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CLINICAL APPLICATIONS

Practical Considerations in the Use of Real-Time Continuous Glucose Monitoring Alerts

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Abstract

Background:

The safety and efficacy of real-time (RT) continuous glucose monitoring (CGM) systems in the management of type 1 diabetes are increasingly apparent. Clinical trials have demonstrated the utility of these systems in lowering hemoglobin A1c, minimizing hypoglycemia, and reducing glycemic variability. These RT systems allow patients to conveniently monitor their glucose levels by displaying concentration and trending information. Several of these RT systems provide preset alerts that sound when absolute glucose thresholds are reached. Additionally, some systems allow for predictive algorithm-based alerts that incorporate rates of change. However, clinical trials have identified significant noncompliance in the use of these devices, most notably in the pediatric and adolescent populations.

A retrospective review of CGM reports shows that many patients set high and low alert thresholds at levels that result in frequent alerts, potentially resulting in patient nuisance, dismissal of consequential alerts, and eventual product abandonment. Therefore, setting the alert thresholds at appropriate high and low settings can determine the balance between either a perceived benefit by the patient and their long-term use of CGM systems or annoyance to the patient and discontinuation.

Conclusion:

Care should be taken to set CGM alerts at levels that result in a manageable number of notifications per day. In some cases, providers should consider not using alerts at all or consider using broad targets when initiating CGM to maximize alert specificity. Real-time CGM is safe and generally well tolerated; however, individualization of alert settings is necessary maximize the system's benefits and patient adherence.

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Introduction

Real-time (RT) continuous glucose monitoring (CGM) products from Abbott, DexCom, and Medtronic (**Figure 1**) have been commercialized over the past several years; the Medtronic Paradigm RT system is unique in that it combines CGM and insulin pump functions in a single device. All currently available CGM systems include glucose

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Abbreviations: (CGM) continuous glucose monitoring, (HbA1c) hemoglobin A1c, (JDRF) Juvenile Diabetes Research Foundation, (MDI) multiple daily injection, (RT) real time

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sensors that are connected to a transmitter on the skin surface, which transmits glucose information to a nearby device for storage and retrospective review. The Paradigm RT system allows data to be uploaded into both a Web-based system for patients and a desktop application for physicians (CareLink™ Personal and CareLink Pro Therapy Management Software, respectively). Most importantly, these systems provide users with RT continuous glucose information in the form of recent glucose values, trend graphs, and directional arrows indicating rates of change. All systems provide alerts to the user when preset glucose thresholds are reached. Additionally, some systems use prediction algorithms to forewarn users of impending events, so treatment can be made in advance of the glucose level reaching a threshold. Lastly, some systems provide rate-of-change alerts to notify users of rapid glucose excursions.

Sensor Accuracy

One of the key determinants of clinical benefit with CGM is the accuracy of the glucose information provided to the user. Improvements in sensor construction and the calibration algorithms used with sensors have led to improved overall accuracy.[1,2] The ability to accurately identify hypoglycemic and hyperglycemic events has dramatically increased, with sensitivities reaching over 80% for threshold alerts alone, which improve to well over 90% when used in conjunction with predictive alerts.[2]

Clinical Evidence

Recently, several clinical studies have been conducted to evaluate the safety and clinical efficacy of CGM systems in patients on pumps or using multiple daily injection (MDI) therapy.[3–14] A large Juvenile Diabetes Research Foundation (JDRF)-sponsored randomized controlled trial[4] and a later subset analysis of CGM in well-controlled type 1 diabetes[5] showed significant hemoglobin A1c (HbA1c) reductions attributed to CGM in patients ≥25 years of age, regardless of how insulin was delivered. The RealTrend Study[6] included 132 adults and children using MDI therapy who transitioned to either standard pump therapy with finger sticks only or to pump therapy combined with CGM using the Paradigm RT platform. The results showed that combined CGM/pump therapy reduced HbA1c more than pump therapy alone, without impacting the rate of hypoglycemia. All studies have demonstrated positive outcomes associated with CGM use, yet several of the studies[4,15] describe situations where users decided to stop using the system. Continuous glucose monitoring has also been shown to have a strong impact in reducing the risk of severe hypoglycemia events.[16]

