

CONTINUOUS GLUCOSE MONITORING



Dave Rengachary, MD, DBIM, FALU
Sr. VP and Chief MD
RGA Reinsurance Company
Chesterfield, MO
drengachary@rgare.com



Lauren Garfield, PhD, MPH
OTR Associate Editor
RGA Reinsurance Company
Chesterfield, MO
lauren.garfield@rgare.com

As the name implies, continuous glucose monitoring (CGM) provides a real-time measure of glucose levels. An estimated 7 million individuals in the US have adopted the technology, representing approximately one out of four potential users. Glucose is typically measured from the (tissue) interstitial fluid and reported once every 5 minutes, providing an exceedingly detailed picture of glucose homeostasis compared to the traditional daily finger prick. Most CGM devices trigger an alarm in response to hypoglycemia, and complex algorithms have been developed that are guiding insulin regimens in a much more tailored fashion. However, despite remarkable advances in technology, CGM devices still have distinct limitations, and the long-term mortality benefits remain unclear.

With a flash glucose or intermittent glucose monitoring system (iCGM), glucose is continuously recorded by a sensor with a filament placed under the skin. It is not considered a true “continuous” system as a scanner must be intermittently placed over the skin to take the measurement. It does give both current readings and a readout of measures over the last 8 hours. It can reasonably be thought of as a replacement for finger sticks. The Abbott FreeStyle Libre system is the only intermittent glucose monitoring system currently available in the US. Because the glucose is measured in the interstitial fluid (instead of blood), it is generally recommended an individual check blood glucose with a traditional finger stick if blood sugars are rapidly changing or do not match the individual’s symptoms. Current models, however, are marketed as factory-calibrated and do not require routine calibration between readings and blood glucose measurements. The sensors need to be replaced every 14 days.

Executive Summary *Continuous glucose monitoring (CGM) allows for real-time measurement of blood glucose, and is a technology being used by an estimated 7 million individuals in the US and growing. Through a sensor placed under the skin, frequent measurements are taken in the interstitial fluid, providing an extremely detailed picture of glucose homeostasis. As these reports become more pervasive in the medical records, underwriters will need to understand their interpretation, associated terminology, limitations and implications for long-term mortality.*

As the name implies, CGM devices offer better real-time measurements of blood glucose. However, these devices still measure interstitial glucose and thus may lag behind blood glucose measurements. For this reason, and for most devices, it is recommended that the individual calibrate measurements routinely. The continuous nature of the device opens a world of analytic possibilities. A key benefit is the setting of alarms to notify the individual both of hypoglycemia and to prevent diabetic ketoacidosis (DKA). CGM devices offer greater capabilities of remote sharing of data with treating physicians. These systems can be further subdivided into “open” and “closed” loop systems. The loop in this case refers to the interaction between glucose sensor and insulin delivery system. In a closed loop system, this interaction takes place automatically. The majority of systems are still open or hybrid systems, requiring some form of user input prior to adjusting the insulin dose. Figure 1 (next page) offers a simplified comparison of the system types.

Figure 1. Comparison of CGM System Types

Characteristic	Real-Time CGM	Flash CGM
Monitoring	Button-push	Scanning
Automated alarms	Yes	No
Calibration FS	Yes	No
Closed-loop	Yes	No
Open system	Yes	No
Remote sharing	Yes	No

Source: Adolfsson. *Eur Endocrinol.* 2018 Apr, 14(1): 24-29.

Benefits and Limitations of CGM

A key benefit of CGM is to address the limitations of hemoglobin A1c (HbA1c) as a measure of diabetes control. This measure can be inaccurate in several clinical contexts including anemia, smoking, hemoglobinopathies and pregnancy. It serves as a measure of average blood glucose over the last 2 to 3 months but gives limited information about the peaks and valleys of glucose control, which of course are heightened in those individuals requiring insulin. Candidates for CGM then include the following:

- Many Type 1 diabetics.
- Insulin-dependent Type 2 diabetics.
- Intensive insulin therapy.
- Hypoglycemic history (especially with hypoglycemic unawareness).
- Highly variable “brittle” diabetics.

Further, the avoidance of finger stick requirements can improve compliance especially in younger or more active individuals. As detailed below, there is increasing evidence that CGM can provide superior glucose control.

However, there are several limitations. As mentioned, given the calibration and validation requirements of some systems, CGM cannot entirely replace blood glucose checks. Other individuals may be unsuitable candidates given complexity, cost and comfort concerns. The lag time effect between interstitial and blood glucose has not been eliminated with newer models. Finally, some personalities may not mesh well with CGM due to information overload or over-reliance upon the algorithms.

