Glycemic Variability and Diabetes Complications: Does It Matter? Simply Put, There Are Better Glycemic Markers!

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There is no argument that improving mean levels of glycemic control as judged by assays for glycated hemoglobin (HbA_{1c}) reduces the risks of microvascular complications and cardiovascular disease events in patients with type 1 and type 2 diabetes. However, observations in some trials have suggested that targeting HbA_{1c} to suggested targets may not always result in improved outcomes for people with long-standing type 2 diabetes. The reasons why the glycemic control strategies that primarily use HbA_{1c} in these studies did not have predicted outcomes are not clear. Thus, controversy remains as to whether there are glycemic metrics beyond HbA_{1c} that can be defined as effective measures that can be used in addition to HbA_{1c} to help in assessing the risk of an individual developing diabetes complications. In this regard, the concept of "glycemic variability" (GV) is one metric that has attracted a lot of attention. GV can be simply defined as the degree to which a patient's blood glucose level fluctuates between high (peaks) and low (nadir) levels. The best and most precise way to assess GV is also one that is still debated. Thus, while there is universal agreement that HbA_{1c} is the current gold standard for the primary clinical target, there is no consensus as to whether other proposed glycemic metrics hold promise to provide additional clinical data or whether there should be additional targets beyond HbA_{1c}. Therefore, given the current controversy, we provide a Point-Counterpoint debate on this issue. In the preceding point narrative, Dr. Hirsch provides his argument that fluctuations in blood glucose as assessed by GV metrics are deleterious and control of GV should be a primary treatment target. In the counterpoint narrative below, Dr. Bergenstal argues that there are better markers to assess the risk of diabetes than GV and provides his consideration of other concepts.

—William T. Cefalu
Editor in Chief, *Diabetes Care*

The goal of a diabetes care team is to help individuals with diabetes live a full and meaningful life as the patient and care team strive to prevent or minimize the potentially devastating complications of diabetes. To continue to make progress on preventing diabetes complications, we will need to further explore both the basic causes of complications and ways to implement innovative management strategies to improve risk factors known to cause complications.

Studies have clearly demonstrated that poor glucose control is one risk factor directly linked to microvascular complications in type 1 diabetes (T1D) and type 2 diabetes (T2D) (1,2). Glucose control has also been shown to influence macrovascular

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disease (3) and, recently, mortality in T1D (4). While it is less clear how much of a primary role glycemic control plays in cardiovascular disease (CVD) development in T2D (compared with smoking cessation, blood pressure control, lipid/statin management, and the use of antiplatelet agents in appropriate high-risk patients), studies do show that good glycemic control early in the T2D disease process appears to positively affect the long-term development of CVD and mortality (5).

I contend that glycemic variability (GV), despite being associated with the activation of proinflammatory proteins and oxidative stress (6), is not ready to be included as a risk factor that, if normalized, will reliably reduce diabetes complications. The key data existing up until 2010 on whether GV, like glycemic control, was a marker of diabetes complications is best summarized by quoting an important article by Hirsch and Brownlee (7). The authors state: "Given the lack of studies specifically aimed at reducing glycemic variability to determine the effect of such reductions on clinical end points, new treatment guidelines targeting glycemic variability per se cannot be justified" (7).

Since 2010, many articles have addressed the possible importance of reducing GV because it seems logical that replicating the smooth and flat 24-h glycemic profile seen in individuals without diabetes (8) should reduce diabetes complications. In 2011, the A1C-Derived Average Glucose (ADAG) study group, which reviewed a vast amount of glucose data (self-monitoring of blood glucose [SMBG] and continuous glucose monitoring [CGM]) correlated with known cardiovascular risk factors, concluded that HbA_{1c} and mean glucose show stronger associations with CV risk factors than do postprandial glycemia or GV in people with diabetes (9).