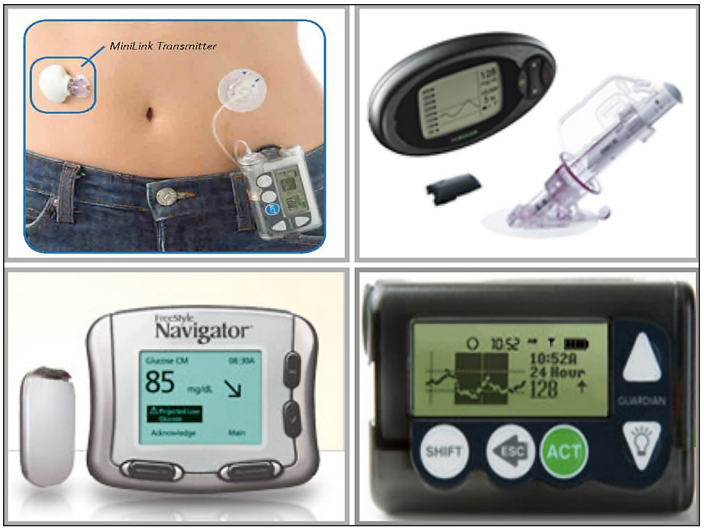


Figure 1. The MiniMed Paradigm REAL-Time (Medtronic Diabetes), DexCom SEVEN (top row), Abbott FreeStyle Navigator, and Guardian REAL-Time (Medtronic Diabetes) (bottom row) CGM systems. Only the Paradigm REAL-Time product combines insulin delivery with CGM.

Why Patients Stop Wearing Continuous Glucose Monitors

Despite the improved accuracy of current systems and the proven advantages of CGM in diabetes management, many patients stop using the system or use it intermittently. In the JDRF CGM study,[17] median sensor wear time (days per week) dropped from 7 to 6.5 in adults, from 6.3 to 3.3 in adolescents, and from 6.8 to 3.7 in pediatric subjects after six months. Adherence was higher in adults and subjects with more frequent prestudy finger stick testing,[14] suggesting that adherent patients are those who recognize the value of finger stick monitoring and can use glucose readings (whether from CGM or finger sticks) appropriately.

There are many factors that can influence a patient's willingness to embrace CGM. Consensus guidelines exist that describe several potential barriers to CGM adoption, including uncertainties about accuracy, inadequate reimbursement, the need for educational infrastructure, and health care provider support.[18] Other considerations that may contribute to CGM abandonment include unfamiliarity with the role of calibration or how calibration affects accuracy; patients may also experience frustration when confronted with tasks related to the programming of alerts and management of accumulated data.[18,19] A strong understanding of glycemic response to meals, basal/bolus insulin action, insulin stacking, and the need to continue meter testing is a prerequisite for appropriate patient outcomes. Some of the key barriers

to long-term adoption are discussed here, with a focus on the patient's perspective.

First and foremost, expectations regarding the product's capabilities are often at odds with its actual features. Many patients contemplating CGM do not completely understand the requirement of continued finger stick testing for both calibration and confirmation before acting on CGM data. Some users believe the system will automatically deliver appropriate insulin and function as an artificial pancreas. And most commonly, many users are disappointed by discordances between CGM and meter readings, in some cases expecting the values to match precisely. These drawbacks can be overcome easily with proper training and education in the materials developed by manufacturers and by the health care team.

Second, the current CGM systems have an inherent hassle factor. Use of CGM requires insertion of a sensor under the skin, and for many people, there is pain and/or discomfort from the sensor, transmitter, or tapes used to secure the device to the body. For patients on pump therapy, use of CGM requires a second appropriate anatomic location at some distance from the insulin catheter site. The system also requires a warm-up period before providing data and periodic calibration thereafter. Once running, the CGM system almost invariably intrudes on the user's attention with messages and alerts regarding glucose concentrations or system maintenance. And of course, the user is tasked with acting on CGM data. Often, patients are not taught how to interpret and use trending data and may become dissatisfied as a result.

