



Comparison of the FreeStyle Libre Pro Flash Continuous Glucose Monitoring (CGM) System and Point-of-Care Capillary Glucose Testing in Hospitalized Patients With Type 2 Diabetes Treated With Basal-Bolus Insulin Regimen

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OBJECTIVE

We compared the performance of the FreeStyle Libre Pro continuous glucose monitoring (CGM) and point-of-care capillary glucose testing (POC) among insulin-treated hospitalized patients with type 2 diabetes (T2D).

RESEARCH DESIGN AND METHODS

This was a prospective study in adult patients with T2D admitted to general medicine and surgery wards. Patients were monitored with POC before meals and bedtime and with CGM during the hospital stay. Study end points included differences between POC and CGM in mean daily blood glucose (BG), hypoglycemia <70 and <54 mg/dL, and nocturnal hypoglycemia. We also calculated the mean absolute relative difference (MARD), $\pm 15\%/15$ mg/dL, $\pm 20\%/20$ mg/dL, and $\pm 30\%/30$ mg/dL and error grid analysis between matched glucose pairs.

RESULTS

Mean daily glucose was significantly higher by POC (188.9 ± 37.3 vs. 176.1 ± 46.9 mg/dL) with an estimated mean difference of 12.8 mg/dL (95% CI 8.3–17.2 mg/dL), and proportions of patients with glucose readings <70 mg/dL (14% vs. 56%) and <54 mg/dL (4.1% vs. 36%) detected by POC BG were significantly lower compared with CGM (all $P < 0.001$). Nocturnal and prolonged CGM hypoglycemia <54 mg/dL were 26% and 12%, respectively. The overall MARD was 14.8%, ranging between 11.4% and 16.7% for glucose values between 70 and 250 mg/dL and higher for 51–69 mg/dL (MARD 28.0%). The percentages of glucose readings within $\pm 15\%/15$ mg/dL, $\pm 20\%/20$ mg/dL, and $\pm 30\%/30$ mg/dL were 62%, 76%, and 91%, respectively. Error grid analysis showed 98.8% of glucose pairs within zones A and B.

CONCLUSIONS

Compared with POC, FreeStyle Libre CGM showed lower mean daily glucose and higher detection of hypoglycemic events, particularly nocturnal and prolonged hypoglycemia in hospitalized patients with T2D. CGM's accuracy was lower in the hypoglycemic range.

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Extensive evidence has associated inpatient hyperglycemia with poor clinical outcomes in patients with and without diabetes (1–3). Several randomized controlled trials and meta-analyses have demonstrated that basal-bolus insulin therapy improves glycemic control and clinical outcomes in non-critically ill hospitalized patients with type 2 diabetes (T2D) (4). Consequently, clinical practice guidelines recommend basal-bolus insulin therapy as the preferred approach for the management of hyperglycemia in hospitalized non-critically ill patients with T2D (5,6).

Bedside point-of-care capillary glucose testing (POC) is the current standard of care to assess glycemic control in the hospital and to adjust insulin therapy (5,6). As recommended by national guidelines, bedside POC is performed before meals and at bedtime, matching meal intake and insulin administration, or every 4–6 h for patients not eating or on continuous enteral feeding (5,6). However, this approach fails to provide a complete 24-h glycemic profile assessment and particularly does not properly detect asymptomatic and/or nocturnal hypoglycemia (7,8), both common complications of inpatient insulin therapy (9).

Continuous glucose monitoring (CGM) provides the advantage of measuring interstitial glucose every 5–15 min, thus providing a comprehensive 24-h glycemic profile, with better assessment of nocturnal and/or asymptomatic hypoglycemia and pattern recognition after each treatment intervention. Several studies using CGM have shown improved glycemic control in insulin-treated ambulatory patients with type 1 diabetes (T1D) and T2D (10,11). Fewer studies with small sample sizes have also reported on the use of CGM in hospitalized non-critically ill patients (12–14). However, no prospective studies have compared the newer factory-calibrated CGM for glucose monitoring in non-critically ill hospitalized patients. Accordingly, we compared the performance and efficacy of the FreeStyle Libre Pro CGM to POC (standard of care) in non-critically ill hospitalized patients with T2D treated with basal-bolus insulin regimen.

