

## Use of the Continuous Glucose Monitoring System to Guide Therapy in Patients With Insulin-Treated Diabetes: A Randomized Controlled Trial

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**OBJECTIVE:** To show improved glycemic control in patients with insulin-treated diabetes after adjustments to the diabetes management plan based on either continuous glucose monitoring using the Continuous Glucose Monitoring System (CGMS) or frequent self-monitoring of blood glucose (SMBG) using a home blood glucose meter.

**PATIENTS AND METHODS:** From January to September 2000, patients aged 19 to 76 years with insulin-treated diabetes were assigned to insulin therapy adjustments based on either CGMS or SMBG values. At the end of the study, patients in both groups used the CGMS for 3 days; these values were used to calculate measures of hypoglycemia. Repeated-measures analysis of variance with post hoc comparisons were used to test differences in hemoglobin A<sub>1c</sub> levels and hypoglycemia between the 2 study groups.

**RESULTS:** A total of 128 patients were enrolled in the study. Nineteen discontinued study participation, leaving 51 in the CGMS group and 58 in the SMBG group. No significant differences were noted in demographics or baseline characteristics between the 2 groups. There were no significant differences in hemoglobin A<sub>1c</sub> levels between the CGMS group and the SMBG group at baseline (9.1%±1.1% vs 9.0%±1.0%,  $P=.70$ ), and both groups showed statistically significant ( $P<.001$ ) and similar ( $P=.95$ ) improvement in hemoglobin A<sub>1c</sub> levels after 12 weeks of study. However, the CGMS group had a significantly shorter duration of hypoglycemia (sensor glucose,  $\leq 60$  mg/dL) at week 12 of the study (49.4±40.8 vs 81.0±61.1 minutes per event,  $P=.009$ ).

**CONCLUSION:** Use of the CGMS to guide therapy adjustments in patients with insulin-treated diabetes reduces the duration of hypoglycemia compared with therapy adjustments guided by SMBG values alone.

*Mayo Clin Proc.* 2004;79(12):1521-1526

CGMS = Continuous Glucose Monitoring System; CI = confidence interval; SMBG = self-monitoring of blood glucose

In the Diabetes Control and Complications Trial, patients were able to significantly improve their glycemic control, as a measure of glycosylated hemoglobin, by adjusting insulin doses according to the results of frequent capillary blood glucose monitoring (ie, intensive therapy).<sup>1</sup> Patients undergoing intensive therapy also demonstrated a significantly increased risk of severe hypoglycemia.<sup>1</sup>

Capillary blood glucose monitoring reflects glucose control at a single point in time. These periodic values allow patients to determine immediate insulin needs in anticipation of meals and physical activity and in response to hypoglycemia and hyperglycemia.<sup>2,3</sup> These values are

also used by physicians to identify episodes of poor glycemic control. However, since patients typically test no more than 3 or 4 times a day and rarely during the night, frequent glucose peaks and episodes of asymptomatic hypoglycemia are overlooked and lead to poor or erratic glucose control.<sup>4</sup> The Continuous Glucose Monitoring System (CGMS) (Medtronic MiniMed, Northridge, Calif) provides a complete, retrospective picture of glycemic control by increasing the number of glucose values available to make appropriate changes to insulin therapy, food intake, and activity in patients with diabetes.

Therapy adjustments based on CGMS downloads have shown improvements in hemoglobin A<sub>1c</sub> levels<sup>5-7</sup> and reductions in hypoglycemia.<sup>3,7,8</sup> These studies have not evaluated improvements in glycemic control when compared with frequent self-monitoring of blood glucose (SMBG). To date, there have been 3 randomized studies, 2 using a parallel design and 1 using a crossover design.<sup>6,7,9</sup> In these studies, patients and their physicians reviewed retrospective glycemic profiles obtained from the CGMS to adjust the patients' intensive therapy regimens. Patients were then followed up for 3 months to assess the effects of CGMS-based therapy changes on glycemic control. Of these 3 randomized studies, 2 were based on a pediatric population

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This study was sponsored by Medtronic MiniMed, Northridge, Calif.

Drs Tanenberg and Bode have received funds from Medtronic MiniMed to conduct studies on devices that improve diabetes therapy and have consultancies with Medtronic MiniMed. Dr Bode is also a member of the Medical Board of Medtronic MiniMed. Drs Gross and Mastrototaro are employed by Medtronic MiniMed and hold stock in Medtronic MiniMed.