Lastly, CGM is designed to alert users when glucose concentrations exceed or fall below specified thresholds or when time series data meet specified criteria. The Guardian RT system provides a tremendous amount of customization for the user and allows for three different alert types: threshold, predictive, and rate of change. Threshold alerts activate when the sensor glucose value meets a preset threshold and are easily understood. By contrast, predictive and rate-of-change alerts are based on time series data—there are more variables to be set than for the threshold alerts, and patients may require additional training before realizing the full value of the alerts. Predictive alerts activate when the sensor glucose values are predicted to reach a threshold in a preprogrammed time period based on the sensor's rate of change; rate-of-change alerts activate when the sensor's rate of change exceeds a preset threshold, independent of where the glucose levels are at that time. Predictive and rate-of-change alerts are available with the Guardian RT system and will be implemented in the next generation of Medtronic insulin pumps; the current generation of Paradigm pumps only allows for threshold alerts but displays trending data as directional arrows.

Alert settings are very flexible. Each alert can be set to detect both low and high glucose events, can be enabled at different times of day, or can have different thresholds at different times of day, allowing flexibility to address a user's needs for both daytime and nighttime periods. In addition, each alert has a repeat setting that determines how frequently the alert will sound for the same event (analogous to the snooze function of an alarm clock). Some devices allow a choice of various sounds (or silent vibration) for each different type of alert. Clearly, there are many options and considerations for users when setting sensor alerts.

Unfortunately, alert settings are often inappropriately set. In many cases, users experience tens of alerts per day, providing a constant reminder of glucose values out of the target range. **Figures 2** and **3** illustrate this problem and show cases where users are subjected to a barrage of alerts throughout the day. In **Figure 2**, the low alert setting of 90 mg/dl, combined with a short snooze interval of 15 min, resulted in numerous alerts followed by a user-initiated pump suspension (perhaps out of frustration or annoyance). A longer low snooze interval or a lower low alert threshold may have been more appropriate for this patient. **Figure 3** shows high alerts occurring at low frequency in response to a many-hour hyperglycemic event. Inappropriately short snooze intervals can result in patient frustration and disenchantment.[18] In addition, patients may become inured to frequent alerts, inappropriately delay treatment for glycemic excursions, or shut off their pumps entirely. This situation is common and persists despite detailed guidelines for optimized use of the system. What follows are some practical considerations around the use of CGM alerts, which should result in a more positive user experience and improve a user's perception and utilization of the product.

Considerations in Setting Sensor Alerts

When a health care team decides to initiate CGM, how should the glucose alerts be set? As a general rule, Hirsch and colleagues[18,19] suggest initial threshold values of 70 and 250 mg/dl and further suggest a stepwise introduction of alarms. Obviously, a knowledge of the patient's HbA1c allows an estimate of average glucose, and a review of meter readings can provide some indication of the extent of glycemic excursions, but these