RESEARCH DESIGN AND METHODS

This was an ancillary study to the Glargine U300 Hospital Trial (NCT03013985,

ClinicalTrials.gov) aiming to evaluate the feasibility and performance of CGM use in non-intensive care unit hospital settings and to obtain preliminary estimates of the role of CGM in non-critically ill hospitalized patients. This study was performed at Grady Memorial Hospital and Emory University Midtown Hospital in Atlanta, GA, and at Hennepin County Medical Center in Minneapolis, MN. We used the FreeStyle Libre CGM Pro, a commercially available factory-calibrated sensor; thus, there was no need for POC blood glucose (BG) testing for sensor calibration. This device measures interstitial glucose in the range of ≥ 40 mg/dL to 500 mg/dL (15).

Study Design

Patients with T2D were treated with basal-bolus regimen with glargine U300 and U100 plus glulisine insulin before meals. We included adult patients >18 years of age admitted to general medicine or surgical services previously treated with diet alone, oral monotherapy, or a combination of oral agents, glucagon-like peptide 1 agonists, or insulin therapy and with admission BG >140 – 400 mg/dL, without evidence of ketoacidosis. We excluded patients with type 1 diabetes and pregnant patients, those with an inability to provide informed consent, or patients with severe liver, kidney, or pancreas disorders or undergoing treatment with steroids. We also aimed to enroll patients with an anticipated length of stay of at least 3 days, as estimated by the primary treating team. The study was approved by each hospital's institutional review board.

Procedures

The study team approached patients shortly after hospital admission to explain the design and potential risks of the study. After obtaining informed consent, sensors were placed by the study team in the posterior upper arm following manufacturer recommendations and under an aseptic technique. The study team reviewed each sensor daily to ensure proper placement and functional status for up to 10 days or until discharge. CGM sensors were removed before surgery, computed tomography scan, or MRI.

Patients and the research team were blinded to the CGM glucose results during the hospital stay. All CGM sensor data were downloaded after hospital discharge using LibreView software. All

glucose values were exported into standard Excel data files for further statistical analysis by the study statistician. Each POC BG was paired with the corresponding CGM value within 5 min and was used for accuracy analysis.

Diabetes was managed by the research team, targeting glucose readings between 70 and 180 mg/dL. Glucose monitoring was performed before meals and at bedtime or as clinically required. Insulin dosage was adjusted daily based on POC BG values obtained by hospital-calibrated Nova StatStrip (Grady Memorial Hospital and Hennepin County Medical Center) and Accu-Chek Inform II glucose meters (Emory University Midtown Hospital).

Outcomes Measures

For clinical efficacy, we adapted CGM metrics defined by an international consensus meeting for ambulatory patients (16,17). Our primary end point was the comparison between POC and CGM on glycemic control metrics in the hospital, including mean daily glucose, time in range (TIR) (defined as percentage of glucose readings and percentage of TIR between 70 and 180 mg/dL), time below range (defined as percentage of glucose and time <70 mg/day, <54 mg/dL, and ≤ 40 mg/dL), and time above range (defined as percentage of glucose readings and percentage of time >180 mg/dL and >250 mg/dL).

We also calculated the number of episodes and proportion of subjects with episodes of hypoglycemia <70 mg/dL and <54 mg/dL for at least 15 min detected by CGM. As previously reported, hypoglycemia was defined as glucose <70 mg/dL or <54 mg/day as measured by hospital-calibrated glucose meters. We calculated and defined nocturnal hypoglycemia occurring from 2200 to 0600 h (only collected by CGM). We also calculated episodes of prolonged hypoglycemia, defined as CGM values recording glucose <54 mg/dL for at least 120 consecutive minutes. Glucose variability was calculated as percentage coefficient of variation = $SD/\text{mean glucose} \times 100\%$.

For performance evaluation, the major outcome was the mean absolute relative difference (MARD) between matched glucose pairs obtained from POC and CGM (within 5 min). Secondary aims included MARD for glucose readings <70 mg/dL, 70–180 mg/dL, >180 mg/dL,

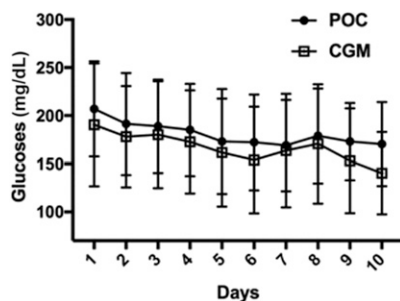


Figure 1—Mean hospital daily glucose as measured by POC (circles) and CGM (squares). The overall mean daily glucose was significantly higher as measured by POC BG compared with CGM (188.9 ± 37.3 vs. 176.1 ± 46.9 mg/dL), with an estimated mean glucose difference of 12.8 mg/dL (CI 8.3–17.2 mg/dL) ($P < 0.001$).

and >250 mg/dL. We also analyzed the overall percentage of CGM values within $\pm 15\%/15$ mg/dL of POC glucose values, the $\pm 20\%/20$ mg/dL and $\pm 30\%/30$ mg/dL, and among different glucose ranges (hyperglycemia and hypoglycemia ranges) (16,17).

