similar when the rtCGM + CSII, i.e. the sensor-augmented insulin pump therapy, were tested against the SMBG + MDI (table 1) and the rtCGM +MDI. Bringing all these data together, it should be acknowledged with the authors of the CLARITY study [34] that the wear of "unbllnded" CGM devices empowers both patients and care givers to better understand the management of diabetes, and contributes to improve glycaemic outcomes. Further studies are warranted to know whether the benefits in terms of diabetic control can be extended to long-term periods.

2.2 Add-on treatments with non-insulin glucose lowering agents: impact on glycaemic variability

Do antidiabetic agents developed during the last past years, such as those acting through either the incretin pathway [70,71] or renal glucose reabsorption [66,72] exert dual effects on both the ambient hyperglycaemia and glucose variability? As at least two classes of these novel glucose-lowering therapies (the GLP-1 Receptor agonists and SGLT2 inhibitors) improve cardiovascular outcomes and should be preferentially prescribed in subjects with established atherosclerotic cardiovascular disease or heart failure [65-69] it is important to raise the aforementioned question and to know whether such therapies are or not to be early implemented in those with a labile diabetes [10], large glucose fluctuations between peaks and nadirs and increased exposure to hypoglycaemic events {64].

2.2.1 Effects of DPP-4 inhibitors on glycaemic variability

In the post-hoc analysis of the OPTIMA study [73,74] we have demonstrated that in patients with type 2 diabetes treated with metformin an add-on therapy with DPP-4 inhibitors (sitagliptin or vildagliptin) reduced both the glycaemic variability and post-prandial excursions assessed from the MAGE and AUCPP (post-prandial glucose increments above pre-prandial glucose values), respectively. In addition the changes in AUCPP from baseline to end point (at week 8) were strongly and positively correlated with those of glycaemic variability (ΔMAGE) with a coefficient of determination r^2 of 0.48 [74], thus indicating that the dependence of glycaemic variability from post-prandial glucose excursions is of 50%, approximately. More recently a meta-analysis of 7 studies comparing DPP-4 inhibitors with other oral antidiabetic drugs (OADs) in type 2 diabetes showed that DPP-4 inhibitors significantly ($p < 0.0001$) reduced the MAGE by 15% in comparison with other OADs regardless of baseline HbA1c levels [75].

2.2.2 Effects of GLP-1 receptor agonists on glycaemic variability

The analysis should separate the effects of short- and long-acting GLP-1 receptor agonists (GLP-1RAs) [76,77] because it is well acknowledged that GLP-1 RAs such as the exenatide [78,79] and lixisenatide [80-82] that exert their activity over 8 to 12 hours are more efficient on post-prandial glucose excursions than on basal hyperglycaemia, whereas the reverse is observed with long GLP-1 RAs, i.e. with those that exert their effect over 24 hours (the liraglutide [80,81,83,84]) or beyond such as the weekly preparations (the dulaglutide [85] and semaglutide [86]). According to this preliminary remark, it can be hypothesized that the short-acting preparations should be more efficient on the glycaemic variability than long-acting GLP-1 RAs.

Consequently, it was not surprising to observe that in the FLAT SUGAR Trial [87] the exenatide (the short-acting GLP-1 RA) has significantly and concomitantly reduced the short-term glycaemic variability and post-meal glucose increments. In this trial insulin-using persons with type 2 diabetes were firstly submitted to a run-in period with a basal bolus insulin regimen. After at least 8 to 10 weeks of stabilization, participants were randomly allocated in equal number to continue the basal-bolus regimen or to switch to a treatment combining a basal insulin regimen (glargine) with a GLP-1 RA (twice daily meal time injections of exenatide) after the bolus of rapid-acting insulin had been discontinued. CGMs were performed at baseline and during the 26-week period of follow-up. Comparisons between the 24-h glycaemic profiles showed that at least two markers of GV (the coefficient of variation for glucose and MAGE) were slightly but significantly improved ($p = 0.047$ and 0.049, respectively) in the group treated with exenatide plus glargine. Even though the magnitudes of post-meal glucose excursions were not quantified at least two increments after breakfast and lunch were reduced in those treated with exenatide.

