PERSPECTIVES IN CARE

The Fallacy of Average: How Using HbA$_{1c}$ Alone to Assess Glycemic Control Can Be Misleading

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HbA$_{1c}$ is a valuable metric for comparing treatment groups in a randomized trial, for assessing glycemic trends in a population over time, or for cross-sectional comparisons of glycemic control in different populations. However, what is not widely appreciated is that HbA$_{1c}$ may not be a good indicator of an individual patient's glycemic control because of the wide range of mean glucose concentrations and glucose profiles that can be associated with a given HbA$_{1c}$ level. To illustrate this point, we plotted mean glucose measured with continuous glucose monitoring (CGM) versus central laboratory–measured HbA$_{1c}$ in 387 participants in three randomized trials, showing that not infrequently HbA$_{1c}$ may underestimate or overestimate mean glucose, sometimes substantially. Thus, if HbA$_{1c}$ is to be used to assess glycemic control, it is imperative to know the patient's actual mean glucose to understand how well HbA$_{1c}$ is an indicator of the patient's glycemic control. With knowledge of the mean glucose, an estimated HbA$_{1c}$ (eA1C) can be calculated with the formula provided in this article to compare with the measured HbA$_{1c}$. Estimating glycemic control from HbA$_{1c}$ alone is in essence applying a population average to an individual, which can be misleading. Thus, a patient's CGM glucose profile has considerable value for optimizing his or her diabetes management. In this era of personalized, precision medicine, there are few better examples with respect to the fallacy of applying a population average to a specific patient rather than using specific information about the patient to determine the optimal approach to treatment.

As expounded by Todd Rose in his book *The End of Average* (1), the mean of a measurement made among a large number of individuals is relevant for describing a population or group but often is not applicable for a given individual and can be misleading. Hemoglobin A$_{1c}$ (HbA$_{1c}$) provides a good example of this. HbA$_{1c}$, which reflects blood glucose concentrations over 3–4 months, is a valuable metric for comparing treatment groups in a randomized trial, for assessing glycemic trends in a population over time, or for cross-sectional comparisons of glycemic control in different populations, and it is the only metric of glycemic control that has been strongly associated with chronic diabetic vascular complications. However, it has been debated whether, for an individual patient, the HbA$_{1c}$ level is the best marker for complication risk or whether the level of glycemia with which the HbA$_{1c}$ is associated is an equal or better marker of the risk of complications. Well recognized is the fact that HbA$_{1c}$ may not accurately reflect glycemic control in the presence of a hemoglobinopathy, hemolytic anemia, or other conditions that affect red blood cell life span or interfere with glucose binding to hemoglobin. However, what is not widely appreciated is that even when no such diagnosed condition is present, HbA$_{1c}$ may not be a good indicator of an

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individual's glycemic control because of the wide range of mean glucose concentrations and glucose profiles that can be associated with a given HbA$_{1c}$ level. It has been postulated that this mean glucose–HbA$_{1c}$ discordance is due to interindividual variation in red blood cell life span (2,3).

This distinction in utilizing HbA$_{1c}$ to compare groups versus its use in determining glycemic control for an individual was illustrated in a recent study we and others conducted assessing racial differences in the mean glucose–HbA$_{1c}$ relationship (4). The study showed that on average HbA$_{1c}$ levels in blacks are about 0.4% (4.4 mmol/mol) higher than those of whites for a given mean glucose concentration determined with continuous glucose monitoring (CGM). However, importantly the data also showed that the interindividual variation in HbA$_{1c}$ for a given mean glucose concentration within race substantially exceeds the average degree of variation between races.

The wide range of mean glucose concentrations associated with a given HbA$_{1c}$ level is not a new observation. It has been known since at least the 1990 publication of Yudkin et al. (5) and has been consistently demonstrated in numerous studies in individuals with prediabetes, type 1 diabetes, and type 2 diabetes (6–13), including the A1c-Derived Average Glucose (ADAG) study, which produced the widely used conversion table to estimate mean glucose for an HbA$_{1c}$ level (14).