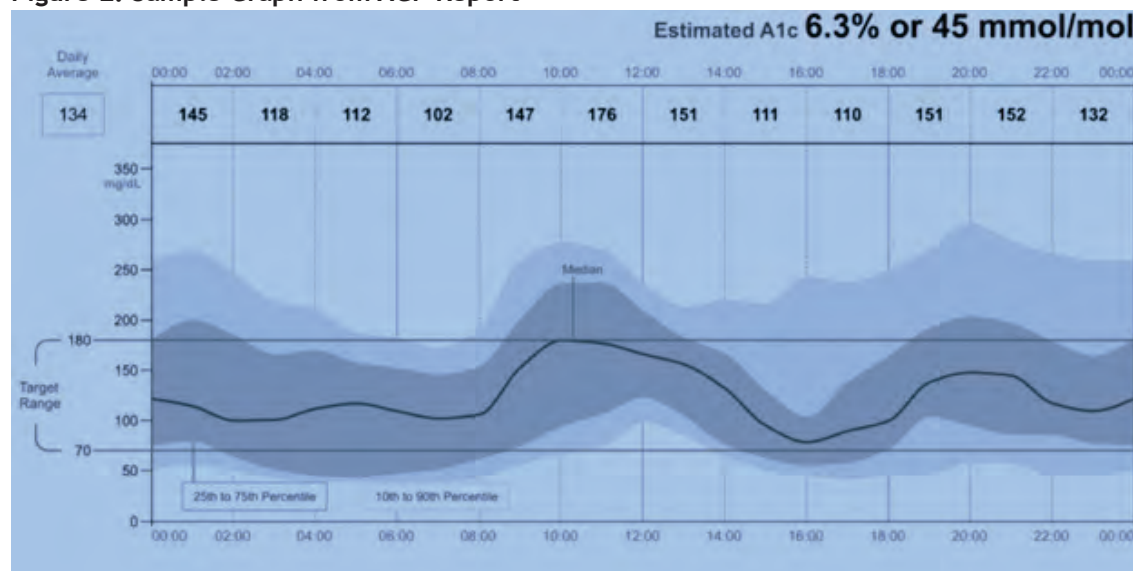
Interpreting a CGM Report

An important trend prompting increasing utilization of CGM has been standardization and simplification of the reporting, resulting in a single-page ambulatory glucose profile (AGP) report (Figure 2).

There are several new measures which underwriters will need to consider in their risk assessment:

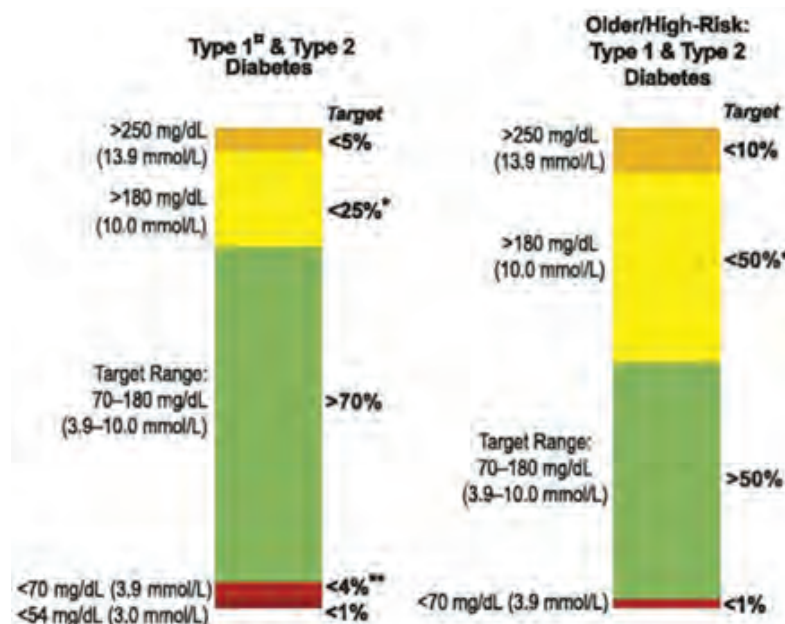
Time in range (TIR) – The percentage of time blood glucose is within the target range. As a general rule of thumb, 70% of readings should be within the desired target range. The target range may vary significantly according to several factors such as diabetes type, age, frequency of hypoglycemic, or DKA episodes. Figure 3 (next page) offers sample target ranges for two commonly represented groups. In addition to the target range, time in the hypoglycemic range (<70 mg/dl) should be kept to less than 4%. The time spent below 70 mg/dl may also be reported as time in hypoglycemia (TIHypo). There is increasing evidence that TIR, like HbA1c, correlates well to the likelihood of diabetic complications.

Figure 2. Sample Graph from AGP Report



Source: https://commons.wikimedia.org/wiki/File:Ambulatory_Glucose_Profile_Sample_Graphs.png Creative Commons License 4.0.

Figure 3. Sample Target Ranges



Source: <https://care.diabetesjournals.org/content/42/8/1593>.