In the VARIATION study [88] 4 groups of patients with type 2diabetes treated with insulin were compared for the GV assessed from the SD around the 24-h mean glucose concentration. Among these groups, one was treated with a basal insulin regimen plus a GLP-1 RA (exenatide or liraglutide). The subjects belonging to this latter group ($n = 40$) exhibited the lowest SD (30.6 ± 9mg/dL) when compared with those treated with either insulin + OADs (34.2 ± 9 mg/dL, $p = 0.03$), premixed insulin regimen (36.06 ± 10.8 mg/dL, $p = 0.01$) or basal-bolus insulin regimen (37.8 ± 9 mg/dL, $p = 0.01$). It worth noting that most people (39 out of 40) of the basal + GLP-1 RA cohort were treated with liraglutide, thus rendering inappropriate any comparison between the two GLP-1 RAs.

The comparisons between liraglutide and lixisenatide (an intermediate-versus a short-acting analog) was conducted in a trial [81] in which both GLP-1 RAs were given as add-on therapy to insulin glargine in type 2 diabetes. In this study lixisenatide and liraglutide improved the diabetic control but

were differing in their effect on 24-h glucose profiles. Even though the glycaemic variability was not assessed, glucose fluctuations appeared to be more blunted with lixisenatide than with liraglutide, because the post-breakfast glucose excursions, the most marked post-meal increments corresponding to the extended dawn phenomenon in type 2 diabetes [89,90] were practically eradicated with the lixisenatide while the liraglutide exerted only a modest effect on glucose excursions after breakfast.

When weekly GLP-1 analogs were tested in type 2 diabetes, controversial results were observed [91-93]. For instance, the 24-h glycaemic profiles recorded at the end of a 24-week period of treatment remained unchanged with the once-weekly injections of dulaglutide while a slight deterioration in short-term glucose variability (MAGE) occurred with the once-daily liraglutide [91]. In a sub-study of the AWARD-4 Trial [92] metrics of short-term glycaemic variability were compared in patients with type 2 diabetes treated with either dulaglutide or glargine both combined with pre-meal boluses of insulin lispro. The parameters of within-day (Mean Of Daily Differences, MODD) glycaemic variability were slightly but significantly ($p < 0.05$) reduced with dulaglutide 1.5 mg compared with glargine. With another long-acting GLP-1 RA, the once-weekly semaglutide [93], it has been observed that in type 2 diabetes a treatment period of 12 weeks with progressive escalation in weekly doses from 0.25 to 1.0 mg improved the overall glucose homoeostasis. However the improvements in 24-h glycaemic profiles before and under treatment with semaglutide were more due to a downward translation of glucose values as a whole than to a reduction in glucose fluctuations from peaks to nadirs, even though lower increments in post breakfast glucose excursions were observed after implemention of semaglutide than at baseline.

Bringing all these studies together and bearing in mind that the mechanisms of action differ between categories of GLP-1 RAs [76], it seems that short-acting GLP-1 RAs have a greater effectiveness for reducing the short-term glycaemic variability than long-acting preparations. However, at present, we are unfortunately suffering from the absence of strong controlled randomized interventional trials and thus further studies are warranted before any clear conclusion can be drawn. In addition, presently no or scarce information has been provided on the effects on post-prandial hyperglycaemia and glycaemic variability with the novel promising dual GIP and GLP-1 agonist, the tirzepatide, according to whether it is compared or not with selective GLP-1 agonists [94,95].

2.2.3 Effects of sodium-glucose cotransporter inhibitors (SGLT2) on glycaemic variability

In an editorial published in 2017 [96] David Nathan raised the question as to whether the new antidiabetic agents such as SGLTs inhibitors should be used as adjunctive therapy in type 1 diabetes. This debate contrasteding with the well adopted position statement that prior consideration has to