The best evidence to support GV being linked to diabetes complications would be a randomized control trial showing a therapeutic strategy aimed at reducing GV versus a strategy focusing on basal glucose control resulting in fewer cardiovascular events. Researchers completed such a study in individuals with T2D at high risk for CVD using a prandial versus basal insulin approach. The trial, known as the HEART2D (Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus) study, failed to demonstrate that reducing GV led to reduced CVD risk (10). The study was discontinued prematurely, however, due to too few CVD events and less-than-expected differences in postprandial glucose values. The HEART2D data were reanalyzed to evaluate if GV had an effect on cardiovascular outcomes (11). Only one of three markers of GV was reduced with the prandial-targeted therapy and this was the newest, least established GV marker. The reduction of this GV marker did not result in a reduction of cardiovascular outcomes (more on the difficulty, but importance, of standardizing the definition of GV below).

An editorial by Monnier, a leader in the GV field, and Colette (12) summarized the data on GV and complications, including the impact of the GV analysis of HEART2D study. They concluded that it is not appropriate to include GV in the list of risk factors for diabetes complications but that further studies are warranted to confirm or refute its role. It turns out that the HEART2D results agree with two retrospective analyses of the Diabetes Control and Complications Trial (DCCT) showing that GV has only a very small contribution to the microvascular complications in T1D (13,14).

Certainly, it makes sense to minimize GV. Although it has not been proved to be linked to diabetes complications, an elevated GV is associated with hypoglycemia (15), reduced patient satisfaction (16), and biochemical abnormalities felt to possibly be linked to diabetes complications (6). Intervening to effectively and safely reduce GV starts with developing a uniform definition or set of definitions of GV so appropriate comparisons can be made (Table 1). While there is no agreed-on "best" GV metric, currently the preferred GV metric for research work is the coefficient of variation (CV or %CV), which is the least influenced by fluctuations in HbA_{1c} or mean glucose level. Most clinicians are more familiar with the standard deviation (SD), and it is often reported on device printouts, but experts in the field have also noted that there are at least eight measures of SD that may have some possible clinical relevance, including the most common and usually reported total SD, as well as the within-day SD and the between-day SD (17). Recognizing that the SD is not regularly distributed around the mean glucose, many have pointed out that the interquartile range (IQR), although strongly correlated with SD, may be a preferred measure of GV (8). Most measures of GV are not well understood by clinicians, and usually the relevance of GV as currently reported is a mystery to people with diabetes. However, because the IQR can be easily visualized on a modal day (standard day or 24-h glucose profile plot) and is part of the proposed international standard or uniform one-page glucose profile report (Ambulatory Glucose Profile [AGP]) (18,19), using IQR as one of the clinical measures of GV can actually have relevance to clinical decision making for the clinician and patient (18,20) (Fig. 1). Another long-used measure of GV is the mean amplitude of glycemic excursions, which is the average of all blood glucose excursions (up or down) that are of a magnitude greater than 1 SD of all glucose measures (21,22). There are many other measures of GV being explored (23). Four additional GV metrics are defined in Table 1, although it is not clear to me if these measures add any helpful clinical decision-making data over the first four more commonly used measures described above and in Table 1. In summary, GV is a glucose metric that deserves clinical attention but has not yet been shown to be strongly linked to complications. How much stronger are the data for HbA_{1c} versus GV as being strongly linked to the development of diabetes complications and thus an essential diabetes management metric today?