Presented in abstract form as a poster at the 63rd Scientific Sessions of the American Diabetes Association, New Orleans, La, June 13-17, 2003, and orally at the 18th Congress of the International Diabetes Federation, Paris, France, August 28, 2003.

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and showed that therapy adjustments based on CGMS downloads improve hemoglobin A<sub>1c</sub> values,<sup>6,9</sup> and the other study showed significant improvement in hemoglobin A<sub>1c</sub> levels in both the control and the treatment groups in adult patients with diabetes.<sup>7</sup> None of these studies provided between-group comparisons. The purpose of this study was to show improved glycemic control in patients with insulin-treated diabetes after adjustments to the diabetes management plan based on either continuous glucose monitoring using the CGMS or frequent SMBG using a home blood glucose meter.

## PATIENTS AND METHODS

Patients 19 to 76 years of age were recruited prospectively from 7 diabetes centers in the United States from January to September 2000. All patients had insulin-treated diabetes and inadequate metabolic control at enrollment as shown by hemoglobin A<sub>1c</sub> values higher than 7.9%.

### STUDY DESIGN AND PROCEDURES

The study had a multicenter, randomized, active-controlled, parallel-group design. A random-number list, computer generated by Medtronic MiniMed with SAS statistical software (SAS Institute Inc, Cary, NC), was used to assign patients to treatment (CGMS group) or control (SMBG group). Review of pilot data for this study<sup>5</sup> indicated a small numerical difference in hemoglobin A<sub>1c</sub> measurements between patients using multiple daily injections to treat their diabetes and those using continuous subcutaneous insulin infusion. Therefore, patients were randomized in blocks of 4, and 2 assignments for each treatment group were made within each block. Neither block size nor randomization sequence was disclosed to the investigators. Random assignments to the treatment or control group were provided to the study centers in sealed envelopes, and each center had randomization assignments for 40 patients.

The SMBG (control) group was instructed to perform capillary blood glucose measurements at least 4 times per day (ie, before meals and at bedtime) and in response to symptoms of hypoglycemia for the duration (12 weeks) of the study. The SMBG values were downloaded at visit 3, and these values were used by the diabetes specialists to adjust the patients' diabetes management plans. These adjustments were evaluated at visit 5 using SMBG value downloads. At this visit, additional changes were made to *optimize* the patients' diabetes management plans. Changes to the patients' diabetes management plans were not made after visit 5.

The CGMS (treatment) group was instructed to perform capillary blood glucose measurements at least 4 times per day and in response to symptoms of hypoglycemia for the

duration of the study. In addition, patients in the CGMS group wore the monitors for 3 days during week 1. Both SMBG and CGMS values were downloaded at visit 3, and these values were used by the diabetes specialists to adjust the patients' diabetes management plans. The CGMS was used again for 3 days during week 3, and adjustments were evaluated using SMBG and CGMS value downloads at visit 5. Additional changes were made to the patients' diabetes management plans to *optimize* therapy. Changes to the patients' diabetes management plans were not made after visit 5.

### CONTINUOUS GLUCOSE MONITORING SYSTEM

The CGMS consists of a glucose oxidase sensor that measures interstitial glucose concentrations, a pager-sized monitor, and a cable that connects them. All glucose sensors were inserted into the subcutaneous tissue of the abdomen by the research coordinators. The CGMS technique has been described previously in detail.<sup>10,11</sup> Briefly, interstitial glucose concentrations, which are known to correlate closely with blood glucose concentrations,<sup>12,13</sup> are assessed continuously during a 72-hour period. Patients obtained at least 4 blood glucose values daily and entered all blood glucose values directly into the CGMS for calibration. While wearing the monitor, patients entered event codes (ie, for meals, insulin bolus or injections, exercise, and the presence of symptoms of hypoglycemia) into the monitor. After data collection, the CGMS values were downloaded to Solutions Software (Medtronic MiniMed, Northridge, Calif) using a personal computer, and glycemic profiles were generated. The CGMS glucose values are reported retrospectively in the range of 40 to 400 mg/dL.