be given to SGLT2 inhibitors especially in diabetic persons with established cardiovascular disease or heart failure [67,68]. In a randomized, double-blind study [97], 351 persons with type 1 diabetes treated with either multiple daily insulin injections (NDI) or continuous subcutaneous insulin infusion (CSII) received canagliflozin (an SGLT2 inhibitor) or placebo for 18 weeks. All participants underwent a 6-point SMBG measurement at baseline and at end of the study period while 89 of 351 were submitted to a sub-study with the wear of a CGM. In the population considered as a whole (n = 351), daily doses of canagliflozin 100 and 300 mg reduced the mean glucose concentration (- 22.4 and - 19.4 mg/dL) and daily glucose SD around the mean glucose value (- 16.4 and - 18.1 mg/dL), respectively. These changes from baseline were due to a downward shift of the 9-point glycaemic profile, but with decreasing effects more marked on post-breakfast and post-dinner glucose excursions than on inter-prandial values. When data analyses were limited to the subset of patients (n = 89) who received a CGM, the reductions in metrics of glycaemic variability were found in those treated with canagliflozin 300 mg: decrement of CV (- 4.8% from a baseline of 42.8%) and of MAGE (- 32.7 mg/dL from a baseline of 166 mg/dL). Unfortunately, the investigators never mentioned whether these decrements were significant or not. In other studies that were conducted either in type 1 or type 2 diabetes and either with SGLT2 or dual SGLT inhibitors [98-105], divergent results were reported even though most of them showed that the GV was improved. Such discrepancies can be due to the fact that SGLT inhibitors exert their beneficial effects both on basal and post-prandial glucose [106] but with different distributions in magnitude depending on the study design.

2.3 Sophisticated insulin delivery systems developed for theoretically providing superior glucose control: Impact on glycaemic variability

In type 2 diabetes it is well recognized that implementation of basal plus 1 or 2 boluses of prandial insulins or of basal-bolus regimens with the addition of prandial insulins before the largest meal or meals with the greatest post-prandial glucose excursions is one of the measure recommended for intensifying the antidiabetic treatment when a satisfactory glycaemic control is not achieved on a basal insulin regimen alone [67]. Prandial insulin regimens alone [17,107,108] or combined with basal insulin [109-111] usually result in improvements of post-prandial glucose excursions. The glycaemic variability was not accurately computed in many studies because the participants did not benefit from the wear of a CGM device. Although the best procedure for estimating the glycaemic variability was not used in such studies, there remains that multiple-point glycemic profiles were recorded using SMBG. By handling the useful information provided by the CGM, it has been demonstrated that the glycaemic variability can diminish independently of either the presence or absence of improvement in metrics that evaluate the overall glucose exposure [8]. Such observations confirm that reductions in ambient hyperglycaemia and glycaemic variability are not tightly linked and

sometimes totally uncoupled/independent justifying the use of different metrics to separately assess the total glucose exposure from such parameters as the HbA1c, percentage of time spent in range (TIR) or above range (TAR) on one side [7,9] and the glycaemic variability from SD, %CV, MAGE and other ones [2-7,10] on the other side. For instance, several studies involving sophisticated insulin delivery systems such as those using the closed-loop technology have demonstrated the following benefits [21-28]: (i) Near normal glycaemic control during nocturnal periods associated with a significant diminished risk for hypoglycaemia during these periods; (ii) Reduction in the overall ambient hyperglycaemia due to a downward shift of the 24-h glycaemic profiles including both nocturnal and diurnal periods. However such beneficial effects that result from a finely tuned, instantaneous glucose-responsive modulation of insulin delivery during nocturnal and more generally inter-prandial periods are not systematically associated with a tighter glycaemic control over phases of rapid changes in glucose concentration such as those occurring during post-prandial periods [23,28]. Such observations offer an explanation as to why the glycaemic fluctuations under fully or hybrid closed-loop systems of insulin delivery during daytime remain similar to those observed with more conventional insulin regimens such as sensor-augmented pumps [25].

In summary it is noteworthy that it is easier to control the total glucose exposure than the short-term glycaemic variability and that most strategies used in type 1 or type 2 diabetes except those targeting the post-prandial glucose excursions usually fail to achieve a near normal control of glycaemic variability.

3. The missing link: Does improvement in glycaemic variability contribute to the additional cardiovascular benefits observed with GLP-1 RAs and SGLT2 inhibitors?

