Toward Defining the Threshold Between Low and High Glucose Variability in Diabetes

Louis Monnier,[1] Claude Colette,[1] Anne Wojtusciszyn,[2] Sylvie Dejager,[3] Eric Renard,[2] Nicolas Molinari,[4] and David R. Owens[5]

Diabetes Care 2017;40:832–838 | https://doi.org/10.2337/dc16-1769

OBJECTIVE

To define the threshold for excess glucose variability (GV), one of the main features of dysglycemia in diabetes.

RESEARCH DESIGN AND METHODS

A total of 376 persons with diabetes investigated at the University Hospital of Montpellier (Montpellier, France) underwent continuous glucose monitoring. Participants with type 2 diabetes were divided into several groups—groups 1, 2a, 2b, and 3 (*n* = 82, 28, 65, and 79, respectively)—according to treatment: *1*) diet and/or insulin sensitizers alone; *2*) oral therapy including an insulinotropic agent, dipeptidyl peptidase 4 inhibitors (group 2a) or sulfonylureas (group 2b); or *3*) insulin. Group 4 included 122 persons with type 1 diabetes. Percentage coefficient of variation for glucose (%CV = [(SD of glucose)/(mean glucose)] × 100) and frequencies of hypoglycemia (interstitial glucose <56 mg/dL [3.1 mmol/L]) were computed.

RESULTS

Percentages of CV (median [interquartile range]; %) increased significantly ($P < 0.0001$) from group 1 (18.1 [15.2–23.9]) to group 4 (37.2 [31.0–42.3]). In group 1, the upper limit of %CV, which served as reference for defining excess GV, was 36%. Percentages of patients with %CVs above this threshold in groups 2a, 2b, 3, and 4 were 0, 12.3, 19.0, and 55.7%, respectively. Hypoglycemia was more frequent in group 2b ($P < 0.01$) and groups 3 and 4 ($P < 0.0001$) when subjects with a %CV >36% were compared with those with %CV ≤36%.

CONCLUSIONS

A %CV of 36% appears to be a suitable threshold to distinguish between stable and unstable glycemia in diabetes because beyond this limit, the frequency of hypoglycemia is significantly increased, especially in insulin-treated subjects.

At present, there is incontrovertible evidence that chronic hyperglycemia is a key player in the pathogenesis of all related complications from diabetes, both in type 1 (1,2) and type 2 diabetes (3,4). However, glucose variability (GV) and hypoglycemia, the second and third components of the "glucose triumvirate" (5), may also be considered as risk factors for vascular complications in diabetes. Excess GV is usually associated with increased risk of hypoglycemic events, necessitating a global therapeutic approach aimed at avoiding hypoglycemic episodes while maintaining the HbA_{1c} levels within an individually defined target range according to patient-centered therapeutic strategies (6). HbA_{1c}-based strategies are limited by the fact that they do not integrate GV, and at present, the role of GV in the development and progression of cardiovascular

[1]Institute of Clinical Research, University of Montpellier, Montpellier, France
[2]Department of Endocrinology, Diabetes, and Nutrition, Montpellier University Hospital, University of Montpellier, Montpellier, France
[3]Department of Endocrinology, Pitiê-Salpétrière Hospital, Paris, France
[4]Department of Statistics and Epidemiology, UMR 5149, Montpellier University Hospital, University of Montpellier, Montpellier, France
[5]Diabetes Research Group, Swansea University, Swansea, Wales, U.K.

Corresponding author: Louis Monnier, louis.monnier@inserm.fr.

Received 16 August 2016 and accepted 5 December 2016.

See accompanying articles, pp. 943 and 951.

diseases remains a subject of controversy (7–9). The proof-of-concept FLAT-SUGAR (FLuctuATion reduction with inSUlin and GLP-1 Added togetheR) randomized interventional study (10) was designed to identify a difference in GV between two groups of insulin-treated subjects with type 2 diabetes. These participants were assigned either to continuous basal-bolus insulin after a run-in period or to replace the premeal short-acting insulin analog with mealtime dosing of exenatide while continuing the basal insulin glargine. The secondary outcome of the FLAT-SUGAR trial was to test the hypothesis that improvements in GV in insulin-requiring diabetes can exert beneficial effects on markers of cardiovascular risk. As hypoglycemic episodes and GV, concomitantly or separately, are potential causative factors for cardiovascular events, the question arises of how to separate the patients with unstable diabetes from those considered stable. Therefore, we should identify a threshold for the amplitude of GV below which the risk of hypoglycemia would be negligible. Consequently, we analyzed continuous glucose profiles from groups of patients with type 1 or type 2 diabetes to gain further insight into this conundrum. Data from those subjects treated with diet alone or with the addition of insulin sensitizers, which represent little or no risk of hypoglycemia (reference group), were used to determine the upper level of GV to define the threshold between stable and unstable diabetes. Patients from the other groups were compared with the reference group to determine the proportion of exaggerated glycemic fluctuations and frequency of accompanying hypoglycemic episodes. This aspect is crucial when it comes to health care providers in order to achieve and sustain optimal glycemic control by achieving and maintaining GV within a reasonable range and with minimal risk of hypoglycemia. Presently, there are clear recommendations for the management of chronic hyperglycemia, with most organizations recommending a target HbA_{1c} level of 7% (53 mmol/mol) (6,11). However, to date, there are no recommendations provided for GV, which this present study is designed to address.