Glucose management indicator (GMI) percentage is an estimate of hemoglobin A1c. Previously some reports used the term “estimated hba1c”; however, the FDA recommended the term be replaced due to potential confusion that it is synonymous with the traditional HbA1c measure. This can be calculated using another measure commonly found in AGP reports, the mean (or average) glucose:

$$\text{GMI (\%)} = 3.31 + 0.02392 \times [\text{mean glucose in mg/dL}] \text{ or } 12.71 + 4.70587 \times [\text{mean glucose in mmol/L}]$$

While HbA1c is typically a measure of average blood glucose over 120 days, GMI can be representative of a much smaller period of data (as little as 14 days). GMI may also differ from HbA1c given the limiting factors described above that change the average life span of the red blood cell or the affinity for the hemoglobin molecule for glucose. However, as long as those factors remain stable, the delta between GMI and HbA1c for a particular individual also tends to remain stable. For underwriting purposes, the differences could be considered modest especially with a relatively stable GMI.

Measures of Glucose Variability: Standard Deviation (SD) and Coefficient of Variation (CV)

Standard deviation is likely the more familiar of the two terms and measures the average variability from the mean. The challenge with standard deviation is that it rises when the mean rises, which can give an inaccurate picture in the context of elevated average glucose readings. The coefficient of variation (CV) is

the ratio of the standard deviation to the mean, expressed as a percent; it essentially helps correct for differences in the mean. The target CV is generally less than 36%.

Summary of Evidence

A growing body of evidence supports the use of CGM in selected diabetic patients. While endpoints can be quite diverse, trials have generally sought to demonstrate better control with the use of CGM or the avoidance of hypoglycemia.

Most trials target measures of control. The GOLD trial in 2017¹ was a crossover trial of 161 Type 1 diabetics on multiple daily insulin (MDI) injections randomized to CGM (Dexcom G4 PLATINUM) or conventional therapy. Treatment periods were for 26 weeks, separated by a washout period of 17 weeks. At the conclusion of the trial, the mean difference in HbA1c at the end of treatment periods was 0.43% (7.92% vs. 8.35%). Glycemic variability was also reduced in the treatment group.

That same year, the DIAMOND trial reported both positive results in Type 1 diabetics² and Type 2 diabetics on MDI³. The latter group included 158 individuals randomized to CGM or traditional monitoring. At 24 weeks, mean HbA1c levels decreased to 7.7% in the CGM group and 8.0% in the control group at 24 weeks, resulting in a modest but statistically significant adjusted mean change of -0.3% [95% CI, -0.5% to 0.0%]; P=0.022.

TIR has also improved with the advent of CGM. In 2006, for example, Garg et al.⁴ demonstrated a 26% improvement in TIR among 91 individuals with Type 1 and Type 2 diabetes. Accordingly, this was accompanied by 23% less time hyperglycemic and 26% time less time hypoglycemic.

Several trials have focused on the prevention of hypoglycemia as the primary endpoint. Bolinder et al.⁵ enrolled 328 patients with well-controlled Type 1 diabetes and then randomly assigned them to flash glucose monitoring or traditional blood glucose strips. Mean TIHypo was reduced in the flash glucose monitoring group.

While the above data is promising, it can also be observed that trial numbers are small, follow-up times are short, and long-term data is sorely lacking around the use of CGM to prevent diabetic complications, and in particular, mortality.

Figure 4. Representative CGM Trial Summaries

Measure	Study	Summary
HbA1C	DIAMOND Trial	- Reduction of 0.6% in Type 1 diabetics. - Reduction of 0.3% in Type 1 MDI.
HbA1C	GOLD Trial JAMA 2017	Reduction of 0.43% in Type 1 diabetics on MDI.
Hypoglycemia	Bolinder et al. Lancet 2016	- Type 1 diabetics on MDI or CSII. 38% reduction in time in hypoglycemia.
Hypoglycemia rtCGM vs. iCGM	Reddy, Diabetes Med 2018	- Type 1 diabetics randomized to rtCGM vs. iCGM. 2.7% rtCGM vs. 6.8% iCGM time in hypoglycemia. - iCGM thought higher time in hypoglycemia at baseline.
TIR	Garg et al., Diabetes Care 2006	- Insulin dependent Type 1 and 2 diabetics. 26% increase in TIR. 23% reduction in time in hypoglycemia.
Hypoglycemia and effects on MACE/ Mortality	Wei et al., Front Endocrinol 2019	Hypoglycemia was associated with increased cardiovascular death (HR 2.6) and all-cause mortality (HR 1.960).