There is now a large body of evidence for the cardioprotective effects of GLP-1 RAs and SGLT2 inhibitors [20,68,112-116], but it is also well acknowledged that the glucose-lowering effect of these classes of antidiabetic agents are not sufficient for explaining the significant reduction in adverse cardiovascular events. This assertion is mainly supported by the discrepancies that were observed between CRTs according to whether GLP1-RAs (REWIND [117], SUSTAIN-6 [118]) and SGLT2 inhibitors (EMPA-REG OUTCOME [119], CANVAS [120) were used or not (ADVANCE [121], VADT [122]) in the intensively treated groups. For instance, for similar decrements in HbA1c from comparable baseline levels except in REWIND and ADVANCE, these CRTs have led to significant (p values from 0.04 to 0.02) reductions in Hazard Ratios (ΔHR) for the risk of Major Adverse Cardiovascular Events (MACE) with either GLP-1 RAs (dulaglutide [117] and semaglutide [118] or SGLT2 inhibitors (empagliflozin [119] and canagliflozin [120] while this risk remained unchanged in the ADVANCE [121] and VADT [122] (p values for ΔHR = 0.32 and 0.14,respectively) when patients were assigned to alternative intensive antidiabetic treatments (table 2). For explaining such differences many hemodynamic and

non-glycaemic mechanistic arguments have been proposed [113,115] but such profusion creates a state of uncertainty and suggests that none of the formulated hypotheses has received general acceptance and neither do we find one of these hypotheses more tenable than the others. Consequently, there arises the question as to whether the glycaemic variability, a glycaemic explanation not based on the total glucose exposure, might or not be the "missing link" that contributes to the additional beneficial effects of GLP-1 RAs and SGLT2 inhibitors in terms of protection against adverse cardiovascular outcomes. Even though the reduction in glycaemic variability remains on the boundaries of statistical significance in users of GLP1-RAs and SGLT2 inhibitors, there nevertheless remains that these two classes of hypoglycaemic agents have the ability to attenuate the post-prandial glucose excursions [81,87,97,105,106] and thus the activation of oxidative stress in endothelial cells, one of the metabolic factor responsible for or involved in the damages of the vascular walls in persons with diabetes [57,123,124].

Concluding remarks

The potential role of a reduction in glycaemic variability as mechanism for explaining the beneficial cardiovascular effects of GLP-1 RAs and SGLT2 inhibitors remains presently purely speculative because we are sadly lacking of any CRT in which the incidence rate of long-term clinical outcomes would be concomitantly recorded with a large panel of glycaemic metrics including those that address more specifically the glycaemic variability [2-4,10]. As mentioned earlier in this review such a trial should be conducted over several years and associated with the sustained wear of a CGM in order to get access to all the parameters provided by the monitoring of 24-hour glycaemic profiles such as the mean glucose concentration, percentages of time spent in and out the recommended glucose range and the parameters used for quantifying the short-term glycaemic variability.

The full assessment of the within- and between-day glucose fluctuations requires to compute several parameters, especially those that are adjusted (%CV) or independent of the mean glucose (the MAGE and MODD) in order to avoid the pitfalls in interpretation that occur when calculations are limited to the SD around the 24-h mean glucose concentrations, a parameter computed from an equation wherein the magnitude of SD is necessarily dependent on the magnitude of the data, i.e. on their mean value. Reverting to the long-term variability of glucose homoeostasis a coefficient of variation of less than 5% for HbA1c could be an appropriate target. As a HbA1c goal of less than 7% (53 mmol/mol) is usually recommended in adults with diabetes and of less than 8% (64mol/mol) in those for whom the adverse effects of treatment are greater than the benefits [55] one could consider that visit-to-visit absolute fluctuations in HbA1c should not exceed 0.35 to 0.40% (5.5 to 6.5 mmol/mol). Such a position is also supported by a post-hoc analysis of the ADVANCE Trial [60] whose results

showed that the mean Hazard Ratio of the risk for macro and microvascular events becomes >1.0 when the within-subject variability of HbA1c (SD of HbA1c) increases beyond a percentage point of 0.48% (approximately 7.5 mmol/mol).