We further assessed the clinical safety using the error grid analysis. Additionally, we recorded the number of sensor failures and/or malfunctions, sensors lost, and sensors removed for procedures/surgery.

Statistical Analysis

Data are presented as mean \pm SD for continuous variables and count (percentage) for categorical variables. We defined CGM variables, ranges, and cutoffs (hypoglycemia, hyperglycemia, percentage of glucose in range, and glycemic variability) as detailed by the International Consensus Conference (16,17). MARD was determined as the average relative difference between the CGM and POC glucose–matched pairs and expressed as a percentage. For CGM performance evaluation, we followed statistical recommendations as provided by Clarke and Kovatchev (18). The numbers of glucose pairs in various risk zones of error grid analyses were determined with the R package “ega,” which is designed for Clarke or Parkes error grid analysis (<https://cran.r-project.org/web/packages/ega/ega.pdf>).

RESULTS

Population

A total of 134 patients were enrolled in this ancillary study, with 72.4% ($n = 97$)

having adequate data for our analyses. Causes for excluding data from the analysis included screen failure ($n = 4$), early study termination/withdrawal ($n = 9$), <24 h of sensor data/ <4 matched glucose pairs ($n = 8$), lost sensor data/removal for imaging/procedures ($n = 6$), sensor loss/unplanned removal by staff ($n = 8$), and sensor malfunction/not data recorded ($n = 2$).

Overall, the mean age was 54.5 ± 11 years, and 63 patients (66%) were male. The mean admission hemoglobin A_{1c} (HbA_{1c}) was $10.2 \pm 2\%$ (88 mmol/mol), BMI was 33.8 ± 9 kg/m², and mean duration of diabetes was 11.5 ± 9 years. The clinical characteristics and outcomes of the study population are displayed in Table 1.

Glycemic Patterns During Hospitalization

The mean daily glucose (Fig. 1) during the hospital stay was significantly higher by POC BG compared with CGM (188.9 ± 37.3 vs. 176.1 ± 46.9 mg/dL) ($P < 0.001$), with an estimated mean glucose difference of 12.8 mg/dL (95% CI 8.3–17.2).

The mean percentage of readings/TIR for POC and CGM glucose values between 70 and 180 mg/dL was $48.4 \pm 22.9\%$ and $53.5 \pm 25.8\%$ ($P = 0.001$), respectively. The percentage of TIR for POC and CGM glucose readings between 70 and 140 mg/dL was $24.5 \pm 18.6\%$ and $32.8 \pm 21.7\%$, respectively ($P < 0.001$). The mean percentage time above range (>180 mg/dL) was $50.5 \pm 23.2\%$ by POC

and $42.2 \pm 27.7\%$ by CGM ($P < 0.001$) and for severe hyperglycemia (>250 mg/dL) was $17.8 \pm 19.1\%$ and $16.1 \pm 20.2\%$, respectively ($P = 0.17$). The mean percentage time below range for glucose readings <70 mg/dL, <54 mg/dL, and ≤ 40 mg/dL was $1.1 \pm 3.9\%$, $0.20 \pm 1.2\%$, and 0% by POC and $4.5 \pm 6.9\%$, $1.58 \pm 3.3\%$, and $0.54 \pm 1.8\%$ by CGM, respectively ($P < 0.01$).

Glycemic variability was stable, as demonstrated by an overall percentage coefficient of variation of $30 \pm 1\%$ as measured by POC and of $32 \pm 1\%$ based on CGM.