RESEARCH DESIGN AND METHODS

Study Design and Participants

A total of 376 persons with either type 1 or type 2 diabetes were included in the study between 2003 and 2012. All participants regularly attended the outpatient clinic of the University Hospital of Montpellier (France) and were entered consecutively without any selection based on HbA_{1c}, age, sex, duration of diabetes, or complications from diabetes. The study was observational in design, and the data were retrospectively analyzed. Out of the 376 patients included in this study, 82 with type 2 diabetes were treated with diet and/or insulin sensitizers alone. These patients, referred to as group 1, were selected to serve as reference for stable glucose homeostasis diabetes. The rationale for this choice was based on two main principles and observations. Firstly, patients treated with insulin sensitizers alone correspond usually to persons who are at an early stage in the natural history of type 2 diabetes. Such patients usually have relatively small glucose fluctuations that are mainly because of postprandial excursions and remain relatively constant across the HbA_{1c} spectrum (12). Secondly, this group corresponds to patients in whom the risk of hypoglycemic episodes is also very low or even absent (13) and who, consequently, have a low likelihood of glycemic variability being compounded by glycemic rebounds because of correction of symptomatic hypoglycemia. Patients with type 2 diabetes treated with oral hypoglycemic agents known to have insulinotropic effects were excluded from the reference group even though dipeptidyl peptidase 4 (DPP-4) inhibitors stimulate the endogenous insulin secretion in a glucose-dependent manner (14), which theoretically excludes the risk for hypoglycemic events.

Besides the reference group, other groups of patients were selected by types of diabetes and categories of antidiabetes treatments. Their detailed characteristics are reported later at the beginning of the RESULTS section.

Considered as a whole, all patients were stable on their respective treatment regimens for at least 3 months prior to the investigations. The 376 patients included in the current study were selected among a total population of 559 subjects with type 1 or type 2 diabetes who underwent 3-day ambulatory continuous glucose monitoring (CGM). Criteria of exclusion from the initial screened list of potential participants included those who had experienced a recent illness or had been treated with steroids during the 3-month period preceding the investigation. In addition, exclusion criteria from the final analysis were unexpected disruptions in the glucose monitoring or insufficient number of capillary tests on whole blood glucose for the calibration of the CGM (four tests were required daily for this purpose). Acceptable calibration meant an accuracy criterion with a correlation coefficient >0.79. All of the investigations were routinely performed in the diabetes outpatient clinic of the University Hospital of Montpellier (France) and were in accordance with the Declaration of Helsinki (15). As the study was observational in design, each participant gave an oral informed consent in accordance with European directives that require no approval from an ethics committee because of the noninterventional design of the study (16).

Clinical Investigations and Laboratory Determinations

All participants underwent ambulatory CGM for 3 consecutive working days, avoiding the weekend, using the same technology during 2003 to 2012 (i.e., second-generation MiniMed system; Medtronic, Northridge, CA). The sensor was inserted on day 0 (before 1200 h) and removed on day 3 at the same time point as on day 0.

Chronic hyperglycemia was assessed on study day 0 based on HbA_{1c} levels determined using a high-performance liquid chromatography assay (17) (Menarini Diagnostics, Florence, Italy).

Analysis of the Data From the CGM

CGM was used to calculate the mean 24-h glucose concentration and SD (SD around the mean glucose value). GV was determined using the percentage coefficient of variation for glucose (%CV) obtained from the following computation: ([SD of glucose]/[mean glucose]) $\times$ 100. The %CV is probably one of the most reliable markers to assess the amplitude of GV, as it is adjusted for the mean glucose value and does not depend on this parameter (18–20). Furthermore, it is well known that all parameters described for assessment of GV are highly intercorrelated (21–23), and some investigators have established that the %CV is a valid GV index especially when used in combination with other more complex metrics of glycemic control (22). It should also be appreciated that health care professionals, by reading simple metrics such

as the mean 24-h glucose value and the SD provided by CGM systems and printed on the files associated with traces of the glycemic profiles, can easily calculate the %CV. For the aforementioned reasons and as the aim of our study is essentially pragmatic in its objectives, we have deliberately not studied the more sophisticated indices of GV such as the mean amplitude of glycemic excursions, mean of daily differences, continuous overlapping net glycemic action, low blood glucose index, and others (24–26). Many of these indices have been widely described and more commonly used in type 1 and not type 2 diabetes (23). In addition, some of these metrics, such as the low blood glucose index for hypoglycemia (27), are more oriented toward the risk analysis of adverse events relevant to GV than toward the specific assessment of GV.

