The Prognostic Value of Time in Range in Type 2 Diabetes

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Continuous glucose monitoring (CGM) is the recommended approach to the assessment of hypoglycemia and glycemic variability in the setting of type 1 diabetes (1). The latest generation of CGM systems measure glucose every minute or every few minutes, with devices providing ~1,300 to up to ~20,000 measurements per person for a 14-day wear period. With this many measurements per person, the question arises of how to summarize the data in the most clinically useful manner and best communicate the results to patients. Time in range has emerged as a CGM metric with clinical utility in the management of type 1 diabetes (2,3).

Time in range is a relatively simple CGM metric, defined as the percent of time spent with glucose values within a target range, usually 70–180 mg/dL (3.9–10 mmol/L), although the target can be individualized. Time in range is automatically calculated and included in CGM system reports, along with percentage of time spent in hypo- and hyperglycemic glucose ranges (i.e., below or above target), average glucose, standard deviation, and coefficient of variation. As costs have come down and device accuracy has improved, the adoption of CGM has increased, with up to 20–30% of some U.S. patient populations with type 1 diabetes currently using the technology (4).

In patients with type 2 diabetes, the benefits and role of CGM in clinical management are less clear than in patients with type 1 diabetes. American Diabetes Association guidelines state that CGM may have a role in selected patients with type 2 diabetes, primarily those who are taking multiple daily injections of insulin (5). There is limited evidence regarding the clinical utility of CGM in type 2 diabetes, and few studies have linked CGM metrics to clinical outcomes in this population.

The study by Lu et al. (6) in this issue of *Diabetes Care* was undertaken to evaluate the association between time in range and risks of all-cause and cardiovascular mortality. The investigators enrolled 6,225 adult inpatients with type 2 diabetes admitted to the Shanghai Jiao Tong University Affiliated Sixth People's Hospital from January 2005 to December 2015. The enrolled patients wore a CGM sensor (CGMS Gold, Medtronic, Northridge, CA) for up to 72 h during their hospital stay. Time in range was calculated as the percentage of time spent in the glucose range 70–180 mg/dL [3.9–10 mmol/L] during a 24-h period (calculated from up to 288 glucose readings). Demographic and other clinical data, including hemoglobin A_{1c} (A1C), were collected from the study participants at the time of hospitalization. The CGM and other study data were linked to mortality records via personal identification numbers, and cause of death was identified using ICD-10 codes. At the time of the analysis, death data were available through 31 December 2018 for a median follow-up time of 6.9 years.

In this inpatient population (mean age 62 years, 55% male, mean A1C 8.9% [74.0 mmol/mol], mean duration of diabetes 9.7 years), Lu et al. found that those persons who had lower percent time in range (compared with those with time in range >85%) had higher risk of all-cause and cardiovascular mortality. The investigators also confirmed that A1C was associated with all-cause and cardiovascular mortality, documenting a J-shaped association, similar to that seen in prior observational studies (7).

There are several important considerations in the interpretation of these study results. First, the generalizability of these findings is unclear. This study population consisted entirely of hospitalized patients, CGM measurements were collected over a 72-h period using an older-generation device, and only 24 h of data for each patient was analyzed. It is generally thought that at least 10 days are necessary to get a reasonable sense of "usual" glucose patterns (8). It is uncertain how the study results might translate to ambulatory diabetes patient populations using current CGM technology and a longer period of data collection. Second, 67% of the participants in the study were described as insulin users, but it was not clear whether the use of insulin was prehospitalization, during the

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hospitalization, and/or continuing after the hospitalization. In-hospital CGM results will be strongly influenced by the use of insulin. Third, a wide range of illnesses can acutely alter glucose. No information was provided in the study regarding the nature of the hospitalizations. The underlying illness or reason for hospitalization may have been an important confounder in this study. Fourth, Lu et al. (6) adjusted for typical demographic and clinical risk factors, but they did not include A1C in any models that also included time in range. We cannot tell from these data if time in range adds prognostic information for mortality above and beyond A1C. Fifth, all participants who were out of range were grouped together in the analyses, so it is not possible to determine from the study results if the mortality risk was being driven by low (hypoglycemic) or high (hyperglycemic) values. Finally, the investigators calculated other CGM metrics including mean glucose and the coefficient of variation, but the associations of these other metrics with mortality were not presented in the article.

A1C is the standard measure used to monitor glucose control in type 1 and type 2 diabetes. There is growing use of CGM wearable technology as an adjunct to A1C. The latest generation of CGM systems are minimally invasive, simple to place on the body, easy to use, and do not require fingerstick calibration, and they interface with smartphones and smart watches. Some devices are now even being marketed (and are available over the counter in Europe) for use outside the setting of diabetes (in athletes, for example). While the accuracy of CGM devices has improved and costs have decreased, these systems are expensive, with sensors that are only used for up to 2 weeks and cost several hundred dollars per month (9). There remain many open questions about how best to employ this technology in clinical practice and how to ensure that it is used in a complementary manner to A1C.

CGM can provide nuanced data on the timing, amplitude, and frequency of hyperglycemia and hypoglycemia. In type 1 diabetes, time in range has emerged as a potent metric for monitoring glucose control and managing hypoglycemia. In type 2 diabetes, important questions are whether CGM can complement A1C, in which patient subgroups, and how best to employ this technology. Reducing hyperglycemia is typically of primary concern, and CGM metrics that reflect hyperglycemia and glycemic variability may be relatively more important than time in range in patients with type 2 diabetes. CGM generates thousands of data points, the devices output many glucose metrics, and using the technology to optimize glucose control is not simple and can be overwhelming for some patients and providers. Thoughtful studies are needed to identify the most relevant CGM metrics that will add value to current clinical care of the patient with type 2 diabetes.

In clinical practice we want tools that are linked to clinical end points and strong evidence that their use will improve patients' lives. Connecting CGM metrics to long-term outcomes is a first step. To move the field forward, it is critical that studies compare newer measures to our standard ones. Epidemiologic studies and randomized clinical trials are needed to rigorously compare the prognostic value of CGM metrics to each other and to A1C and to demonstrate that using CGM can complement A1C and improve outcomes in patients with type 2 diabetes. This is the evidence we need to guide the use of this technology and facilitate wider adoption of CGM in clinical practice.

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