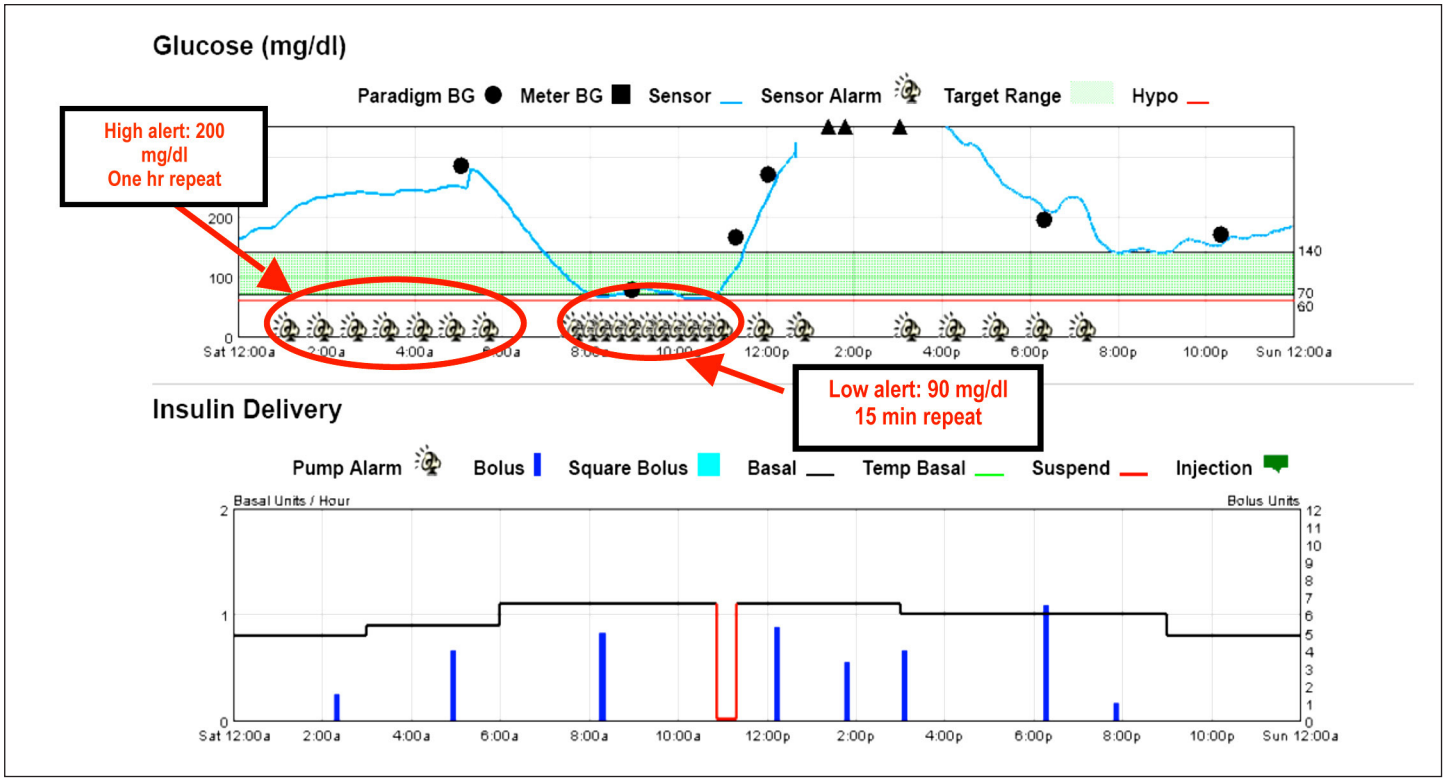


Figure 2. Daily summary report from Medtronic CareLink Personal of CGM and insulin delivery data. The top panel shows the user's glucose excursions over a 24 h period. The light blue tracing is the sensor data, black dots represent meter blood glucose values used for calibration, and black triangles indicate meter readings above the scale limit of 350 mg/dl. Several of the alerts are circled on the bottom of the chart, indicating when the high and low thresholds were exceeded. The bottom panel shows the basal rate (solid black line), suspended basal (red line), and boluses (blue bars). This user experienced numerous alerts throughout the day, which were accurately indicating glucose excursions beyond the programmed thresholds. BG, blood glucose.

readings are often only taken at times convenient to the patient and do not represent the complete glycemic picture. Also, until a person is actually experiencing the system, it is difficult to ascertain their willingness to accept frequent notifications of glycemic excursions. Consequently, selection of initial alert settings is difficult, and providers should consider not using any alerts for an initial period of 1–2 weeks of sensor use, unless the user frequently experiences hypoglycemia or has hypoglycemic unawareness; in such cases, a low alert may be indicated from the outset. Some providers, mindful of the risk of unexpected hypoglycemia, will activate the low alert in all CGM-using patients. This phased approach allows the user to become comfortable with other aspects of system maintenance and avoid a potentially overwhelming multitude of high and low alerts.