Based on two validated 24-h glycemic profiles on study days 1 and 2, the SDs, 24-h mean glucose values, and %CVs were averaged for these 2 consecutive days. The data recorded on day 0 were excluded from the analysis in order to avoid any bias because of glucose stabilization between the sensor and the interstitial fluid during the first hours after insertion of the device. Calculations were made at 5-min time intervals. In each group, the relative frequency for distributions of %CV values was tested for normality using the Shapiro-Wilk test (28). However, as this test failed to demonstrate a unimodal, nonskewed Gaussian distribution, the analyses were performed using nonparametric statistics: medians and interquartile ranges (IQRs). As mentioned above, patients in group 1 were taken as reference for stable diabetes, in view of the small/absent risk of hypoglycemia and limited glucose fluctuations. The upper limit of %CVs in group 1 ($\%CV_{max1}$) was referred to as the threshold between stable and unstable glycemic control. In all groups, including group 1, the presence of hypoglycemia based on the 24-h glucose profile was considered as a whole. When applicable (i.e., when some individuals of a given group had %CV greater than the $\%CV_{max1}$), the patients of the group were tested for the presence of hypoglycemia after they had been divided into two subgroups according to whether %CVs were above or below the $\%CV_{max1}$ determined in the reference group. Hypoglycemia was defined as three consecutive interstitial glucose levels <56 mg/dL (3.1 mmol/L) with time spent ≥15 min. Hypoglycemic episodes were reported by reading the 24-h glucose profiles.

Additional Calculations and Statistical Analysis

Except for hypoglycemia, comparisons between groups or subgroups were made using the nonparametric Kruskal-Wallis or the Mann–Whitney test as appropriate. In groups 2a, 2b, 3, and 4, percentages of %CVs above the $\%CV_{max1}$ were calculated. Comparisons between percentages in the different groups were made using the χ^2 or Fisher exact test. The number of hypoglycemic episodes expressed as number per patient-day was compared between groups and between subgroups exhibiting stable ($\%CV \leq \%CV_{max1}$) and unstable ($\%CV > \%CV_{max1}$) glucose homeostasis. For that purpose, Poisson regression models were fitted after plotting the number of hypoglycemic episodes as the dependent variable and groups of patients as the explanatory variable. Simple correlations between either SD or %CV and mean glucose values were calculated using the Spearman rank test. All *P* values were considered significant when <0.05. Data were analyzed using R software version 3.2.3.

RESULTS

Of the 376 persons who were included in the current study, 122 had type 1 diabetes and 254 type 2 diabetes, and were further divided into several groups. Among those with type 2 diabetes, 82 (group 1) were on either dietary measures alone (*n* = 8) or treatment combining diet with insulin sensitizers (metformin and/or glitazones; *n* = 74), and 93 (group 2) received dual or triple oral antidiabetes therapy combining one or two insulin sensitizers with at least one insulinotropic agent, either a DPP-4 inhibitor (sitagliptin or vildagliptin, subgroup 2a; *n* = 28) or a sulfonylurea (glimepiride or glibenclamide, subgroup 2b; *n* = 65). Finally, 79 (group 3) subjects were on insulin treatment prescribed as either basal insulin alone (*n* = 33) or basal-bolus insulin regimens (*n* = 46). The 122 subjects with type 1 diabetes (group 4) were treated with either basal-bolus regimens delivered as multiple injections (*n* = 97) or by subcutaneous insulin pumps (*n* = 25). Demographic characteristics of patients, treatment categories, and laboratory data in the different groups are shown in Table 1.

Comparison of Parameters of Glycemic Control in the Different Groups

The median HbA_{1c} levels were significantly lower ($P < 0.0001$) in the orally treated groups (1, 2a, and 2b) than in insulin-treated groups (3 and 4). The SDs (median [IQR]; mg/dL) steadily and significantly ($P < 0.0001$) increased from group 1 (25 [19–33]) and group 2a (23 [19–28]) to group 4 (58 [44–73]). Similar results were observed for %CVs (median [IQR]; %) that increased from 18.1 (15.2–23.9) in group 1 and 18.6 (16.6–22.4) in group 2a to 37.2 (31.0–42.3) in group 4 ($P < 0.0001$). Furthermore, in group 3, the %CVs (median [IQR]) were approximately the same in patients on basal insulin (29.7 [23.1–35.1]; *n* = 33) as in those on basal-bolus insulin regimen (26.9 [19.5–34.3]; *n* = 46).

Distributions of %CV for Glucose in the Different Groups

Histograms of relative frequency distributions for %CVs are given in Fig. 1. In the reference group (group 1), the upper limit of the distribution of %CV was found to be of 36%, which was adopted as a reference threshold ($\%CV_{max1}$) to separate stable from unstable glycemia. In the particular setting of our population, percentages of patients exhibiting %CVs above this upper limit were found to be 0, 12.3, 19.0, and 55.7% in groups 2a, 2b, 3, and 4, respectively. Differences among percentages were statistically significant ($P < 0.0001$) when group 4 was compared with groups 2a, 2b, and 3. Furthermore, by pooling all subjects with type 2 diabetes without any hypoglycemia (*n* = 154), the upper limit of distribution of %CV was 38% (i.e., a value quite similar to that observed in the reference group [36%]).