### SELF-MONITORING OF BLOOD GLUCOSE

All patients received home blood glucose meter training and were instructed to perform capillary blood glucose measurements using a home blood glucose meter (OneTouch FastTake, Lifescan, a Johnson & Johnson Company, Milpitas, Calif) at least 4 times each day (ie, before meals and at bedtime) and in response to symptoms of hypoglycemia for the duration of this study. Test results are plasma calibrated and are reported in the range of 20 to 600 mg/dL. The meter stores up to 150 blood glucose values that can be downloaded to a personal computer for review.<sup>14</sup>

### DATA COLLECTION

Collection of clinical data was approved by the investigational review boards of the participating centers, and all patients provided written informed consent before participation in the study. Data of interest for this study were hemoglobin A<sub>1c</sub> values, capillary blood glucose values,

sensor glucose values, and frequency and duration of hypoglycemia and hyperglycemia.

To protect against lost blood samples or invalid test results, 2 vials of blood were collected for hemoglobin A<sub>1c</sub> analysis; 1 sample was sent to a central laboratory, and 1 sample was retained at the investigational site. Neither the investigators nor the patients were blinded to the hemoglobin A<sub>1c</sub> results.

Hypoglycemia was defined as sensor glucose values of 60 mg/dL or less, and the end of a hypoglycemic event was defined as the absence of hypoglycemic sensor readings for 30 minutes or longer. Hyperglycemia was defined as sensor glucose values of 200 mg/dL or higher, and the end of a hyperglycemic event was defined as the absence of hyperglycemic sensor readings for 30 minutes or longer. To test for differences in the frequency and duration of hypoglycemia and hyperglycemia between the CGMS group and the SMBG group, all patients used the CGMS for 3 consecutive days during week 12.

#### STATISTICAL ANALYSES

The study was powered according to the results of a 5-week pilot study. In the pilot study, 9 patients were followed up for 4 weeks after therapy adjustments based on CGMS downloads.<sup>5</sup> During this period, mean change from baseline hemoglobin A<sub>1c</sub> level was  $-1.1\% \pm 0.6\%$ . A 95% confidence interval (CI) for the population SD of change scores was calculated with an upper limit of 1.3%. Using this value as an estimate, 60 patients per group would yield 95% power to detect a 1% difference in hemoglobin A<sub>1c</sub> level decrease between the treatment group and the control group. This sample size would also provide 75% power to detect a 0.5% difference in hemoglobin A<sub>1c</sub> improvement.

Sensor performance was evaluated using the home blood glucose meter as the reference. Mean absolute percent difference was used to evaluate the accuracy of the CGMS, and correlation provided an assessment of the ability of the CGMS to track glycemic patterns or trends. Repeated-measures analysis of variance was used to test for a change from baseline hemoglobin A<sub>1c</sub> level in the CGMS group and the SMBG group. Independent *t* tests were used to compare the frequency and duration of hypoglycemia between the 2 groups using CGMS downloads from week 12. Results are presented as mean  $\pm$  SD unless indicated otherwise.

#### RESULTS

A total of 128 patients were recruited into the study (62 in the CGMS group and 66 in the SMBG group). Nineteen patients (14.8%) discontinued participation in the study, 11 in the CGMS group and 8 in the SMBG group (Figure 1).

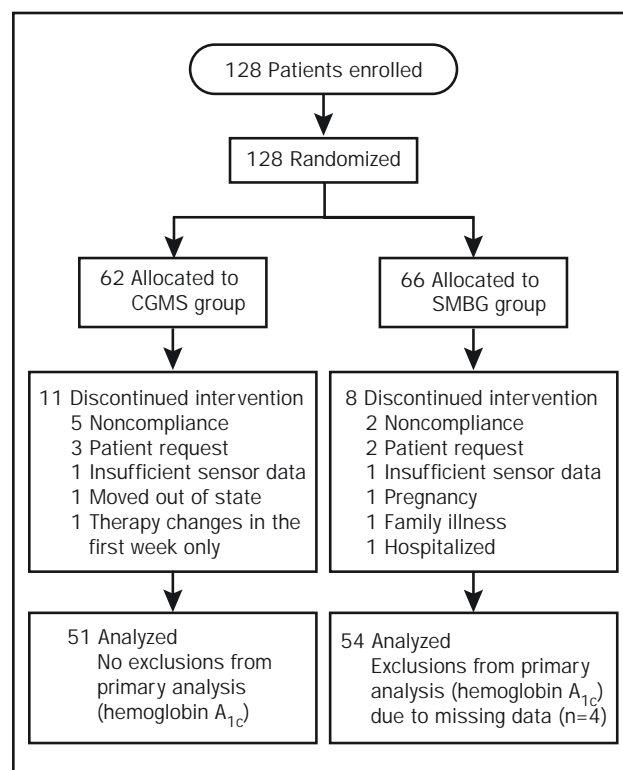


FIGURE 1. Progress of patients through the study. CGMS = Continuous Glucose Monitoring System; SMBG = self-monitoring of blood glucose.