After the first week of use, and following upload of data into the CareLink Personal or Pro Therapy Management software, patients and providers have the opportunity to review several days of CGM data. **Figure 4** shows an example of a sensor daily overlay report from CareLink Personal, which superimposes one week's data on a single graph. From this overlay, the health care team can decide which initial alert settings are appropriate for the user, based on the number of alerts the system will likely generate, and the person's willingness to deal with alerts. Although not universal, keeping the average number of alerts to 2–3 per day minimizes burden to the user. Low threshold alerts are especially valuable when they lead to corrective action and avoidance of severe hypoglycemic episodes; high threshold alerts are also valuable but may not mandate immediate intervention. Predictive alerts, if appropriately triggered and acted on, may help patients avoid excursions entirely. More sophisticated rate-of-change alerts may be useful in pattern detection and for fine-tuning insulin therapy.

As described earlier, some CGM systems allow a wide variety of alert settings, and when setting up alerts, it may be inappropriate to enable all of the alert types at once. For low glucose excursions, we recommend using the low threshold and low predictive alert with a 10–15 min predictive horizon to aid in timely detection and avoidance of hypoglycemia. Conversely, for the high

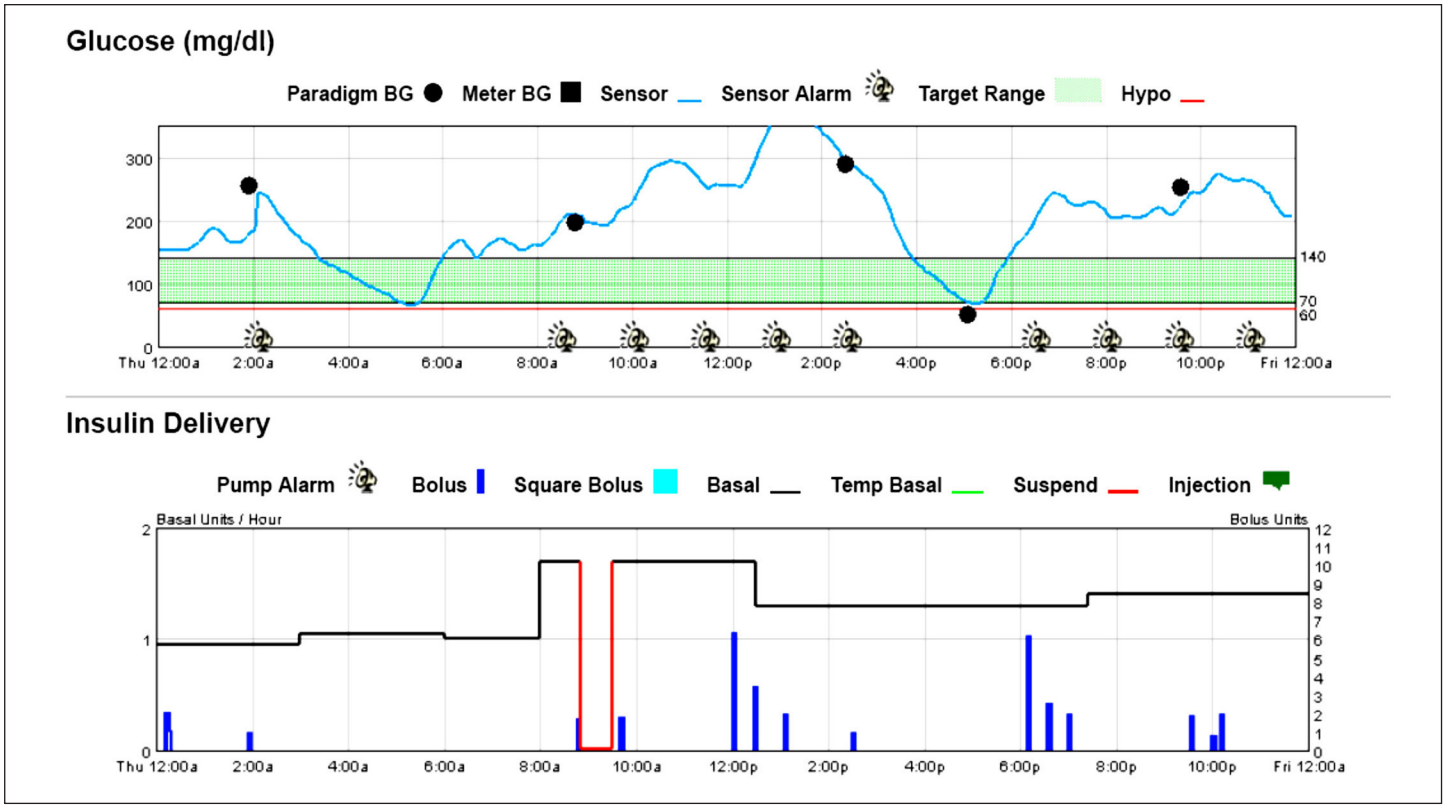
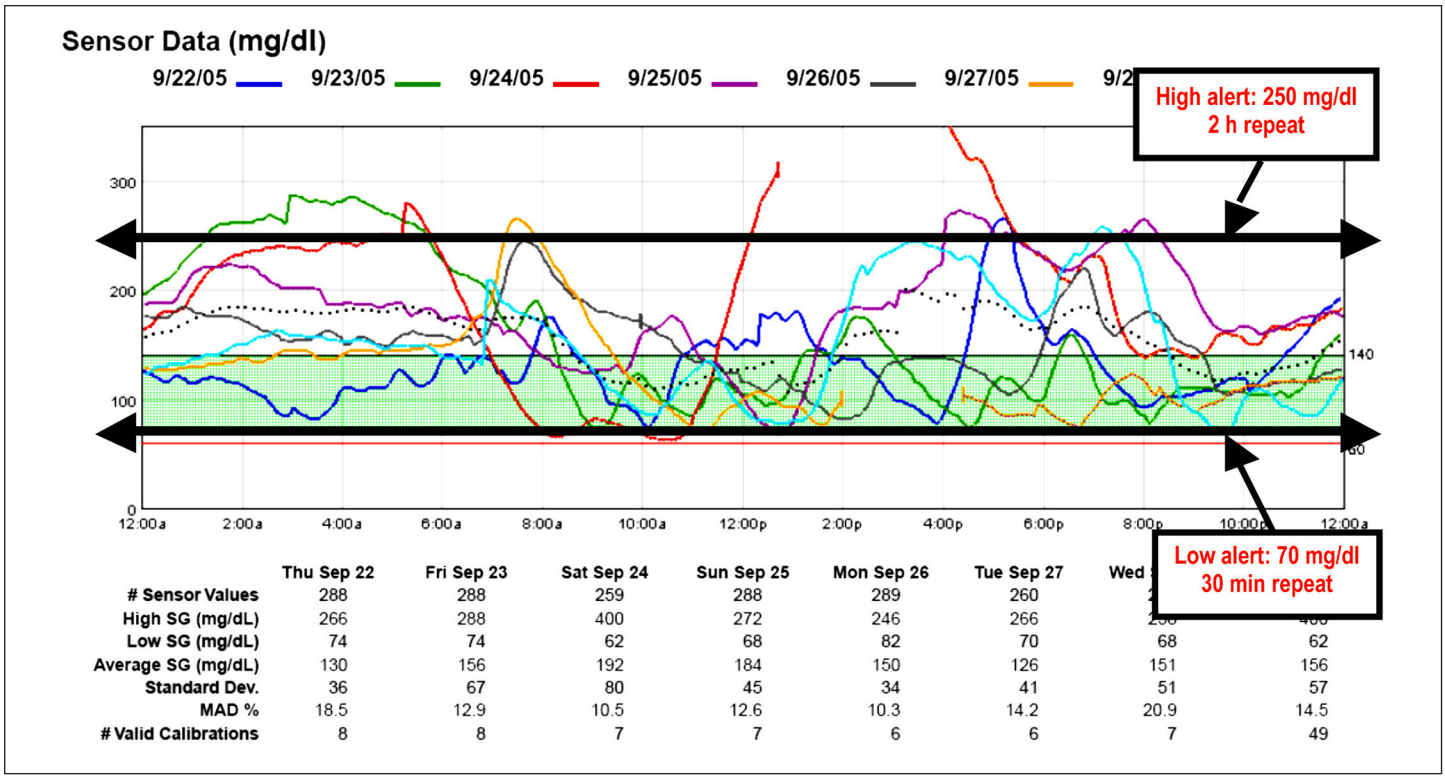


Figure 3. Example of a CareLink Personal daily summary report showing three hyperglycemia events, with two persisting for many hours. Use of an alert setting at 200 mg/dl resulted in alerts for more than 16 h of the day. BG, blood glucose.