Number of Hypoglycemic Episodes in the Different Groups

The results are represented in Figs. 2 and 3. Patients in groups 1 (reference group) and 2a (DPP-4 inhibitor plus insulin sensitizers) were almost devoid of hypoglycemia. Hypoglycemia occurred in all of the other groups and was more prevalent in patients with type 1 diabetes ($P < 0.0001$, group 4 vs. groups

Table 1—Demographic, clinical, and laboratory characteristics of the patients enrolled in the different groups

	Type 2 diabetes treated					
	Without any insulin secretagogue (group 1)	With a DPP-4 inhibitor plus insulin sensitizers (group 2a)	With a sulfonylurea plus insulin sensitizers (group 2b)	With insulin (group 3)	Type 1 diabetes (group 4)	*P* value
No. of subjects	*N* = 82	*N* = 28	*N* = 65	*N* = 79	*N* = 122	
Age (years)	63 (56–67)	57 (55–65)	62 (57–69)	64 (59–73)	52 (43–72)	<0.0001
Men/women (*n*)	52/30	17/11	49/16	38/41	67/55	
BMI (kg/m^2)	30.2 (27.5–33.6)	29.9 (27.0–33.6)	28.7 (24.3–33.2)	29.6 (25.2–33.3)	24.2 (22.4–27.3)	<0.0001
Diabetes duration (years)	4 (2–8)	4.5 (1–8)	10.0 (4–17)	18 (11–28)	28 (20–35)	<0.0001
Diabetes treatment (%)						
Any insulin sensitizer	90.2	100	100	50.6	0	
Any DPP-4 inhibitor	0	100	0	0	0	
Any sulfonylurea	0	0	100	53.2	0	
Type of insulin treatment if any (%)						
Basal regimen				41.8	0	<0.0001
Basal-bolus regimen				58.2	79.5	
Pump therapy					20.5	
HbA_{1c} (%)	7.1 (6.8–7.7)	6.8 (6.4–7.0)	7.6 (7.1–8.6)	8.6 (8.0–9.2)	8.0 (7.4–8.9)	<0.0001
HbA_{1c} (mmol/mol)	54 (51–61)	51 (46–53)	60 (54–70)	70 (64–77)	64 (57–74)	
24-h mean glucose concentration (mg/dL)	137 (123–151)	120 (113–131)	139 (125–165)	175 (153–207)	154 (136–198)	<0.0001
SD of mean glucose value (mg/dL)	25 (19–33)	23 (19–28)	33 (24–43)	47 (36–61)	58 (44–73)	<0.0001
%CV for glucose	18.1 (15.2–23.9)	18.6 (16.6–22.4)	23.7 (16.8–29.0)	27.8 (21.2–34.4)	37.2 (31.0–42.3)	<0.0001

Data are median (IQR) unless otherwise indicated. Comparisons were made using nonparametric statistics and *P* values are indicated when significant ($P < 0.05$).

1, 2a, 2b, and 3) (Fig. 2). As illustrated in Fig. 3, the frequency of hypoglycemia was significantly greater in the subgroups with a %CV >36% than in the subgroups with values ≤36% ($P < 0.01$ in group 2b; $P < 0.0001$ in groups 3 and 4). Medians of 24-h mean glucose values between subgroups with a %CV > or ≤36% were slightly different in group 3 ($P = 0.018$) but not in groups 2b and 4 (Fig. 3).

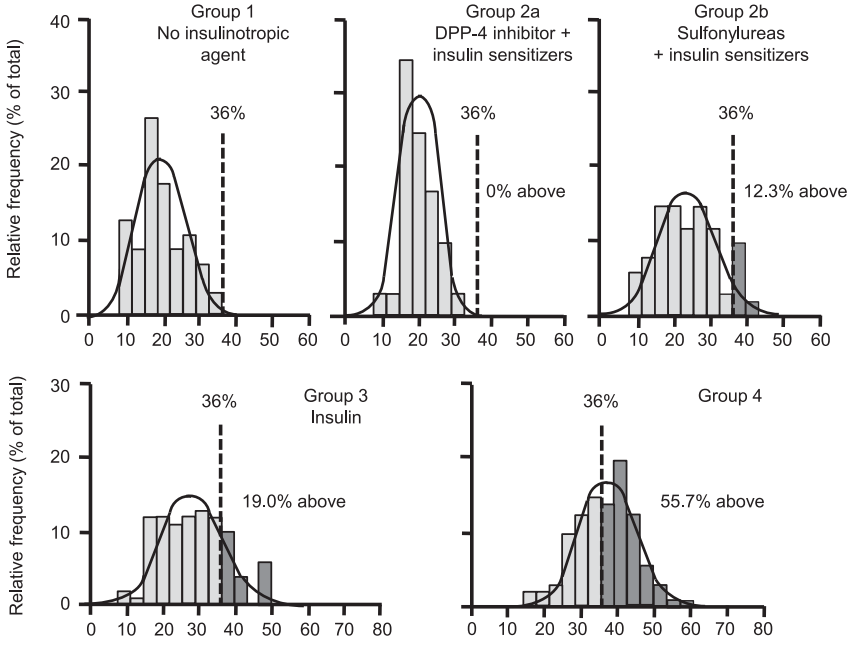

Figure 1—Histograms of relative frequency distributions for %CVs for glucose in the five groups of persons with either type 2 (groups 1, 2a, 2b, and 3) or type 1 diabetes (group 4). The upper limit of the distribution of %CV (%CV_{max1} = 36%) in group 1 (no insulinotropic agent) is taken as reference to discern stable from unstable diabetes. In the four other groups, the percentages of patients above this threshold value of 36% are indicated as appropriate in the corresponding panels.