Hypoglycemia Detection

Overall, the proportion of patients with hypoglycemia <70 mg/dL (14% [$n = 14$] vs. 56% [$n = 54$]; $P < 0.001$) and <54 mg/dL (4.1% [$n = 4$] vs. 36% [$n = 35$]; $P < 0.001$) detected by POC BG was significantly lower compared with CGM, respectively (Fig. 2). Among those patients with hypoglycemia, the average number of episodes of glucose values <70 mg/dL (1.86 ± 0.95 vs. 5.14 ± 3.88 ; $P < 0.001$) and of glucose values <54 mg/dL was also significantly lower (1 ± 0 vs. 4.5 ± 6.4 ; $P < 0.001$) by POC compared with CGM. There were no episodes of severe hypoglycemia ≤ 40 mg/dL detected by either method.

The prevalence of nocturnal CGM hypoglycemia (from 2200 to 0600 h) <70 mg/dL and <54 mg/dL was 41% ($n = 40$) and 26% ($n = 25$), respectively, as shown in Fig. 2. The prevalence of prolonged CGM hypoglycemia (<54 mg/dL) was 12.3% ($n = 12$).

Table 1—Study participant characteristics

Characteristic	
Age, years	54.5 ± 11
Sex, male, n (%)	63 (66)
Race: White/Black/other/Hispanic (%)	16/78/3.1/2.1
BMI, kg/m ²	33.8 ± 9
Duration of diabetes, years	11.5 ± 9
Admission HbA _{1c} , %	10.2 ± 2
Length of stay (median [minimum–maximum]), days	7.5 (2–30)
Admission causes, n (%)	
Cardiovascular	23 (28)
Pulmonary	2 (2.4)
Cancer	1 (1.2)
Renal	1 (1.2)
Infectious	34 (41)
Gastrointestinal	3 (3.7)
Neurological	6 (7.3)

Data are means \pm SD unless otherwise indicated.

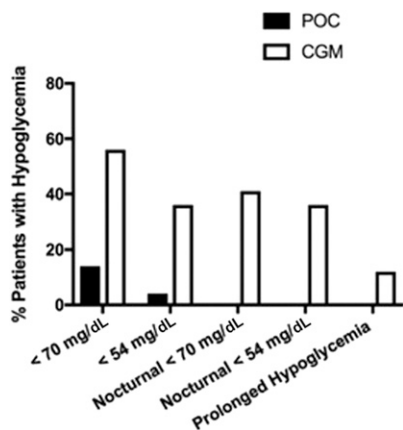


Figure 2—Hypoglycemia detection by POC (filled bars) and CGM (open bars).

CGM Performance and Clarke Error Grid Analysis

Among 1,829 POC-CGM–matched glucose pairs, the overall MARD was 14.8% (as shown in Table 2). MARD ranged from 11.4% to 16.7% for glucose readings >70 to 250 mg/dL and was higher for glucose readings 51–69 mg/dL (MARD 28.0%). However, there were limited matched glucose pairs (*n* = 13) in hypoglycemic range.

The overall percentages of glucose values within ±15%/15 mg/dL, ±20%/20 mg/dL, and ±30%/30 mg/dL of the POC reference value were 61.5%, 75.8%, and 90.4%, respectively. The percentages ±15%/15 mg/dL, ±20%/20 mg/dL, and ±30%/30 mg/dL for glucose values >70 to 250 mg/dL ranged from 54.9 to 71.5, 70.2 to 88.1, and 87.8 to 95.3, respectively. For glucose readings 51–69 mg/dL, the ±15%/15 mg/dL, ±20%/20 mg/dL, and ±30%/30 mg/dL were 53.8%, 53.8%, and 76.9%, respectively. We performed additional comparisons for the above-described accuracy outcomes (data not shown), including from day 2 to day 10 (excluding day 1), different age groups (<40, 41–65, and >65 years of age), and

BMI categories (<30 and >30 kg/m²), and found no relevant differences.

As shown in Supplementary Fig. 1, the error grid analysis showed acceptable clinical accuracy with 98.8% of glucose values falling into zones A (75.1%; *n* = 1,184) and B (23.7%; *n* = 374), based on established evaluation tools (17,19). Accuracy was lower for glucose readings <70 mg/dL; however, there were limited matched glucose pairs in hypoglycemic range (*n* = 13).