There were no significant differences between the demographic and baseline characteristics of patients in the CGMS group vs patients in the SMBG group (Table 1). Sensitivity analysis of the remaining 51 patients in the CGMS group and 58 patients in the SMBG group provided approximately 70% power to detect a 0.5% difference in hemoglobin A<sub>1c</sub> improvement. Every patient who completed the study protocol and had an end-of-study CGMS download was included in the comparison of hypoglycemic and hyperglycemic events between the 2 groups. In each group, 14 patients had incomplete end-of-study downloads. When complete study downloads were unavailable, an analysis of cause determined that it was due to failure of the center to transmit data for central analysis. These patients were excluded from analysis. No significant differences were observed in the percentage of patients in the CGMS group and the SMBG group who did not have week 12 downloads (27% vs 24%,  $P=.85$ ).

Patients in the CGMS group entered a mean of  $6.6 \pm 2.8$  values from their home blood glucose meters into their CGMS monitors, and patients in the SMBG group entered a mean of  $6.9 \pm 5.6$  values from their home blood glucose meters into their CGMS monitors during week 12 ( $P=.79$ ).

Table 1. Demographics and Baseline Characteristics of Patients Who Completed the Study\*

Characteristics	CGMS group (n=51)	SMBG group (n=58)
Age (y)	44.0±10.2	44.5±12.6
Sex		
Male	19	25
Female	32	33
Race		
White	44	48
Other	7	10
Duration of diabetes (y)	20.4±10.7	19.5±11.9
Hemoglobin A <sub>1c</sub> (%)	9.1±1.1	9.0±1.0
Weight (kg)	77.0±18.4	76.9±15.9
Therapy		
Continuous subcutaneous insulin infusion	25	25
Multiple daily injections	25†	33
Total daily insulin dose (U/kg)		
Continuous subcutaneous insulin infusion	41.8±22.1	42.3±19.0
Multiple daily injections	60.4±36.0	55.3±30.9
Diagnosis		
Type 1	46	51
Type 2	5	5‡
Blood glucose self-monitoring (frequency per day)	4.0±1.7	3.9±1.6
Hypoglycemia (events per week)	1.9±1.6	2.3±2.3
Severe hypoglycemia§		
None	41	45
≥1 event	9†	13
Diabetic ketoacidosis events§		
None	47	56
1 event	3†	2
Hospital admissions§		
None	46	56
1 admission	4†	2

\*Data are presented as mean ± SD or number of patients. No significant differences were found between the 2 groups. CGMS = Continuous Glucose Monitoring System; SMBG = self-monitoring of blood glucose.

†Not reported for 1 patient.

‡Not reported for 2 patients.

§In the 3 months before study.

The mean absolute percent difference between the paired sensor-meter values was 19.0±7.5 in the CGMS group and 21.1±8.2 in the SMBG group ( $P=.26$ ). The correlation between sensor-meter pairs was 0.85±0.11 and 0.79±0.30, respectively ( $P=.22$ ).

Patients who had therapy adjustments based on CGMS downloads had significant improvements in hemoglobin A<sub>1c</sub> levels from baseline values at week 8 ( $\Delta -0.75\% \pm 0.90\%$ ; 95% CI, 0.50%-1.00%) and at week 12 ( $\Delta -0.74\% \pm 0.95\%$ ; 95% CI, 0.47%-1.00%). Similar improvements in hemoglobin A<sub>1c</sub> level at week 8 ( $\Delta -0.64\% \pm 0.96\%$ ; 95% CI, 0.34%-0.90%) and at week 12 ( $\Delta -0.73\% \pm 1.17\%$ ; 95% CI, 0.41%-1.05%) were observed in the SMBG group. However, there were no significant differences in hemoglobin A<sub>1c</sub> values between the CGMS group and the SMBG group at week 8 ( $P=.90$ ) or at week 12 ( $P=.70$ ) (Figure 2).