Relationships Between Parameters of GV and 24-h Mean Glucose Concentrations

In the study population considered as a whole (*n* = 376), SD correlated positively and significantly with 24-h mean glucose concentration ($\rho = 0.50$; $P < 0.0001$), whereas the %CV did not ($\rho = 0.04$; $P = 0.42$).

CONCLUSIONS

There are two main messages emanating from the current study. Firstly, GV represented by the %CV was greater in the subjects with type 1 than in those with type 2 diabetes, and there was a steadily increasing GV across the continuum of type 2 diabetes from those on diet with or without insulin sensitizers and those treated with DPP-4 inhibitors to those receiving sulfonylureas and finally those subjects on different insulin regimens. Secondly, a threshold for %CV of 36% permits discrimination between those with stable or unstable glucose homeostasis. However, one of the remaining questions is to know whether GV should be assessed in diabetes care, as we are still awaiting the findings from interventional studies designed

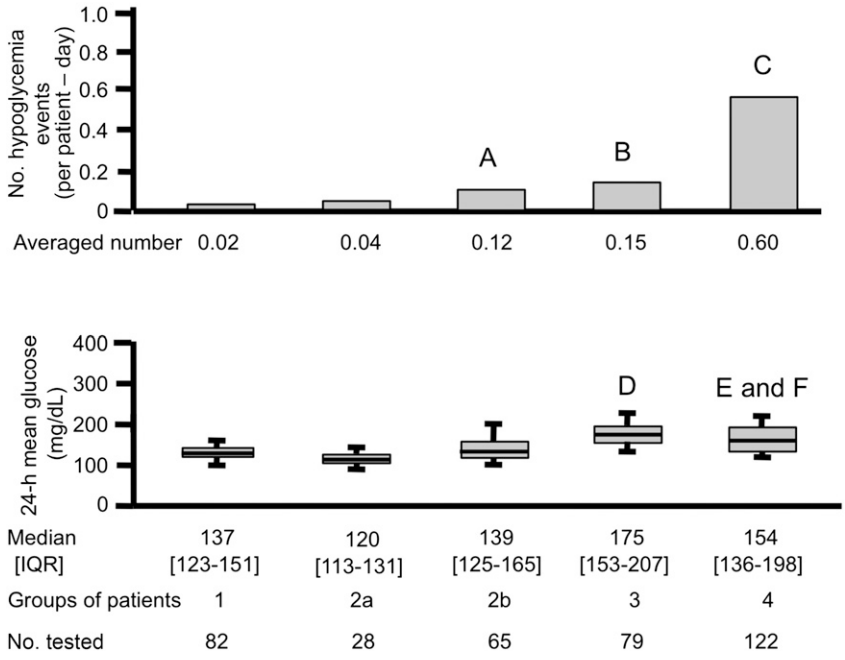

Figure 2—Incidence of hypoglycemia (top panel) and results of 24-h mean interstitial glucose values given as medians with IQRs and 10th and 90th percentiles (bottom panel). Statistical comparisons among groups 1, 2a, 2b, 3, and 4: group 2b vs. 1 and 2a ($P < 0.01$) (A); group 3 vs. 1 and 2a ($P < 0.001$) (B); group 4 vs. 1, 2a, 2b, and 3 ($P < 0.0001$) (C); group 3 vs. 1, 2a, and 2b ($P < 0.0001$) (D); group 4 vs. 1 and 2a ($P < 0.0001$) (E); and group 4 vs. 2b ($P < 0.01$) (F).

to evaluate whether lowering GV to within near normal limits can prevent the development and/or progression of complications from diabetes. However, the recent publication of the results of the FLAT-SUGAR Trial (29) does not provide any compelling evidence that reduction of GV can result in improvements of certain cardiovascular biomarkers such as CRP, interleukin-6, or urinary prostaglandin $F_{2\alpha}$, representing the inflammatory or oxidative stress status (30).

Nevertheless, even though the relationship between GV per se and adverse cardiovascular outcomes has not been established, it remains that increased glucose fluctuations can play a consistent role in precipitating hypoglycemia (26,31). Highly significant correlations have been observed in persons with diabetes treated with insulin between %CV and risk of hypoglycemia (20,22). Fabris et al. (22) reported a correlation coefficient as high as 0.81 between the %CV and percentage of values below a glucose target set at 70–180 mg/dL (supplementary data). In the current study, we similarly found a relationship between the %CV and frequency of hypoglycemia, which was significantly greater in subjects who had a value >36% than in those who were below this threshold. It should be noted that this evaluation was mainly conducted to validate our primary objective (i.e., the determination of the threshold between low and high GV in persons with diabetes in the particular setting of our study). Bringing all of these observations together, health care professionals should be encouraged to achieve a lowering of GV, especially when patients are affected by exaggerated glucose oscillations. Such an approach requires the definition of an upper limit of GV in order that clear instructions can be provided to both patients and health care providers. Therefore, indices recommended for the GV assessment must be easily accessible and computable by any health care professional. Consequently, determining the %CV appears to be more suitable than the other more complex indices mentioned above (18,19,24). According to our results, obtained by analyzing the frequency distribution of GV in the reference group, a threshold for %CV of ~36% seems appropriate for this purpose. A few years ago, basing his statement on personal observations, Hirsch (32) proposed as the ideal target for glycemic variability an SD calculated from the following formula: SD × 3 < mean glucose (i.e., a %CV <33%). More recently, Rodbard (19) found that by stratifying insulin-treated patients (with both type 1 and 2 diabetes) according to whether the %CV corresponded to the 25th, 50th, or 75th percentile of the data distribution, a cutoff value between high