Underwriting Considerations

- Underwriting guidance around CGM measures need to address scenarios when both GMI% and HbA1c are available. Given the current lack of well-established, long-term data on diabetic complications and mortality associated with use of CGM, use of HbA1c may be advised.
- In the absence of recently available HbA1c, however, GMI% may be considered a reasonable substitute.
- For cases where CGM measures such as TIR, TIH, GMI% and coefficient of variance are available, these may provide additional detail allowing for greater precision or adjustment to base ratings. For example, for those who show exceptional stability of blood glucose by TIR (e.g., > 80%), a crediting adjustment could be considered.

Notes

- Lind, Marcus, William Polonsky, Irl B. Hirsch, Tim Heise, Jan Bolinder, Sofia Dahlqvist, Erik Schwarz, et al. "Continuous Glucose Monitoring vs. Conventional Therapy for Glycemic Control in Adults With Type 1 Diabetes Treated With Multiple Daily Insulin Injections: The GOLD Randomized Clinical Trial." *JAMA* 317, no. 4 (January 24, 2017): 379. <https://doi.org/10.1001/jama.2016.19976>.

- Beck, Roy W., Tonya Riddlesworth, Katrina Ruedy, Andrew Ahmann, Richard Bergenstal, Stacie Haller, Craig Kollman, et al. "Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections: The DIAMOND Randomized Clinical Trial." *JAMA* 317, no. 4 (January 24, 2017): 371. <https://doi.org/10.1001/jama.2016.19975>.
- Beck, Roy W., Tonya D. Riddlesworth, Katrina Ruedy, Andrew Ahmann, Stacie Haller, Davida Kruger, Janet B. McGill, et al. "Continuous Glucose Monitoring Vs. Usual Care in Patients With Type 2 Diabetes Receiving Multiple Daily Insulin Injections." *Annals of Internal Medicine* 167, no. 6 (August 22, 2017): 365–74. <https://doi.org/10.7326/M16-2855>.
- Garg, Satish, Howard Zisser, Sherwyn Schwartz, Timothy Bailey, Roy Kaplan, Samuel Ellis, and Lois Jovanovic. "Improvement in Glycemic Excursions with a Transcutaneous, Real-Time Continuous Glucose Sensor: A Randomized Controlled Trial." *Diabetes Care* 29, no. 1 (January 2006): 44–50. <https://doi.org/10.2337/diacare.29.01.06.dc05-1686>.
- Bolinder, Jan, Ramiro Antuna, Petronella Geelhoed-Duijvestijn, Jens Kröger, and Raimund Weitgasser. "Novel Glucose-Sensing Technology and Hypoglycaemia in Type 1 Diabetes: A Multicentre, Non-Masked, Randomised Controlled Trial." *Lancet* (London, England) 388, no. 10057 (November 5, 2016): 2254–63. [https://doi.org/10.1016/S0140-6736\(16\)31535-5](https://doi.org/10.1016/S0140-6736(16)31535-5).

Additional Reference

- Lu, Jingyi, Chunfang Wang, Yun Shen, Lei Chen, Lei Zhang, Jinghao Cai, Wei Lu, et al. "Time in Range in Relation to All-Cause and Cardiovascular Mortality in Patients With Type 2 Diabetes: A Prospective Cohort Study." *Diabetes Care* 44, no. 2 (February 1, 2021): 549–55. <https://doi.org/10.2337/dc20-1862>.

About the Author

Dave Rengachary, MD, DBIM, FALU, is Senior Vice President and Chief Medical Director for US Mortality Markets at RGA Reinsurance Company. Prior to joining RGA in 2013, he was a general neurologist in practice at Missouri Baptist Medical Center where he also served as medical director for its Primary Stroke Center. Dr. Rengachary attended the Honors Program in Medical Education at Northwestern University. He then completed an adult neurology residency at Washington University followed by a fellowship in Clinical Neurophysiology. He is the primary author and editor of the Washington University Neurology Survival Guide. He serves on the board of directors of Memory Home Care Solutions and Oasis, non-profit organizations respectively dedicated to Alzheimer's caregiver support and healthy aging. In 2020, Dr. Rengachary accepted a position as vice-chair of ACLI's Risk Classification Committee. He is a past president of the Midwestern Medical Directors Association (MMDA), current Deputy Director of the Longer Life Foundation, Medical Consultant for the Academy of Life Underwriting (ALU), and a member of the Educational Committee of the American Academy of Insurance Medicine (AAIM).

ACADEMY OF LIFE UNDERWRITING

MISSION

To be the recognized leaders in providing professional educational opportunities to life underwriters worldwide.



SIGN UP

To register go to the ALU store:
<https://alu-web.com>

Email: registrar@alu-web.com

BASIC ECG TUTORIALS

This four-part series, moderated by Dr. William Camm, presents the skills necessary to differentiate between normal and abnormal ECGs.

For only \$50.00, you get indefinite access to the tutorials! rapid interpretation of ECGs by Dr. Dale Dubin (not included) is recommended as a resource to complement the tutorials.