CONCLUSIONS

In this prospective study, we compared the performance of FreeStyle Libre CGM and POC in non–critically ill insulin-treated hospitalized patients with diabetes. Compared with the current POC (standard of care), our results showed a tendency for lower glucose concentration with CGM measurements, with an estimated mean daily glucose difference of 12.8 mg/dL (95% CI 8.3–17.2 mg/dL). Based on established CGM performance evaluation tools (15–18), the clinical accuracy was acceptable, with an overall MARD of 14.4% and with 98.8% of glucose readings falling into zones A and B. MARD ranged between 11% and 16% for glucose values between 70 and 250 mg/dL. The CGM accuracy was lower for glucose values <70 mg/dL; however, there were lower numbers of matched POC-CGM pairs in hypoglycemia range. As expected, CGM detected more nocturnal and prolonged hypoglycemic episodes compared with limited daily testing with POC.

Bedside POC is the standard of care to assess glycemic control in the hospital. Diabetes guidelines recommend bedside POC before meals and at bedtime to assess glycemic control and to adjust insulin therapy in the hospital (5,6). This approach has been shown to fail to detect nocturnal hypoglycemia and asymptomatic

hypoglycemia, a common scenario in the hospital setting (9). In addition, the POC approach is labor intensive, costly, and prone to errors and mismatched measurements (20). Hence, there is a need for an improved method to monitor glycemic control in the hospital setting.

CGM utilization has expanded significantly in recent years, with several studies showing improved outcomes in ambulatory patients (10,11,16,21). CGM provides the advantage of measuring interstitial glucose every 5–15 min, thus providing a comprehensive 24-h glyce-mic profile, with better assessment of nocturnal and/or asymptomatic hypoglycemia and pattern recognition after each treatment intervention. Large studies using CGM have been shown to facilitate and improve diabetes care in insulin-treated ambulatory patients with T1D and T2D (10,11). Few studies, however, have reported on the use of CGM in hospitalized patients, particularly in non–critically ill patients (12–14). These studies have shown good correlation between CGM and capillary and/or laboratory glucose values (7,22,23).

In our study, we found an overall MARD percentage of 14.4%, ranging between 11% and 16% for glucose values between 70 and 250 mg/dL. These values agree with those reported in previous studies, in which the MARD percentage ranged from 11.4% to 14.3% in patients with T1D and T2D. In addition, in the pivotal studies of the FreeStyle Libre Pro CGM, an overall 66.5%, 79.4%, and 93.4% of values were within ±15%/15 mg/dL, ±20%/20 mg/dL, or ±30%/30 mg/dL of the capillary glucose reference (FreeStyle Precision Meter), respectively. In agreement with these studies, we found overall percentages of glucose values within ±15%/15 mg/dL, ±20%/20 mg/dL, or ±30%/30 mg/dL of the POC reference value were 63%, 78%, and 92%, respectively (15,24–27). The FreeStyle

Table 2—Comparison of the FreeStyle Libre Pro CGM and POC among non–critically ill hospitalized patients with T2D treated with basal-bolus insulin therapy

Glucose range (mg/dL)	Matched pairs (<i>n</i>)	MARD (%)	±15%/15 mg/dL (%)	±20%/20 mg/dL (%)	±30%/30 mg/dL (%)
Overall	1,829	14.8	61.5	75.8	90.4
51–69*	13	27.9	53.8	53.8	76.9
70–180	829	16.7	54.9	70.2	87.8
>180	731	12.1	69.2	82.6	94.4
>250	253	11.4	71.5	88.1	95.3

*There were only three paired matched glucose values for glucose readings <51 mg/dL.

Libre CGM is a commercially available, factory-calibrated sensor system; thus, there is no need for POC BG testing for sensor calibration. Prior studies in the non-critically ill hospitalized population were performed with previous CGM technology (7,22,23,28) requiring capillary glucose for calibration, including Medtronic MiniMed Gold and Medtronic iPro2, reporting up to 91.9–99% (7,22) of values falling into zones A and B of the error grid analysis, respectively. Our error grid analyses showed acceptable clinical accuracy, with 98.8% of glucose readings falling into zones A (75.1%; $n = 1,184$) and B (23.7%; $n = 374$).

Potential explanations for our differences in performance from the pivotal studies of the FreeStyle Libre CGM could be explained by the real-world design in the hospital setting and the use of hospital-calibrated, hand-held glucose meters (6). Future studies should compare glucose values obtained from CGM to more sophisticated references, such as the Yellow Springs Instrument or by standard laboratory assays. By using glucose meters with validated accuracy in our study (29), we provide good correlation estimates. FreeStyle Libre and other CGM systems have been reported to have lower accuracy in the hypoglycemic range (26,27,30). Newer data presented at the recent American Diabetes Association Scientific Sessions in 2019 on FreeStyle Libre 2 suggest improved accuracy results (31).