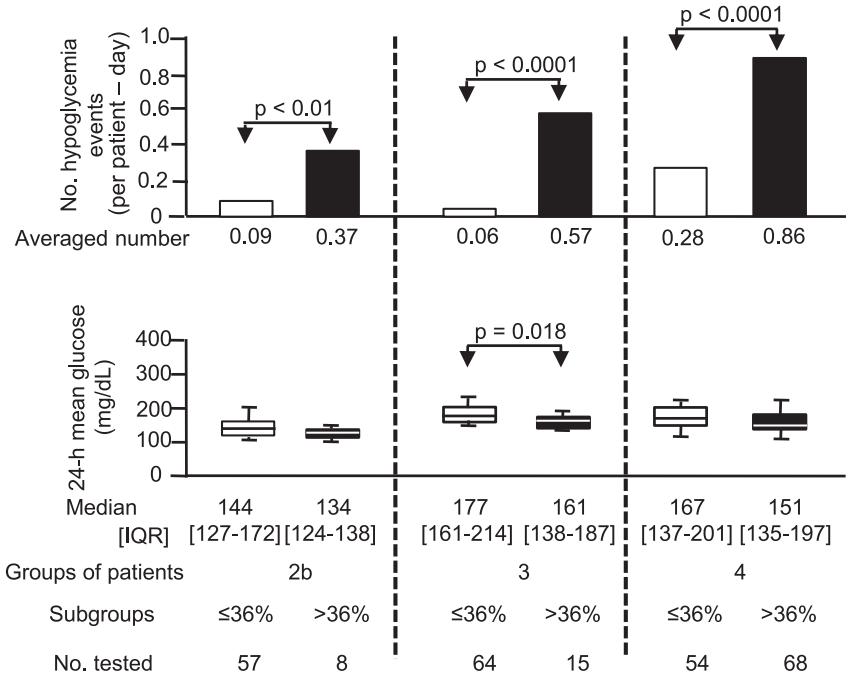

Figure 3—Incidence of hypoglycemia (top panel) and results of 24-h mean interstitial glucose values given as medians, with IQRs and 10th and 90th percentiles (bottom panel) when patients of each group were divided into two subgroups according to whether %CVs were >36 or ≤36%. Statistical significances are indicated when P values were <0.05.

(fair and poor) and low (good and excellent) of 36% can be set. This threshold is exactly the same as that observed in our study. However, one of the strengths of our approach was to show that the distribution of %CV was different in subjects with type 1 diabetes and in those with type 2 diabetes on insulin treatment as indicated in Fig. 1. Reverting to the study by Rodbard (19), no difference was found in GV between type 1 and insulin-treated type 2 diabetes. However, it should be noted that all patients were on basal-bolus insulin regimens, whereas, in our study, approximately one-half of the subjects with type 2 diabetes treated with insulin were on once-daily basal insulin alone. This difference in insulin regimens could explain the apparent discrepancies between the findings in the two studies.

Even though the rationale for the selection of the upper limit of %CV in our reference group can be debated, this choice seems to be a posteriori validated by several observations. Firstly, the upper limit of distribution in the reference group (36%) (i.e., in patients with type 2 diabetes) treated only with diet and/or insulin sensitizers was approximately the same as that observed by using another approach that consisted of assessing this upper limit after pooling in a single group all patients with type 2 diabetes without any hypoglycemia. Secondly, we observed a three- to ninefold increase in the frequency of hypoglycemia when adopting this threshold across the various groups of patients included in this study. In the group of persons with type 2 diabetes treated with DPP-4 inhibitors, no patient was above the threshold of 36%. In contrast, 12.3% of type 2 diabetes subjects treated with sulfonylureas were above this threshold of 36% and thus defined as unstable with a risk of hypoglycemia three times greater than in those below this threshold. Also, when using this threshold of 36%, the percentage of insulin-treated patients designated as unstable was found to be as high as 19.0 and 55.7% in type 2 and type 1 diabetes, respectively. These observations were associated with the fact that in the current study, the %CV progressively increased across the spectrum of diabetes from non-insulin–treated type 2 diabetes to insulin-treated type 2 diabetes and finally to type 1 diabetes. Our results are in agreement with those reported by Kohnert et al. (23) and Midyett et al. (33) presented at the 76th Scientific Sessions of the American Diabetes Association held in June 2016. In addition, our findings indicate that GV is markedly increased in persons with diabetes irrespective of the group considered when compared with individuals without diabetes (34). These observations suggest that disease progression is reflected in worsening of GV compounded by the necessary escalation of treatment. However, it should be noted that there is no difference between patients with type 2 diabetes treated with basal insulin when compared with those on basal-bolus regimen.