End-of-study CGMS downloads for all patients in both the CGMS and the SMBG groups exhibited hypoglycemic readings. The mean duration of hypoglycemia was 49.4±40.8 minutes per event in the CGMS group and 81.0±61.1 minutes per event in the SMBG group ( $P=.009$ ), and patients in the CGMS group had 1.4±1.1 events per day vs 1.7±1.2 events per day in the SMBG group ( $P=.30$ ) (Figure 3). There were no statistically significant differences in either the frequency or the duration of hyperglycemia. The mean duration of hyperglycemia was 208.5±135.3 minutes per event in the CGMS group and 171.6±90.6 minutes per event in the SMBG group ( $P=.15$ ), and patients in the CGMS group had 2.9±1.2 events per day vs 2.8±1.2 events per day in the SMBG group ( $P=.65$ ).

One patient in the CGMS group reported 2 severe hypoglycemic events, and 1 patient in the SMBG group reported 1 severe hypoglycemic event during the study. Additionally, there were 5 monitor-related adverse reactions.

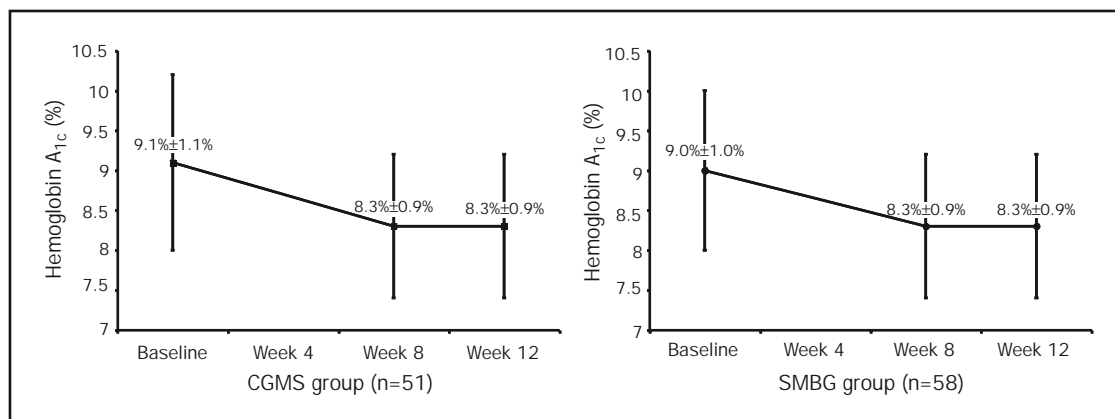


FIGURE 2. Changes in hemoglobin A<sub>1c</sub> levels from baseline values after therapy adjustments based on either Continuous Glucose Monitoring System (CGMS) or self-monitoring of blood glucose (SMBG) data. There was a statistically significant ( $P<.001$ ) and similar ( $P=.95$ ) improvement in the mean hemoglobin A<sub>1c</sub> level in both the CGMS and the SMBG groups from baseline to values at week 8 and week 12. Error bars indicate SD.