	Thu Sep 22	Fri Sep 23	Sat Sep 24	Sun Sep 25	Mon Sep 26	Tue Sep 27	Wed	
# Sensor Values	288	288	259	288	289	260		
High SG (mg/dL)	266	288	400	272	246	266		
Low SG (mg/dL)	74	74	62	68	82	70	68	62
Average SG (mg/dL)	130	156	192	184	150	126	151	156
Standard Dev.	36	67	80	45	34	41	51	57
MAD %	18.5	12.9	10.5	12.6	10.3	14.2	20.9	14.5
# Valid Calibrations	8	8	7	7	6	6	7	49

Figure 4. Upload of CGM data shown on the CareLink Personal Sensor daily overlay report. Superimposed on the top graph are solid horizontal lines at 70 and 250 mg/dl. Setting the high alert at 250 mg/dl and the low alert at 70 mg/dl as indicated by the lines would result in 2–3 alerts per day versus the large number of alerts shown in **Figures 2** and **3.** Using a 2 h repeat for the high alert and 30 min repeat for the low alert would also minimize the number of repeat alerts for the same event. SG, sensor glucose; MAD, mean absolute deviation.

alert, we suggest using only the threshold alert initially since early detection of these episodes is not as critical.

Resolving a hyperglycemic event will almost always take more time than recovering from a low episode due to insulin pharmacodynamics, so the snooze interval for hyperglycemia is generally set longer than that for hypoglycemia. The maximum snooze settings on the Paradigm pump (3 and 1 h for high and low excursions, respectively) are expected to minimize redundant alarms. Many patients find a snooze setting of 2–3 h ideal for the high alert, while 30 min is often used for the low alert setting.

The process of periodically uploading accumulated CGM data into CareLink is not only important for adjusting alert settings, but also critical for optimizing basal rates, insulin-to-carbohydrate ratios, and insulin sensitivity factors. It also allows the health care team an opportunity to evaluate the timing of premeal boluses and to determine the effect of exercise or other daily events on glucose control. With judicious therapy adjustments, many patients are able to achieve very good control throughout the day and adjust alert settings accordingly. Despite a relatively stringent hyperglycemia alert threshold of 180 mg/dl, the patient shown in **Figure 5** only experienced two alarms during the 24 h shown.

Discussion

The adoption of CGM is expanding rapidly due to the recognized utility of RT information and improved reimbursement policies adopted by third-party payors. As CGM becomes more widely used, it is critical to better understand the merits and liabilities of the technology, as well as its optimal usage and overall best practices. Success with CGM requires detailed education and training in diabetes management coupled with extensive training in the use of CGM. Understanding the timing and importance of calibration, how to interpret CGM data during glucose excursions, and how CGM can supplement finger stick testing to provide valuable trending information and identify glucose excursions are equally critical. Lastly, patient acceptance and outcomes will suffer unless judicious choices regarding sensitivity and specificity of alerts are made. Alert settings must