A recent panel of experts on inpatient diabetes care reported that CGM could more effectively identify trends toward hypoglycemia and hyperglycemia, allowing for better and safer management of patients with inpatient hyperglycemia (14). In a recent study, Gómez et al. (7) compared the efficacy of a blinded/professional CGM (iPro Medtronic) versus POC in non-critically ill hospitalized patients with T2D treated with basal-bolus insulin. CGM detected a higher number of hypoglycemic events, with 60% of events occurring at night or early morning between dinner and 0600 h. Moreover, CGM was able to detect up to 86% of the asymptomatic hypoglycemic events. In agreement with these studies, we found a higher proportion of patients with hypoglycemia <70 mg/dL detected by the factory-calibrated CGM compared with POC.

The assessment of nocturnal hypoglycemia and the duration of hypoglycemia

events are poorly assessed by POC before meals and bedtime, the current standard of care. In our study, CGM detected nocturnal CGM hypoglycemia (from 2200 to 0600 h) <70 mg/dL in 41% of participants and <54 mg/dL in 26%. Prolonged CGM hypoglycemia <54 mg/dL for >120 consecutive minutes was detected in 12%. In a recent prospective observational study, we reported that $\sim 45\%$ of insulin-treated hospitalized patients with glucose <70 mg/dL had asymptomatic hypoglycemia (9). These findings are clinically relevant and underlie the potential impact of CGM in hospitalized patients, because improved detection of hypoglycemia in hospitalized patients may facilitate better insulin adjustments and potentially reduce hypoglycemia-related morbidity and mortality. To fill this gap, we are currently testing the use of CGM technology integrated with a telemetry system to alert nurses and providers about downtrending glucose levels (<80 mg/dL) to intervene early and prevent hypoglycemia.

Our study has several limitations, including a small sample size and the low number of hypoglycemic episodes observed. Subsequent studies should aim for larger sample sizes with power to detect differences in low glucose ranges and compare glucose values obtained from CGM to more sophisticated references, such as the Yellow Springs Instrument or by standard laboratory assays. Because the exact time of collection and sample processing of venous glucose is not correctly documented in the medical records, we did not pair CGM values with those of venous samples. These studies are in process and will be needed to confirm the accuracy of CGM in the hospital under diverse clinical situations (medicine vs. surgery, hypoxia, edema, etc.). Current prospective randomized studies (NCT03877068 and NCT03508934) are evaluating whether the use of real-time CGM, with an alarm system transmitting glucose values from the patient's room to the nursing station, can reduce the frequency of clinically significant and severe hypoglycemia events. Another limitation is that patients received different basal insulin formulations; however, because we evaluated the accuracy between matched glucose pairs, it is unlikely that treatment assignment would have influenced our results. Despite these limitations, we believe that our study provides significant

evidence on methodology and implementation for further interventional studies using CGM systems among hospitalized patients. With increased use of CGM among ambulatory patients and high rates of patient satisfaction and improved quality of life, one can expect an increasing number of patients choosing to continue using CGM while hospitalized. Moreover, CGM provides a more comprehensive evaluation of glycemic patterns (i.e., TIR) that may facilitate the study of new glucose control metrics and their impact on clinical outcomes in the hospital, as recently demonstrated by studies in ambulatory settings (32,33).

In conclusion, compared with POC glucose meter measurements, FreeStyle Libre CGM showed a tendency toward lower mean glucose, with an estimated mean glucose difference of 12.8 mg/dL (95% CI 8.3–17.2 mg/dL). As expected, compared with limited measurements with POC BG before each meal and bedtime, CGM provided a higher detection of hypoglycemic events, particularly nocturnal hypoglycemia, and prolonged hypoglycemia. The clinical implications of higher detection of hypoglycemia with these devices need further investigations given the known tendency to overread hypoglycemia at lower glucose levels. Ongoing studies are testing the accuracy of other devices and the effectiveness of glucose management based on a glucose telemetry system using CGM technology. Based on established performance evaluation tools, the CGM performance in this study appears to be acceptable for glycemic monitoring among hospitalized non-critically ill patients with T2D. Larger studies are needed to determine the performance of the CGM in hypoglycemia range.

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