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Legends for figures and tables

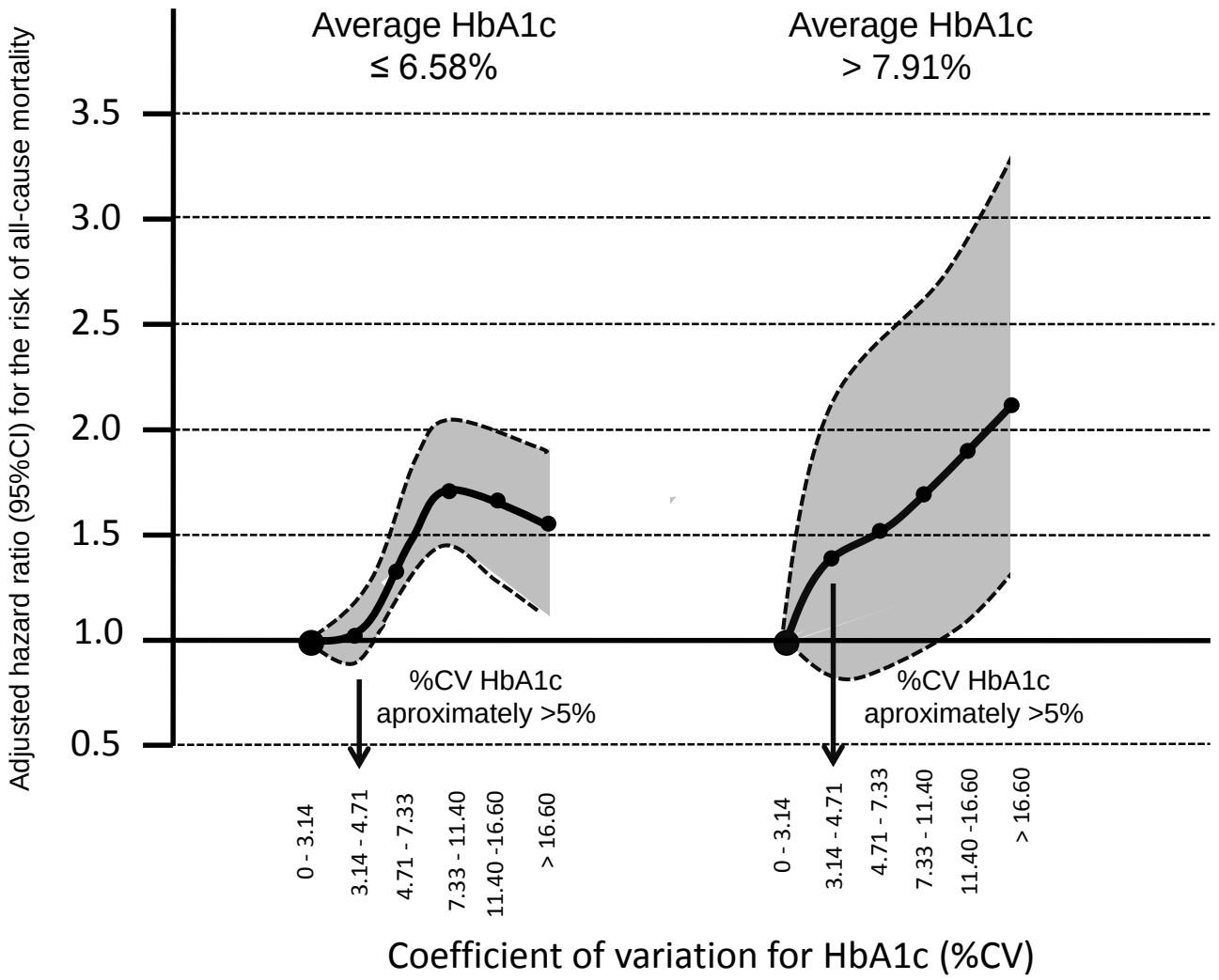
Figure 1: Relationship between HbA1c variability (expressed as %CV for HbA1c) and risk for all-cause mortality, at high (> 7.91%) and low (≤ 6.58%) values of average HbA1c. The incidence rate of all-cause mortality is significantly increased above the reference group (%CV ranging from 0 to 3.14%) when the %CV for HbA1c becomes higher than 4.71%, i.e. a value approximately equal to 5.0% (from reference 38).