It has been 32 years (1983) since the start of the DCCT and 22 years (1993) since the DCCT findings were published showing that intensive therapy, including a reduction in HbA_{1c}, reduced microvascular complications (1). Follow-up of the DCCT volunteers in the Epidemiology of Diabetes Interventions and Complications (EDIC) trial expanded the evidence to show that early good HbA_{1c} control in T1D is also an established marker of reduced risk for

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Table 1—GV metrics at a glance

GV metric	Definition	Clinical implications of GV metric*	Normal reference range (2 SD around mean)
SD	The amount of variation or dispersion of a data set. The SD of the data set is the square root of its variance.	Variation measure most familiar to clinicians and easy to calculate	SD_T 10–26 mg/dL†
	At least eight subtypes of SD: the three most commonly used are *1*) overall (total) SD, SD_T (SD of all data, all days); *2*) within-day SD, SD_W (average of SD for each day); and *3*) between-day SD, SD_{dm} (SD of the daily means of each day)	Most accurate if values are "normally distributed around the mean," which is often not the case	
%CV	The extent of variability in relation to the mean of the population	Less influenced when comparing data sets with widely different mean glucose values (or HbA_{1c})	19–25%†
	100 × SD/mean of the observations	Possibly the "best" single research measure to compare GV over time or between data sets	
IQR	The spread of values 25% above and 25% below the median, sometimes called the middle fifty	Likely the "best" metric for visualizing GV around the median glucose curve	13–29 mg/dL†
		Plotting the IQR (around the median glucose curve) on a modal day glucose profile makes it is easy to spot what time of day has the most GV and needs attention	
Mean amplitude of glycemic excursions	Average of all blood glucose excursions or swings (peak to trough) that are greater than 1 SD of all measures for a given glucose profile	Most common measure of glucose spikes, swings, or excursions as opposed to glucose dispersion	41 and 48 mg/dL# (results from day 1 and 2 for one normal individual using CGM for 48 h)
		Used for many years; can be applied to SMBG or CGM data	
Continuous overall net glycemic action (1–24 h)	Intraday (within-day) glycemic variation	No clear benefit of these measures compared with the four more commonly used measures listed above	Few normal studies
CONGA (1–24 h)	The standard deviation of the differences of glucose readings for a defined period of hours		
Mean of daily differences	Interday (between-day) glycemic variation		
	The absolute value of the difference between glucose values taken on two consecutive days at the same time		
Mean absolute difference	Mean absolute difference of consecutive blood glucose values derived from SMBG data performed five times per 24 h		
Mean absolute glucose	The summed differences between sequential 7-point SMBG profiles per 24 h divided by the time in hours between the first and last blood glucose measurement		

*Author's assessment/opinion, †per Mazze et al. (8), #per Service (22).

macrovascular disease (3) and a reduced mortality rate (1).

Over that last two decades, HbA_{1c} has become the:

- Goal standard for assessing the risk of diabetes complications
- Goal standard for measuring level of overall glycemic control achieved
- Goal standard as the glycemic target in diabetes algorithms guiding the need for treatment change
- Key variable in diabetes pay-for-performance and diabetes quality rankings
- Main outcome marker for U.S. Food and Drug Administration approval (efficacy or safety) of new glucose-lowering drugs and technology for diabetes management
- New diagnostic criteria for diabetes

The last 22 years could be referred to as the "HbA_{1c} era," in which HbA_{1c} has been the main glycemic metric for guiding therapy changes and rating the

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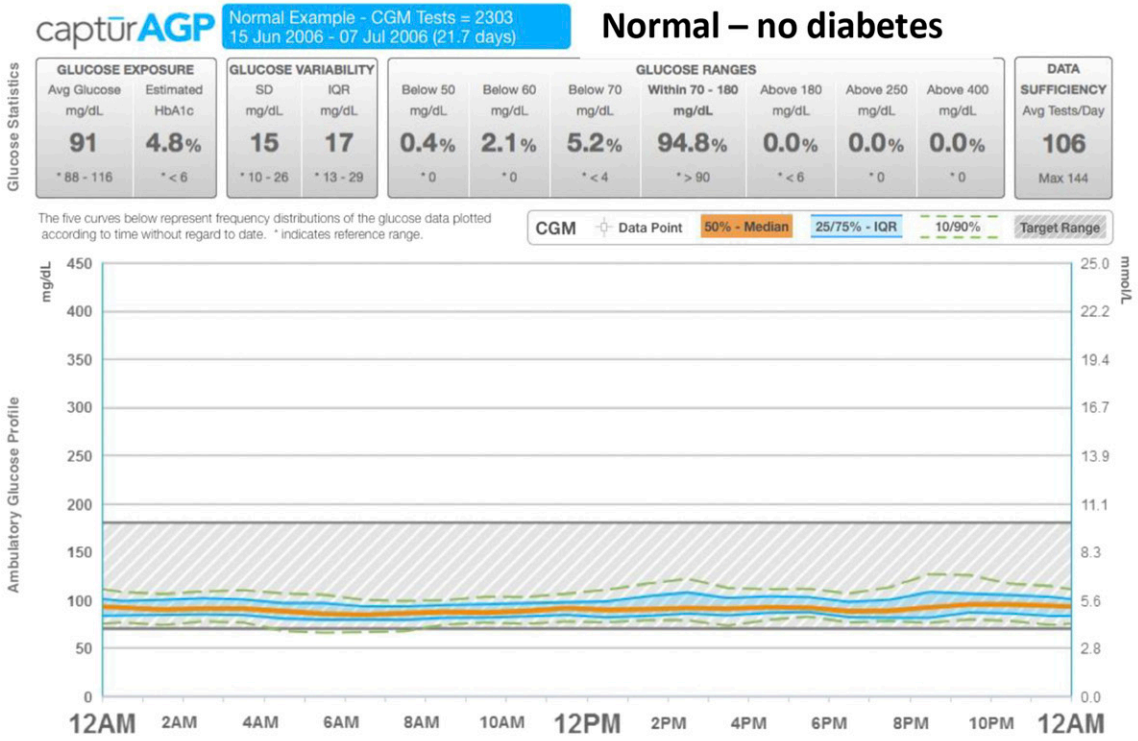

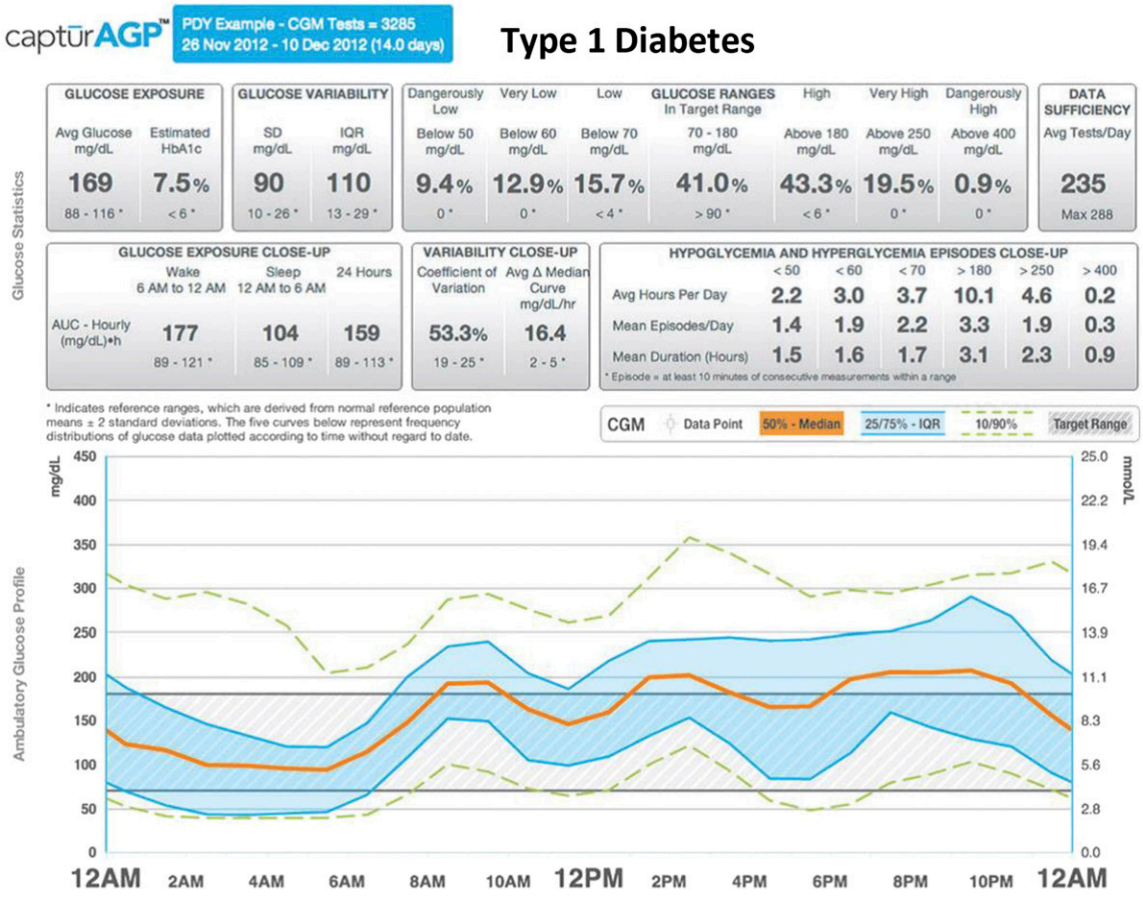

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Figure 1—AGP of a person without diabetes (normal) and of a person with diabetes. Adapted with permission from Bergenstal et al. (18).

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quality of diabetes care. How have patients with diabetes fared over the last 22 years with HbA_{1c} as the main glycemic target? For DCCT/EDIC patients living with diabetes now for at least 30 years, those with good HbA_{1c} control during the DCCT had about half the rate of microvascular and macrovascular complications compared with those with higher HbA_{1c} during the DCCT, and less than 1% of those achieving good glucose control developed blindness, needed a kidney transplant or dialysis, or had an amputation (24). In addition, HbA_{1c} levels, reported by the Centers for Disease Control and Prevention from successive National Health and Nutrition Examination Surveys, improved over time for the U.S. population (those having an HbA_{1c} <7% went from 44.3 to 52.2% from 1999–2002 to 2007–2010, respectively) (25). Complication rates, also recently reported by the Centers for Disease Control and Prevention, are also going down rather dramatically during the HbA_{1c} era (26) (Fig. 2). In summary, HbA_{1c} has been linked to or is predictive of mortality, various diabetes complications, emergency department visits, hospitalizations, and total cost of care, and intensive therapy does not negatively affect quality of life.

HbA_{1c} represents an average of the glucose levels an individual is exposed to over approximately a 3-month period. Even though HbA_{1c} appears to be a good marker of the risk of diabetes complications and mortality, it does not define an individual's overall glucose profile or the minute-to-minute glucose variations or even reveal if a given patient has had many dangerously low or dangerously high blood glucose readings. This reality has led clinicians and researchers to explore whether there are other glucose metrics beyond HbA_{1c} that would be even better at predicting the risk of diabetes complications or facilitating more effective clinical decision making.

Looking for glycemic metrics beyond HbA_{1c} could be defined as trying to find a measure to replace HbA_{1c} or it could mean finding measures in addition to HbA_{1c} that help sort out the risk of an individual developing diabetes complications. I think it makes sense to explore the use of glycemic markers to supplement the use of HbA_{1c} if they have a sufficient evidence base to demonstrate they are linked to the development of diabetes complications, quality of life, or use of health care resources.

Hypoglycemia is the obvious glucose metric that can greatly enhance the clinical interpretation of the HbA_{1c}, is critical for effective clinical decision making, and is clearly linked to diabetes complications (27). Hypoglycemia is well established as the primary barrier to optimizing glucose control (HbA_{1c}) in both T1D and T2D (28). In addition, recent data reveal that annually there are now more emergency department visits and hospital admissions for hypoglycemia than there are for hyperglycemia (29). Hypoglycemia has long been known to cause seizures, coma, and death but is also strongly associated with CVD (30), all-site cancer (31), dementia (32), reduced quality of life, and excess resource utilization (33). While there is strong evidence supporting the link between HbA_{1c} and hypoglycemia with diabetes complications, the current evidence is much weaker for GV being a direct cause of diabetes complications (Table 2). In fact, one of the great pioneers in the field of hypoglycemia, Philip E. Cryer, recently proposed that the selection of a glycemic goal (target) should be linked to the risk of hypoglycemia—and that the appropriate target might actually be the lowest HbA_{1c} that does not cause severe hypoglycemia and little symptomatic or asymptomatic hypoglycemia (34). His approach is an important reinforcement of the concept of a composite measure of glucose control, one that combines HbA_{1c} and some yet-to-be-agreed-on quantification of hypoglycemia. If one uses SMBG as the measure of plasma glucose, the most reliable composite is a combination of HbA_{1c} and the amount of severe hypoglycemia experienced, as it is difficult to accurately record, quantitate, and compare symptomatic and asymptomatic hypoglycemic events but individuals report severe hypoglycemia fairly reliably (particularly if surveyed every 3 months or so).

It is now time to use CGM to more accurately measure and quantitate hypoglycemia. We will need to derive a well-validated, clinically meaningful, and standardized measure of CGM-

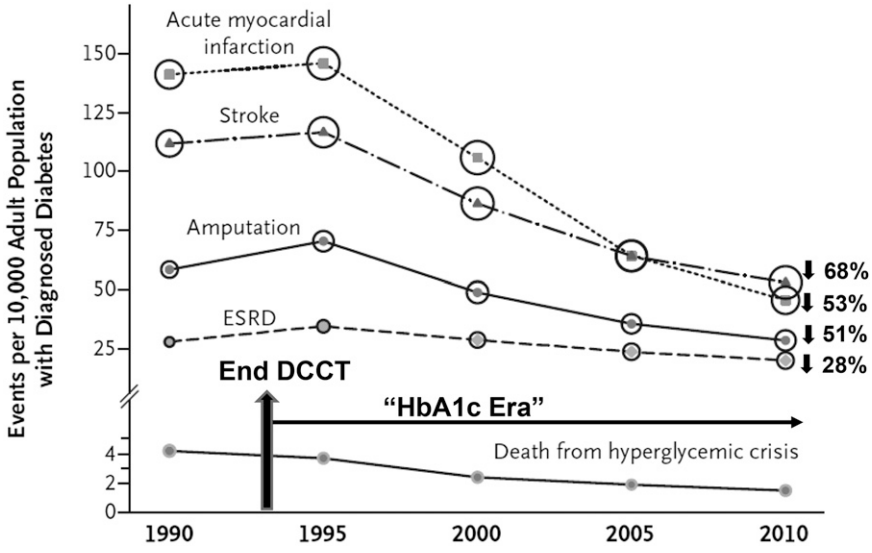

Figure 2—Changes in diabetes-related complications in the U.S. ESRD, end-stage renal disease. Adapted with permission from Gregg et al. (26).

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Table 2—Link between HbA_{1c}, hypoglycemia, and GV and adverse effects

Adverse effect	↑HbA_{1c}	↑Hypoglycemia	↑GV
Mortality	Yes	Yes	No
Complications	Yes	Yes	Possible minor effect (on microvascular complications)
Emergency department visits/hospitalizations	Yes	Yes	Unknown
Increased cost	Yes	Yes	Unknown
Decreased quality of life or patient satisfaction	Neutral	Yes	Yes (few studies)
Increased reactive oxygen species	Unknown	Unknown	Yes
Increased inflammatory proteins	Unknown	Unknown	Yes

detected hypoglycemia, first in the clinical research setting and then in practice.

Just as the diabetes community needs to agree on the metrics for GV, it also must agree on metrics for CGM-measured quantification of hypoglycemia. One approach would be to use the uniform glucose report (AGP standard glucose report) as a template that breaks down hypoglycemia into the percent of time spent low (<70 mg/dL), very low (<60 mg/dL), or dangerously low (<50 mg/dL) over a 2-week period of CGM readings (18) (Fig. 1). Therefore, assessment of glucose control would be based on *1*) the HbA_{1c}, *2*) the percent of time spent in these three categories of hypoglycemia, and *3*) any episodes of severe hypoglycemia, defined clinically as requiring the assistance of another person to recover. This composite assessment could then be easily compared across clinical trials and in clinical practice settings as a regulatory benchmark. Over time, acceptable metrics for excellent and poor overall glucose control can be determined. In addition to Cryer, others are starting to look at innovative ways to visualize a combined measure of HbA_{1c} and hypoglycemia (35,36).

As clinicians, patients, researchers, regulators, and payers become accustomed to patients using CGM-derived glucose data, the goal-standard HbA_{1c} may give way to a very comparable measure of glucose exposure by CGM (from which one can estimate an HbA_{1c} if necessary), along with the metrics for glucose time in range and several categories of time below range and time above range. These definitions need to be standardized and, ultimately, correlated with complications, so we finally have a measure of glycemic control that patients and clinicians can use to adjust day-to-day therapy, judge the risk of developing complications, evaluate effects on quality of life and patient experience, and assess resource utilization.

In the last three decades, at least four categories of treatment strategies—what may be referred to as the 4Ts—have emerged as critical to improving glycemic control:

1. Carefully defining **targets** for glycemic control (population/performance measurement and personalized/individualized targets)
2. Utilizing **teams** (patient-centered team care, shared decision making, self-management training, use of the medical home model of care and support)
3. Developing advanced **therapeutics** (new oral and injectable glucose-lowering drugs)
4. Applying new **technologies** (insulin pumps; continuous glucose monitors; big data/electronic medical records; smartphone apps for tracking glucose, diet, and exercise; and tools for remote communication between the patient and team)

Only when each individual with diabetes has a clearly defined and agreed-on glycemic target can we then effectively use care teams, new therapies, and advanced technology as needed to safely reach the glucose target. One glycemic target does not fit all, but all need a glycemic target.

During the HbA_{1c} era of the past 20 years, using HbA_{1c} as the main target for glucose control along with comprehensive cardiovascular risk factor management has helped dramatically reduce the risk of diabetes complications for a population of people with diabetes. By adding a well-defined set of measures of hypoglycemia, we can now set safe and effective personal HbA_{1c} targets (and eventually glucose time-in-range targets) for individuals and work to reduce the long-term complications while minimizing hypoglycemia. Reducing GV will be one of many means to reduce hypoglycemia.

In this issue of *Diabetes Care*, the design of the Fluctuation Reduction With Insulin and GLP-1 Added Together (FLAT-SUGAR) study is presented (37). The FLAT-SUGAR study is a randomized trial comparing the ability of prandial insulin versus prandial exenatide together with basal insulin to reduce GV (note that CV is the GV primary outcome metric). If this study succeeds in showing a difference in GV while maintaining comparable HbA_{1c} levels, the authors state the next logical step would be a trial evaluating if GV is a marker of diabetes complications. This methodical approach of gathering data to confirm a hypothesis supports my contention that while there is reason to work to reduce GV, we do not yet have outcomes data to determine if GV is a true marker of diabetes complications.

While the critical studies on GV and complications are being completed, let us work together now on a consensus around glycemic targets that include both HbA_{1c} (or time in range [CGM derived]) and standardized metrics to define the degree of hypoglycemia (CGM derived). It is time to use glucose data to address both population health and personalized care in diabetes management.

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