Using CGM raises the question as to whether abnormally high GV remains underdiagnosed when using self-monitoring of blood glucose, especially in patients with type 2 diabetes treated with insulinotropic agents (sulfonylureas) and/or insulin therapy. Is there an argument in favor of a broader use of CGM data for detecting silent hypoglycemic events in such patients, at least in those who are considered "vulnerable" and prone to hypoglycemia?

As frequency of hypoglycemic episodes might also result from lower mean glucose value (26,31,35,36), this parameter should be taken into account in interpreting our results. In the current study, the potential impact of a low mean glucose concentration on the incidence of hypoglycemia can be ignored in persons with type 1 diabetes, because the 24-h mean glucose values were similar in this group of patients, irrespective of the magnitude of the GV based on a %CV of >36 or $\leq 36\%$. Furthermore, the %CV has the main advantage of not being dependent on the mean glucose concentration (18,19).

The present work has a number of limitations. Firstly, all measurements were made using an older generation of CGM, but in our group of patients with type 2 diabetes treated with insulin, the means of %CV were approximately the same as the values observed at baseline in the population of the FLAT-SUGAR trial (10,29) using a newer generation of CGM (SEVEN PLUS or G4; Dexcom). In addition, all assessments of GV were limited to the monitoring of 24-h glycemic profiles on 2 consecutive days and the determination of a single parameter.

In the future, longer monitoring with newer generations of devices and other markers of GV may be required to confirm our findings. However, using CGM is never devoid of between- and within-setting variations (37). Finally, the interstitial glucose value of 56 mg/dL (3.1 mmol/L), which was selected as the threshold for hypoglycemia in the current study, is a compromise between the technical limitation of CGM and the definition of hypoglycemia that was set at 70 mg/dL by the American Diabetes Association in 2005 (38). With the older technology of CGM used in the current study, the monitoring system underestimated the real glucose value (7,39,40). Throughout the time course of hypoglycemia (i.e., in non–steady-state conditions), the relative difference between sensor readings and plasma glucose values varied between 0 and 20% (39). In steady-state conditions, absolute differences of -12 (40) to -19 mg/dL (7) were observed between interstitial glucose and the glucose value using the reference method when, like in the current study, the CGM was calibrated against capillary glucose concentrations. As it has been established that capillary and interstitial glucose values were underestimated at a similar extent when compared with the reference method (40), and as we have chosen to set the plasma-to-interstitial gradient at its upper limit of -20%, a subcutaneous value of 56 mg/dL (3.1 mmol/L) corresponded approximately to a plasma glucose concentration of 70 mg/dL (3.9 mmol/L).

Despite these limitations, and in summary, it now seems timely to include targeting GV to the assessment of chronic hyperglycemia using HbA_{1c} (11). Our findings indicate that setting a threshold for GV based on %CV of blood glucose at 36% could be used to discern between stable and unstable glucose homeostasis. A more graded scale such as low, fair, moderate, or high would also be welcomed. The proposed threshold of 36% is supported by the observation of an increased frequency of hypoglycemia in patients with type 1 diabetes and in those with type 2 diabetes on insulin therapy as soon as this threshold is transgressed. Finally, we strongly recommend that more consideration be given to the assessment of GV, primarily in type 1 diabetes, but also in type 2 diabetes, when on insulin treatment or, more generally, when any medication with a risk of hypoglycemia is implemented.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.
Author Contributions. L.M. participated in the study design, data collection and interpretation,