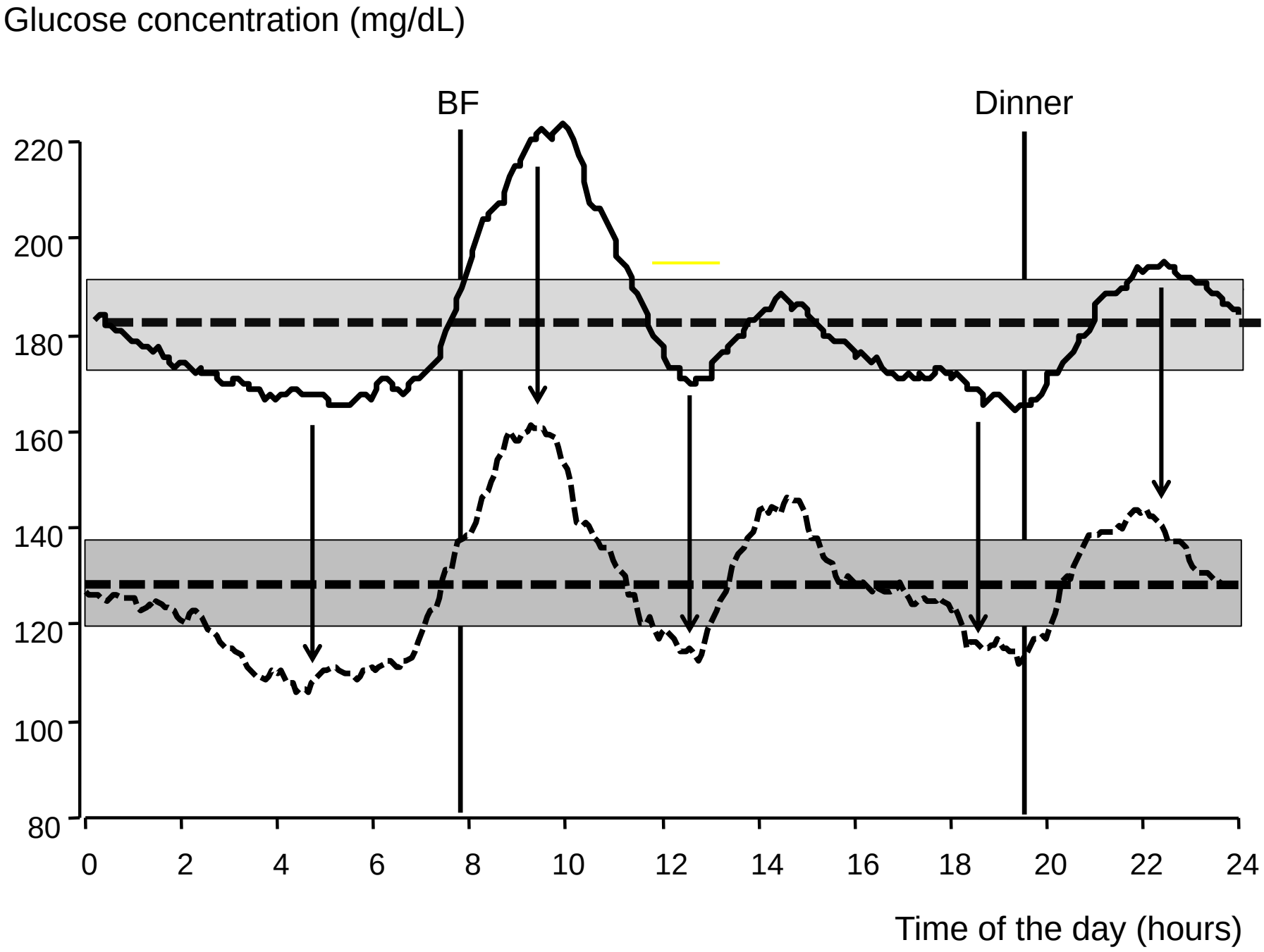
Figure 2a: Effect of an antidiabetic treatment with a downward shift of the 24-h glycaemic profile and which results in a reduction in the 24-h mean glucose concentration without any change in the SD around the mean. A paradoxical increase in the %CV (SD/mean) is observed with the treatment.