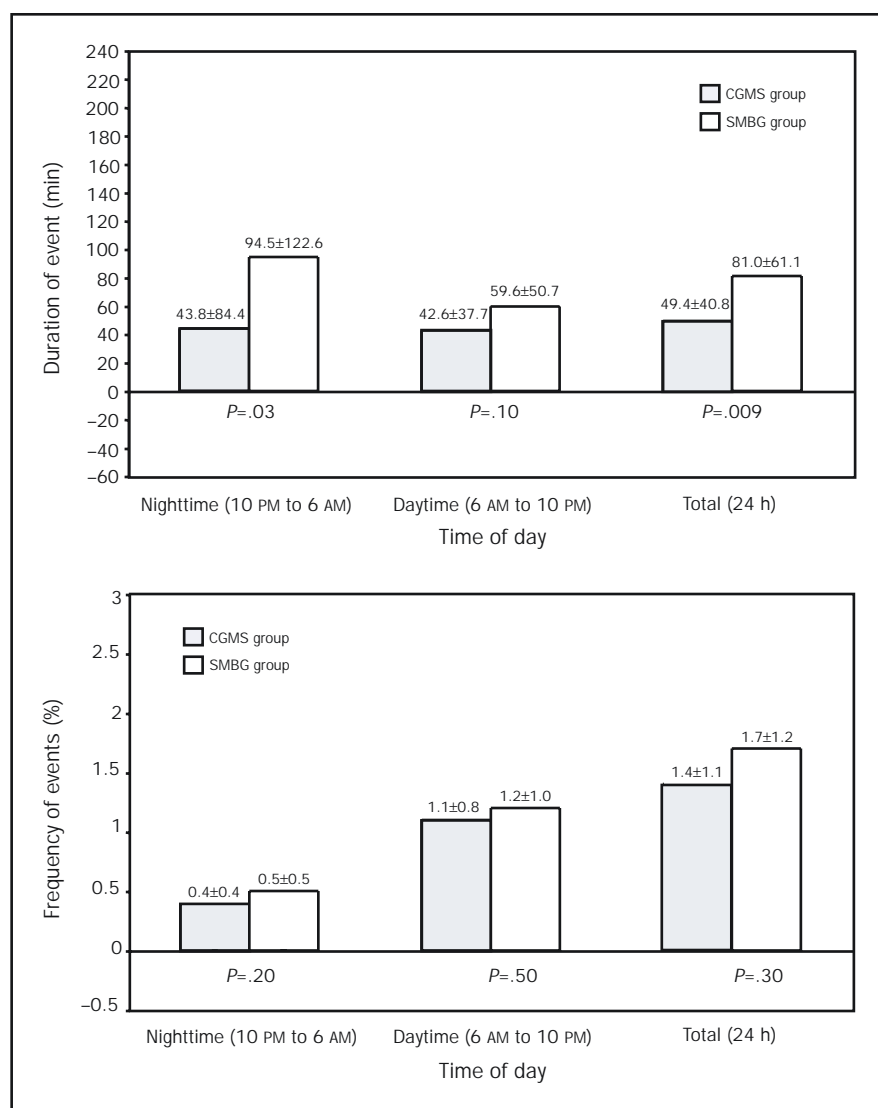


FIGURE 3. Differences in mean duration of events (top) and frequency of events (bottom) at nighttime, daytime, and total between the Continuous Glucose Monitoring System (CGMS) group and the self-monitoring of blood glucose (SMBG) group at week 12.

All were clinically mild and were limited to bleeding, pain, tenderness, or swelling at the insertion site that resolved after sensor removal.

## DISCUSSION

Hypoglycemia is the most common adverse event associated with intensive therapy,<sup>1</sup> with the risk of severe hypoglycemia increasing as hemoglobin A<sub>1c</sub> values decrease.<sup>15</sup> Consequently, many people with insulin-treated diabetes maintain hemoglobin A<sub>1c</sub> values above recommended thresholds to reduce their risk of severe hypoglycemic events.<sup>16</sup> Sensor downloads have previously revealed un-

detected hypoglycemia,<sup>4</sup> and in the current study, similar findings in the CGMS group may have led investigators to make changes in insulin administration to reduce hypoglycemic excursions but not necessarily to reduce hemoglobin A<sub>1c</sub> values.

Improvements in hemoglobin A<sub>1c</sub> values in both the CGMS and the SMBG groups may have been attributed to patients self-monitoring their capillary blood glucose 7 times per day during the study period. However, in the CGMS group, these improvements were accompanied by a reduction in hypoglycemia compared with the SMBG group, indicating that frequent capillary blood glucose monitoring can improve hemoglobin A<sub>1c</sub> values but not

without significantly increasing the risk of hypoglycemia.<sup>1</sup> The American Diabetes Association currently recommends that patients with insulin-treated diabetes perform SMBG at least 3 to 4 times per day.<sup>17</sup> Patients who perform blood glucose monitoring in accordance with these recommendations have clinically and statistically better hemoglobin A<sub>1c</sub> values than patients who perform SMBG less frequently.<sup>17,18</sup> However, adherence to frequent blood glucose monitoring is low, and less than 54% of patients with insulin-treated diabetes are reported to self-monitor their blood glucose at least 3 times each day.<sup>18</sup>

### CONCLUSION

The CGMS-guided therapy adjustments can be used to improve glycemic control in patients with insulin-treated diabetes without increasing the risk of hypoglycemia compared with therapy adjustments based on SMBG values alone. These findings are well supported<sup>3,5-8,11</sup> and suggest that a 3-day retrospective review of glucose values may help health care providers make guided changes to the diabetes management plan that result in improved hemoglobin A<sub>1c</sub> values with reductions in hypoglycemia.

*We thank the following individuals for collection, reporting, and quality control of the study data: Melissa Comerio, RN, Evelyne Fleury-Milfort, MSN, Angie Gaumond, RN, Mindy Saenz, RD, Lauren Somma, RN, Kelly McCulloch, MA, and Laurie Want, MSN. We are also indebted to Carla Rother, MS, Anna ter Veer, MS, and Lilly Jeng, MS, for statistical analysis and to Rebecca de León, MS, for preparation of the submitted manuscript.*

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