and writing of the manuscript. C.C., A.W., S.D., E.R., and D.R.O. participated equally in the study design, data interpretation, and critical revision of the manuscript. N.M. carried out the statistical analysis. L.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986
2. Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Intensive diabetic treatment and cardiovascular outcomes in type 1 diabetes: The DCCT/EDIC study 30-year follow-up. Diabetes Care 2016;39:686–693
3. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–1589
4. Hayward RA, Reaven PD, Wiitala WL, et al.; VADT Investigators. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015;372:2197–2206
5. Monnier L, Colette C, Owens D. The glycemic triumvirate and diabetic complications: is the whole greater than the sum of its component parts? Diabetes Res Clin Pract 2012;95:303–311
6. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38:140–149
7. Monnier L, Mas E, Ginet C, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA 2006;295:1681–1687
8. Hirsch IB. Glycemic variability and diabetes complications: Does it matter? Of course it does! Diabetes Care 2015;38:1610–1614
9. Bergenstal RM. Glycemic variability and diabetes complications: does it matter? Simply put, there are better glycemic markers! Diabetes Care 2015;38:1615–1621
10. Probstfield JL, Hirsch I, O'Brien K, et al.; FLAT-SUGAR Trial Investigators. Design of FLAT-SUGAR randomized trial of prandial insulin versus prandial GLP-1 receptor agonist together with basal insulin and metformin for high-risk type 2 diabetes. Diabetes Care 2015;38:1558–1566
11. American Diabetes Association. Glycemic targets. Sec. 5. In *Standards of Medical Care in Diabetes—2016.* Diabetes Care 2016;39(Suppl. 1): S39–S46
12. Monnier L, Colette C, Dejager S, Owens DR. Near normal HbA1c with stable glucose homeostasis: the ultimate target/aim of diabetes therapy. Rev Endocr Metab Disord 2016;17:91–101
13. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352:854–865
14. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 2006;368:1696–1705
15. World Medical Association Declaration of Helsinki. World Medical Association Declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. JAMA 1997;277:925–926
16. Directive 2001/20/EC of the European Parliament and of the council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical trials on medicinal products for human use [Internet], 2001. Luxembourg, Official Journal of the European Communities. Available from https://www.eortc.be/services/doc/clinical-eu-directive-04-april-01.pdf. Accessed 15 December 2016
17. John WG, Braconnier F, Miedema K, Aulesa C, Piras G. Evaluation of the Menarini-Arkray HA 8140 hemoglobin A1c analyzer. Clin Chem 1997; 43:968–975
18. DeVries JH. Glucose variability: where it is important and how to measure it. Diabetes 2013;62:1405–1408
19. Rodbard D. Clinical interpretation of indices of quality of glycemic control and glycemic variability. Postgrad Med 2011;123:107–118
20. Rodbard D. Hypo- and hyperglycemia in relation to the mean, standard deviation, coefficient of variation, and nature of the glucose distribution. Diabetes Technol Ther 2012;14: 868–876
21. Rodbard D. New and improved methods to characterize glycemic variability using continuous glucose monitoring. Diabetes Technol Ther 2009;11:551–565
22. Fabris C, Facchinetti A, Sparacino G, et al. Glucose variability indices in type 1 diabetes: parsimonious set of indices revealed by sparse principal component analysis. Diabetes Technol Ther 2014;16:644–652
23. Kohnert K-D, Heinke P, Fritzsche G, Vogt L, Augstein P, Salzsieder E. Evaluation of the mean absolute glucose change as a measure of glycemic variability using continuous glucose monitoring data. Diabetes Technol Ther 2013;15:448–454
24. Weber C, Schnell O. The assessment of glycemic variability and its impact on diabetes-related complications: an overview. Diabetes Technol Ther 2009;11:623–633
25. Kovatchev BP, Cox DJ, Gonder-Frederick LA, Young-Hyman D, Schlundt D, Clarke W. Assessment of risk for severe hypoglycemia among adults with IDDM: validation of the low blood glucose index. Diabetes Care 1998;21:1870–1875
26. Kovatchev B, Cobelli C. Glucose variability: Timing, risk analysis, and relationship to hypoglycemia in diabetes. Diabetes Care 2016;39: 502–510
27. Cox DJ, Gonder-Frederick L, Ritterband L, Clarke W, Kovatchev BP. Prediction of severe hypoglycemia. Diabetes Care 2007;30:1370–1373
28. Zar JH. *Biostatistical Analysis*. 4th ed. Upper Saddle River, NJ, Prentice Hall, 1999
29. FLAT-SUGAR Trial Investigators. Glucose variability in a 26-week randomized comparison of mealtime treatment with rapid-acting insulin versus GLP-1 agonist in participants with type 2 diabetes at high cardiovascular risk. Diabetes Care 2016;39:973–981
30. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005; 352:1685–1695
31. Monnier L, Wojtusciszyn A, Colette C, Owens D. The contribution of glucose variability to asymptomatic hypoglycemia in persons with type 2 diabetes. Diabetes Technol Ther 2011;13:813–818
32. Hirsch IB. Glycemic variability: it's not just about A1C anymore! Diabetes Technol Ther 2005;7:780–783
33. Midyett K, Cheung D, Unger JR, et al. Assessment of glucose variability by professional flash glucose monitoring across therapy groups for type 2 diabetes. Diabetes 2016;65(Suppl. 1):A222
34. Salkind SJ, Huizenga R, Fonda SJ, Walker MS, Vigersky RA. Glycemic variability in nondiabetic morbidly obese persons: results of an observational study and review of the literature. J Diabetes Sci Technol 2014;8:1042–1047
35. Kilpatrick ES, Rigby AS, Goode K, Atkin SL. Relating mean blood glucose and glucose variability to the risk of multiple episodes of hypoglycaemia in type 1 diabetes. Diabetologia 2007; 50:2553–2561
36. Cryer PE. Glycemic goals in diabetes: trade-off between glycemic control and iatrogenic hypoglycemia. Diabetes 2014;63:2188–2195
37. Luijf YM, Avogaro A, Benesch C, et al.; AP@home consortium. Continuous glucose monitoring accuracy results vary between assessment at home and assessment at the clinical research center. J Diabetes Sci Technol 2012;6:1103–1106
38. American Diabetes Association Workshop on Hypoglycemia. Defining and reporting hypoglycemia in diabetes. Diabetes Care 2005;28: 1245–1249
39. Monsod TP, Flanagan DE, Rife F, et al. Do sensor glucose levels accurately predict plasma glucose concentrations during hypoglycemia and hyperinsulinemia? Diabetes Care 2002;25:889–893
40. Guerci B, Floriot M, Böhme P, et al. Clinical performance of CGMS in type 1 diabetic patients treated by continuous subcutaneous insulin infusion using insulin analogs. Diabetes Care 2003;26:582–589