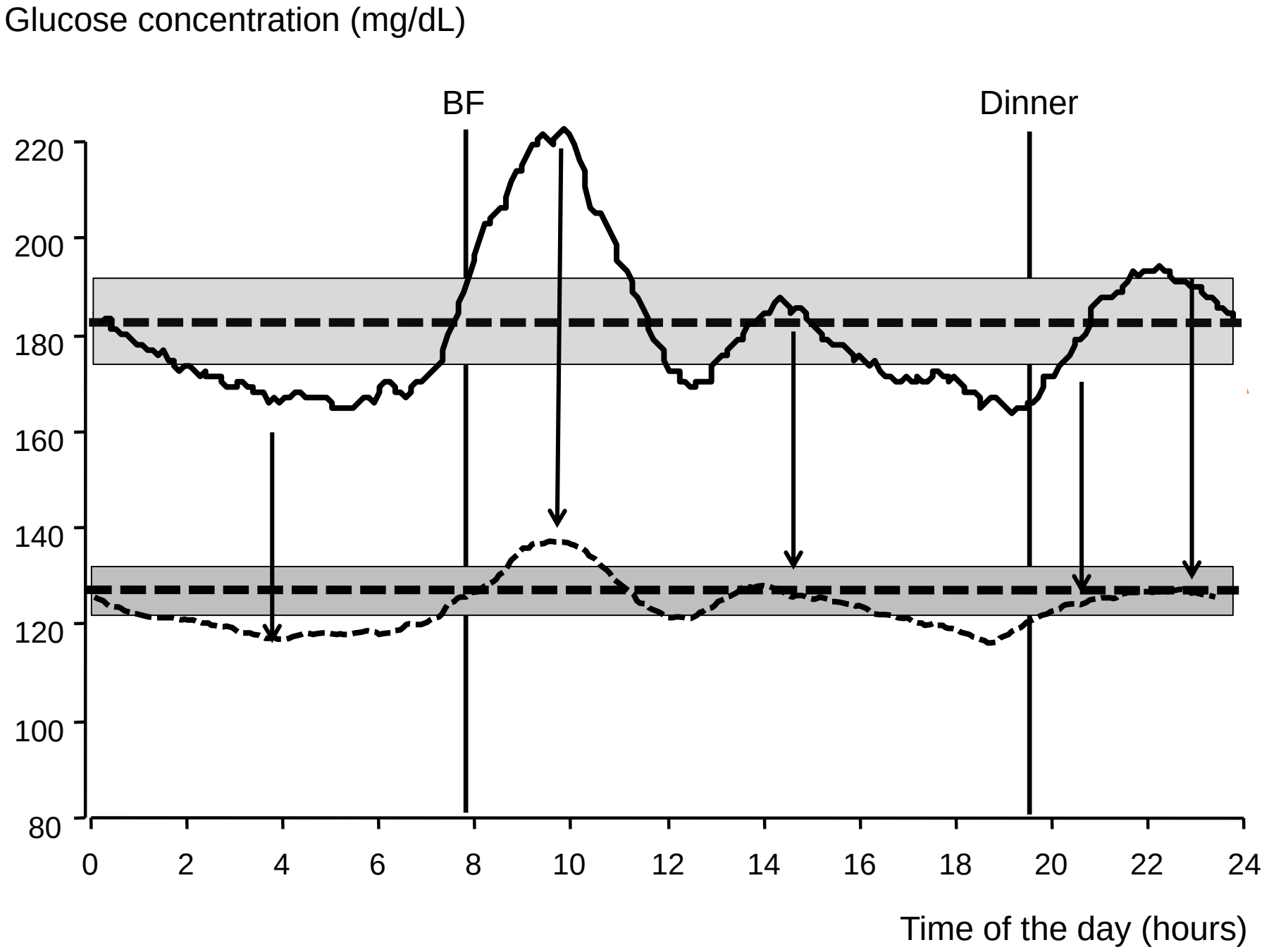
Figure 2b: Effect of an antidiabetic treatment that results in reductions of both mean glucose concentration and SD around the mean. In this situation the %CV can increase, decrease or remain unchanged according to whether the changes in SD are lower, greater than or equivalent to those of the mean glucose concentration

Table 1: Effects of the wear of a CGM on ambient hyperglycaemia (mean glucose concentration or HbA1c) and different metrics of glycaemic variability (SD around the 24-h mean glucose value, %CV for glucose = SD/mean, and MAGE). Results expressed as either means [SD]* or medians [95% CI]**are reported from 5 CRTs in which the antidiabetic treatment was maintained unchanged.