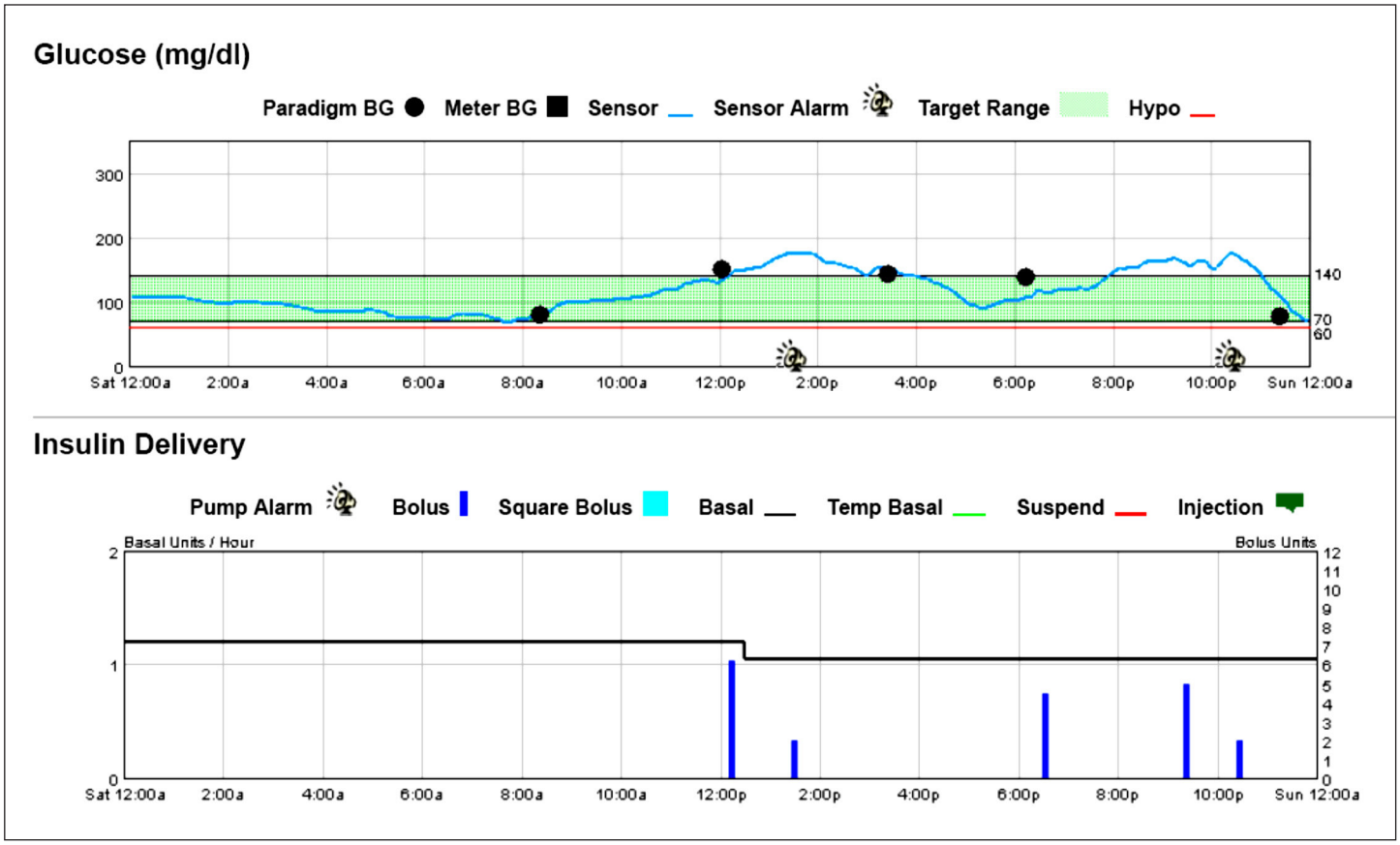


Figure 5. CareLink Personal daily summary report for a patient with minimal glycemic excursions after many months using CGM. Even with a hyperglycemia alert threshold set at 180 mg/dl, only two brief events occur. BG, blood glucose.

balance the appropriate detection of untoward glycemic events with the number of nuisance alerts issued by the system.

The ultimate goal of diabetes management—sustained euglycemia—remains elusive, even with integrated systems for CGM and insulin delivery. Improvements in our ability to use continuous glucose information appropriately, combined with improvements in product design and reliability, will continue to serve patients well. Training and education efforts are also necessary ingredients that, combined with these devices and technologies, will lighten the burden of diabetes for patients and their families.

Disclosure:

John Mastrototaro, John B. Welsh, and Scott Lee are employees of Medtronic Diabetes.

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