The ADAG study was conducted in 2006–2007, utilizing CGM, which was not as accurate as current generation

Table 1—Range of mean glucose concentrations for observed HbA$_{1c}$ levels in pooled data from three recent studies* and the ADAG study

HbA$_{1c}$, % (mmol/mol)	Estimated mean glucose concentration (mg/dL) for a given HbA$_{1c}$, 95% CI†	
	Current study* (N = 387)	ADAG study (N = 507)
6 (42)	101–163	100–152
7 (53)	128–190	123–185
8 (64)	155–218	147–217
9 (75)	182–249	170–249
10 (86)	209–273	193–282

*The three studies from which data were obtained using the Dexcom G4 Platinum CGM System with an enhanced algorithm, software 505, pooled for the analyses herein are refs. 15, 16, and 28 (ClinicalTrials.gov identifiers NCT02282397, NCT02282397, and NCT02258373, respectively). †95% CI for a patient's mean glucose concentration for a measured HbA$_{1c}$ level.
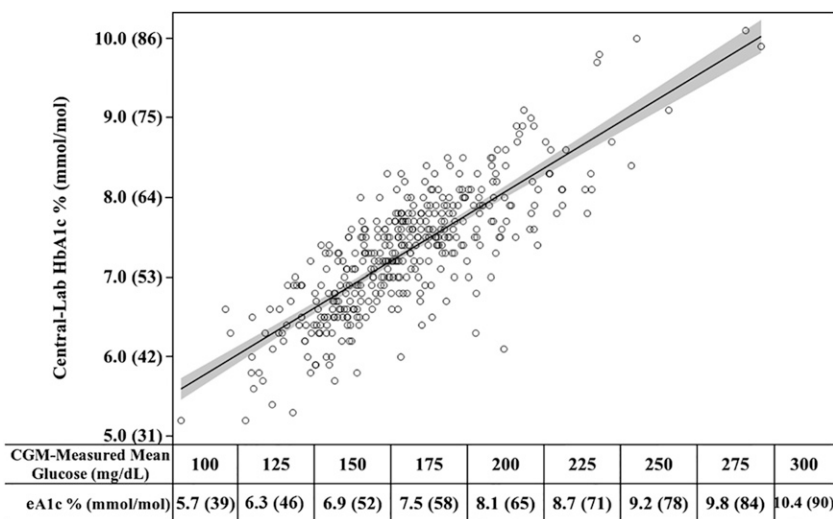
CGMs, as well as blood glucose meter measurements to determine the mean glucose concentration. The analysis was conducted on a data set with a median of 13 days of CGM measurements plus 39 days of fingerstick blood glucose measurements. To assess the mean glucose–HbA$_{1c}$ relationship with current CGM technology and a greater amount of data, we pooled data collected in 387 participants (age range 20–78 years, 83% white, 315 with type 1 diabetes and 72 with type 2 diabetes) in three randomized trials using the Dexcom G4 Platinum CGM System with an enhanced algorithm, software 505 (Dexcom, Inc., San Diego, CA) (4,15,16). Mean glucose concentration was determined for each participant using up to 13 weeks of CGM data (median amount of CGM data 66 days) and plotted versus HbA$_{1c}$ measured

following the collection of the CGM data at the Northwest Lipid Research Laboratories, University of Washington, Seattle, WA, using nonporous ion exchange high-performance chromatography (TOSOH, Biosciences, Inc., South San Francisco, CA).

As shown in Fig. 1, in the compiled data from the three studies, there is a wide range of mean glucose concentrations for a given HbA$_{1c}$ level. For an HbA$_{1c}$ of 8.0% (64 mmol/mol), the 95% prediction interval for mean glucose concentration is 155 to 218 mg/dL, substantially overlapping the CI for HbA$_{1c}$ of 7.0% (53 mmol/mol) of 128 to 190 mg/dL and HbA$_{1c}$ of 9.0% (75 mmol/mol) of 182 to 249 mg/dL. So, an HbA$_{1c}$ of 8.0% (64 mmol/mol) could be associated with good, fair, or poor glycemic control as judged by potential mean glucose levels of 128 to 249 mg/dL.
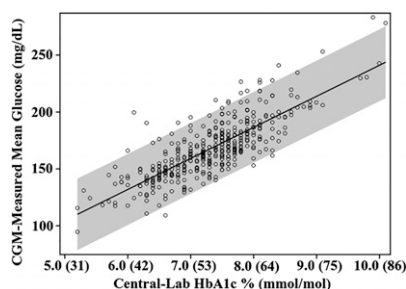
Figure 1—Plot of CGM-measured mean glucose concentration vs. laboratory-measured HbA$_{1c}$. The shaded area represents the 95% prediction interval (analogous to an individual CI) for a patient's mean glucose concentration for a measured HbA$_{1c}$ level, demonstrating the wide range of mean glucose concentration values that are possible for any HbA$_{1c}$ value.

CGM-Measured Mean Glucose (mg/dL)	100	125	150	175	200	225	250	275	300
eA1c % (mmol/mol)	5.7 (39)	6.3 (46)	6.9 (52)	7.5 (58)	8.1 (65)	8.7 (71)	9.2 (78)	9.8 (84)	10.4 (90)

Figure 2—Plot of laboratory-measured HbA$_{1c}$ vs. CGM-measured mean glucose concentration used to derive eA1C. The shaded area represents the 95% CI for the population mean HbA$_{1c}$ estimated from a mean glucose concentration. Equation to estimate HbA$_{1c}$ for a given mean glucose concentration: $eA1C = 3.38 + 0.02345 \times [mean\ glucose]$ (23,24).
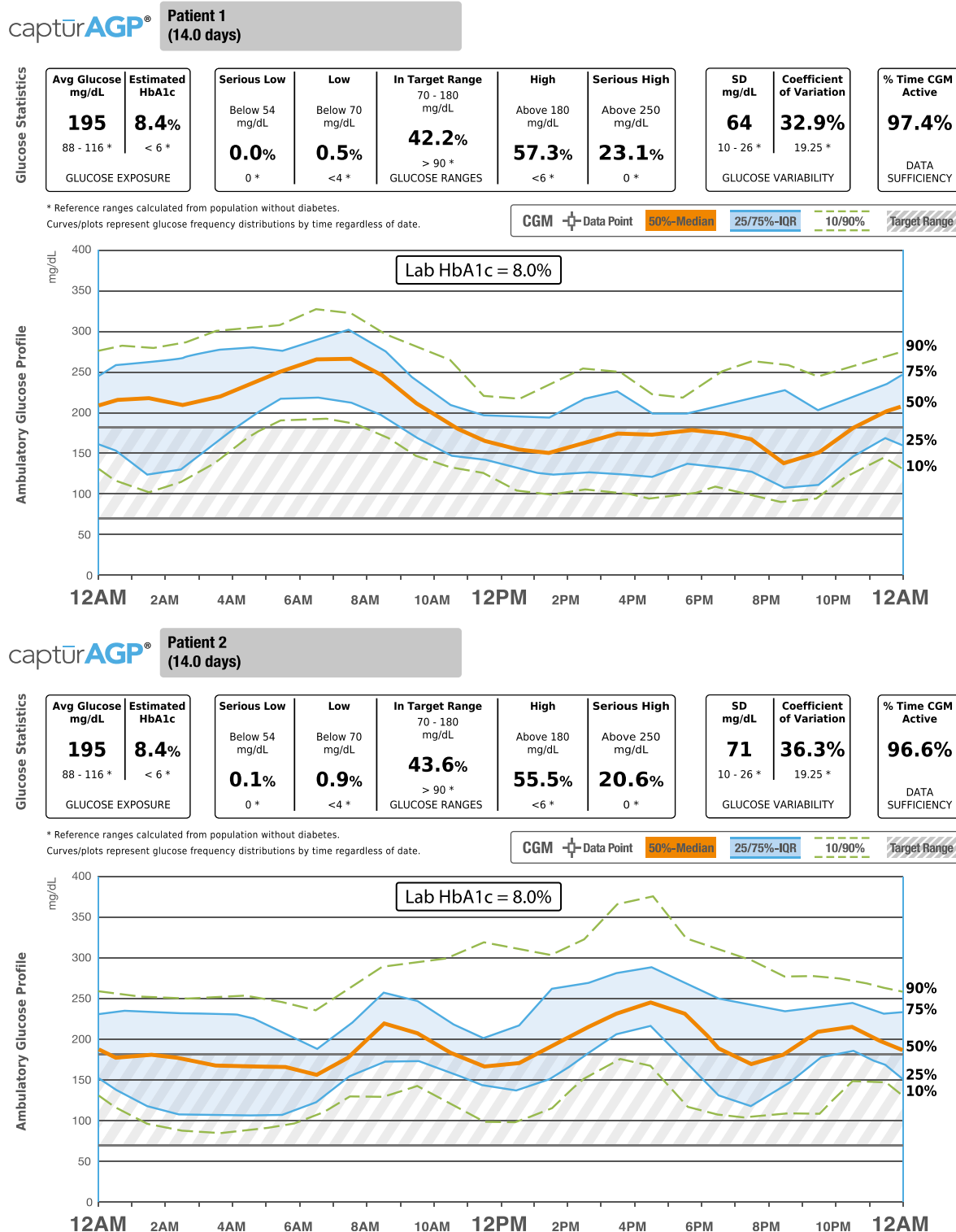
Figure 3—AGPs from four patients with laboratory-measured HbA$_{1c}$ of 8.0%. AGPs are shown for four adults with type 1 diabetes using multiple daily injections of insulin, all with an HbA$_{1c}$ of 8.0% from the same central reference laboratory. Displayed are 2 weeks of CGM data (up to 288 CGM values/day) for each patient measured just prior to the HbA$_{1c}$ laboratory test. The CGM is displayed as a modal or standard day. Shown are the median lines of all the glucose values over 2 weeks, the 25% and 75% lines (enclosing the shaded interquartile range [IQR]), and the 10% and 90% lines (dashed). The hatched area is the target glucose range of 70–180 mg/dL. Clinical note 1: Although each of the four patients has the same HbA$_{1c}$, the AGP patterns are very different and would suggest different insulin and or lifestyle interventions. Clinical note 2: The mean glucose varies from 156 to 195 mg/dL among the four patients. For patients 1 and 2, eA1C (8.4%) based on mean CGM glucose (195 mg/dL) is slightly higher than the measured HbA$_{1c}$ (8.0%), indicating that the measured HbA$_{1c}$ is slightly underestimating the mean glucose and that despite the same mean glucose, the daily pattern varies considerably. For patients 3 and 4, eA1C (7.0% and 7.3%, respectively) based on the mean CGM glucose (156 and 163 mg/dL, respectively) is substantially lower than the measured HbA$_{1c}$ (8.0%), indicating that the measured HbA$_{1c}$ is overestimating the mean glucose. Again, despite similar mean glucose concentrations, the daily pattern has considerable variation between the two patients. Avg, average.

captūrAGP® Patient 3 (14.0 days)

Glucose Statistics

Avg Glucose mg/dL	Estimated HbA1c		Serious Low Below 54 mg/dL	Low Below 70 mg/dL	In Target Range 70 - 180 mg/dL	High Above 180 mg/dL	Serious High Above 250 mg/dL		SD mg/dL	Coefficient of Variation		% Time CGM Active
156	**7.0%**		**4.4%**	**10.1%**	**54.5%**	**35.4%**	**11.3%**		**72**	**46.3%**		**70.6%**
88 - 116 *	< 6 *		0 *	<4 *	> 90 *	<6 *	0 *		10 - 26 *	19.25 *		
GLUCOSE EXPOSURE					GLUCOSE RANGES				GLUCOSE VARIABILITY			DATA SUFFICIENCY

* Reference ranges calculated from population without diabetes.
Curves/plots represent glucose frequency distributions by time regardless of date.

CGM ┼ Data Point | 50%-Median | 25/75%-IQR | 10/90% | Target Range

Lab HbA1c = 8.0%

Ambulatory Glucose Profile (mg/dL)

90% / 75% / 50% / 25% / 10%

12AM 2AM 4AM 6AM 8AM 10AM 12PM 2PM 4PM 6PM 8PM 10PM 12AM

captūrAGP® Patient 4 (14.0 days)

Glucose Statistics

Avg Glucose mg/dL	Estimated HbA1c		Serious Low Below 54 mg/dL	Low Below 70 mg/dL	In Target Range 70 - 180 mg/dL	High Above 180 mg/dL	Serious High Above 250 mg/dL		SD mg/dL	Coefficient of Variation		% Time CGM Active
163	**7.3%**		**0.5%**	**3.1%**	**63.8%**	**33.1%**	**9.8%**		**66**	**40.9%**		**98.1%**
88 - 116 *	< 6 *		0 *	<4 *	> 90 *	<6 *	0 *		10 - 26 *	19.25 *		
GLUCOSE EXPOSURE					GLUCOSE RANGES				GLUCOSE VARIABILITY			DATA SUFFICIENCY

* Reference ranges calculated from population without diabetes.
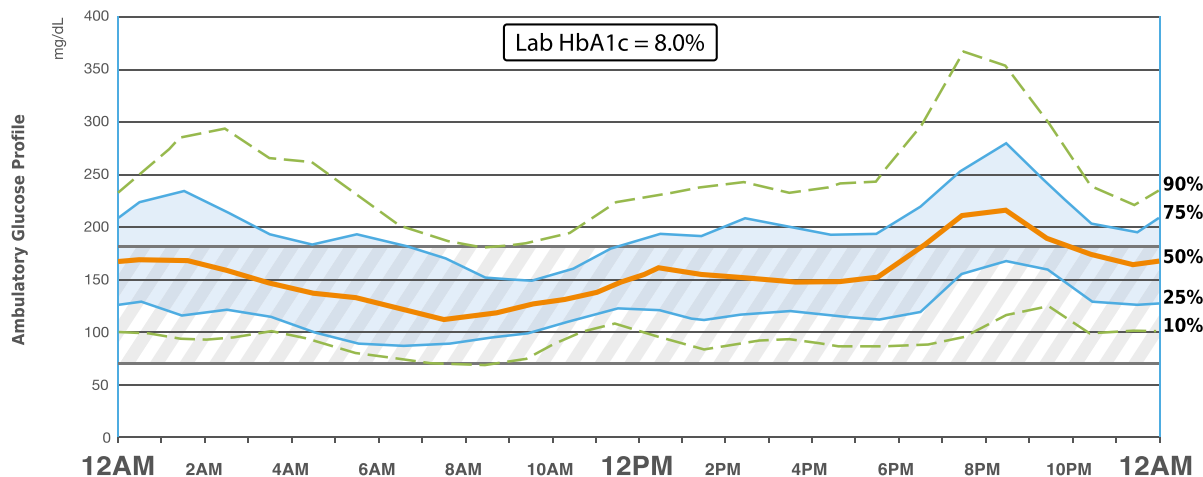Curves/plots represent glucose frequency distributions by time regardless of date.

CGM ┼ Data Point | 50%-Median | 25/75%-IQR | 10/90% | Target Range

Lab HbA1c = 8.0%

Ambulatory Glucose Profile (mg/dL)

90% / 75% / 50% / 25% / 10%

12AM 2AM 4AM 6AM 8AM 10AM 12PM 2PM 4PM 6PM 8PM 10PM 12AM

Figure 3—Continued.

These results are quite similar to the results of the ADAG study (Table 1). Thus, estimating glycemic control by HbA1c alone may not be accurate for some patients. As a result, utilizing HbA1c alone to judge health care provider performance in treating patients with diabetes may be problematic.

The potential impact of mean glucose–HbA1c discordance is illustrated in the post hoc analysis of the Action to Control Cardiovascular Risk in Diabetes (ACCORD)

study data by Hempe et al. (17). ACCORD, a study of type 2 diabetes, had the unexpected finding of an increased mortality rate in the intensively treated group (*N* = 10,251, mean age 62 years, median HbA$_{1c}$ 8.1%), which had an HbA$_{1c}$ target of <6.0%. Hempe et al. (17) showed that a higher mortality rate was present only in the subjects in the intensive treatment group whose HbA$_{1c}$ level was higher than the level predicted from fasting glucose concentration and that such subjects were more likely to have experienced severe hypoglycemia than those with an HbA$_{1c}$ lower than predicted. Regardless of whether this finding is a possible explanation for the ACCORD mortality results, this analysis illustrates the problem and in some cases potential danger of determining a patient's treatment regimen and glycemia goal from HbA$_{1c}$ alone without knowledge of the patient's mean glucose–HbA$_{1c}$ relationship and glucose profile.

IMPLICATIONS FOR CLINICAL PRACTICE

The best way to determine whether a given HbA$_{1c}$ might be over- or underestimating a patient's level of glycemic control is with CGM. CGM technology has advanced to where this can be done accurately and easily. For patients not already using CGM, a blinded CGM sensor could be worn once to compute a mean glucose concentration that can be compared with the patient's HbA$_{1c}$. Ideally CGM data should be obtained for at least 14 days immediately preceding the measurement of HbA$_{1c}$ during a period when diabetes treatment and glycemic control are reasonably stable (18). Several studies have demonstrated that an individual's mean glucose–HbA$_{1c}$ relationship tends to be reasonably constant over time (7,19–22). Although interval blinded CGM is useful for identifying patterns of glycemic control, a single blinded 14-day CGM wear to measure mean glucose concentration should be sufficient to estimate HbA$_{1c}$ to determine how well the actual HbA$_{1c}$ measurement estimates overall glycemic control for the patient. We recognize that this may not be realistic currently for all patients with diabetes, especially those with type 2 diabetes, but as sensor technology advances, that could become part of standard practice.

With knowledge of an individual's mean glucose concentration, a CGM-estimated HbA$_{1c}$ can be determined from the plot shown in Fig. 2 or by plugging the mean glucose concentration into the following formula: 3.38 + 0.02345 × [mean glucose] (23,24). Then, to inform how well an HbA$_{1c}$ measurement estimates the mean glucose concentration for a patient, the estimated HbA$_{1c}$ (eA1C) can be compared with the observed HbA$_{1c}$, which has been referred to as the hemoglobin glycation index (observed HbA$_{1c}$ minus predicted HbA$_{1c}$) (9).

While potentially better than HbA$_{1c}$ in understanding an individual patient's glycemic control, mean glucose itself is an average, and different degrees of glycemic variability and many different glycemic patterns could produce similar mean glucose concentrations and similar HbA$_{1c}$ levels. Figure 3 shows 2 weeks of CGM data (up to 288 sensor glucose measurements/day) displayed as a modal day or an ambulatory glucose profile (AGP) for four patients with type 1 diabetes using multiple daily injections of insulin. While each patient has a central laboratory–measured HbA$_{1c}$ of 8%, the AGP glucose patterns vary greatly and would each lead to different clinical advice for lifestyle changes or insulin adjustments. This is where retrospective review of CGM data has considerable benefit. CGM profiles provide far more information than just the mean glucose concentration by identifying patterns of hyperglycemia and hypoglycemia as well as potentially dangerous high or low glucose concentrations that are often missed with self-monitoring of blood glucose. The results of secondary analyses of two major studies (the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care [EXAMINE] trial and the Atherosclerosis Risk in Communities [ARIC] Study) (25,26) that found an association between hypoglycemia and cardiovascular events emphasize the importance of understanding a patient's glucose profile with CGM to potentially identify patients who may be at high risk for these events. Thus CGM by providing more clinical insights than HbA$_{1c}$ or self-monitoring of blood glucose measurements can help optimize and personalize glucose control and diabetes management (27).

CONCLUSIONS

We have written this Perspective to raise awareness of the need to know a patient's actual mean glucose concentration, ideally by using CGM, if HbA$_{1c}$ is to be used to assess a patient's glycemic control and make diabetes management decisions. As long as HbA$_{1c}$ is being used to define a glycemic target, we hope that eA1C becomes a standard metric used by clinicians and patients in assessing the level of glycemic control. Beyond that, a patient's CGM glucose profile, or AGP, has considerable value for optimizing diabetes management. Estimating glycemic control from HbA$_{1c}$ alone is in essence applying a population average to an individual, which can be misleading. In this era of personalized, precision medicine, there are few better examples than this one with respect to the fallacy of applying a population average to a specific patient rather than using specific information about the patient to determine the optimal approach to treatment.

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