Table 2: Effects of different antidiabetic therapeutic strategies on the reduction of the Hazard Ratio (ΔHR) for MACE (Major Adverse Cardiovascular Events) in which standard control or placebo groups were compared with either intensively controlled groups. Intense controls were achieved by either attempting to target HbA1c values < 6.5% (ADVANCE [121] and VADT [122]) or implementing GLP-1RAs (REWIND [116] and SUSTAIN-6 [117]) and SGLT2 inhibitors (EMPA-REG OUTCOME [119] and CANVAS [120]). P values for ΔHR are only significant ($p < 0.05$) in studies involving GLP-1 RAs or SGLT2 inhibitors




Glucose concentration (mg/dL)
BF
Dinner
220
200
180
160
140
120
100
80
0
2
4
6
8
10
12
14
16
18
20
22
24
Time of the day (hours)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Time of the day (hours)

STUDY	Type of comparison	Metrics	Between-group differences	P value
DIAMOND [29]	CGM vs SMBG (control)	HbA1c (%)	- 0.6 [- 0.81 to 0.8]**	<0.001
		CV for glucose (%)	- 4 [- 6 to - 2]**	<0.001
GOLD [30]	CGM vs SMBG (control)	HbA1c (%)	- 0.43 [- 0.57 to - 0.29]**	<0.001
		SD for glucose (mg/dL)	- 8.69 [-10.76 to - 6.61]**	<0.003
		MAGE (mg/dL)	- 19.36 [- 24.26 to -14.46]**	<0.001
SILVER [31]	CGM vs SMBG (control)	HbA1c (%)	- 0.345 [0.789]*	<0.0001
		Mean glucose (mmol/L)	- 0.53 [2.05]*	0.016
		SD for glucose (mmol/L)	- 0.62 [0.86]*	<0.0001
		MAGE (mmol/L)	- 2.26 [1.92]*	<0.0001
COMISAIR [33]	rtCGM +MDI vs SMBG+MDI	HbA1c (%)	- 0.87 [- 1.38 to - 0.35]**	0.0016
		Mean glucose (mg/dL)	- 27 [- 42.3 to 12.24]**	0.0007
		SD for glucose (mg/dL)	- 12.24 [- 18.6 to 5.94]**	0.0003
COMISAIR [33]	rtCGM+CSII vs SMBG+MDI	HbA1c (%)	- 0.99 [- 1.45 to - 0.52]**	<0.0001
		Mean glucose (mg/dL)	- 29.2 [- 42.66 to 15.84]**	<0.0001
		SD for glucose (mg/dL)	- 12.06 [- 18.54 to 5.58]**	0.0006

Table I

Study	Type of comparison	Mean HbA1c (%) at baseline in the Intensively treated groups	ΔHbA1c (%): Intensively treated groups vs either placebo or standard groups	Δ HR for MACE Median [95% CI]	P value for ΔHR
REWIND [116]	Dulaglutide vs placebo	7.3	-0.61	- 0.12 [- 0.21 to - 0.01]	0.026
SUSTAIN-6 [117]	Semaglutide vs placebo	8.5	- 0.70 (sema 0.50 mg) or - 1.00 (sema 1 mg)	- 0.26 [- 0.42 to - 0.05]	0.02
EMPA-REG [119]	Empagliflozin vs placebo	8.0	- 0.24 (empa) 10 mg or - 0.36 (empa 25 mg)	- 0.14 [- 0.26 to - 0.01]	0.04
CANVAS [120]	Canagliflozin vs placebo	8.2	- 0.58	- 0.14 [- 0.25 to - 0.03]	0.02
ADVANCE [121]	Intensive vs standard control	7.5	- 0.67	- 0.08 [- 0.16 to + 0.06]	0.32
VADT [122]	Intensive vs standard control	9.0	- 1.51	- 0.12 [- 0.16 to + 0.05]	0.14

Table II

Conflict of interest statement

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: