

## The Effect of Continuous Glucose Monitoring in Well-controlled Type 1 Diabetes

Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group\*

\*The members of the writing committee and the full listing of the members of the study group are included in the Acknowledgements.

**Corresponding Author:**  
Roy W. Beck, M.D., Ph.D.  
E-mail: [rbeck@jaeb.org](mailto:rbeck@jaeb.org)

Clinical Trial Registry Number: NCT00406133, [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

Additional information for this article can be found in an online appendix at <http://care.diabetesjournals.org>

Submitted 20 January 2009 and accepted 27 April 2009.

This is an uncopyedited electronic version of an article accepted for publication in *Diabetes Care*. The American Diabetes Association, publisher of *Diabetes Care*, is not responsible for any errors or omissions in this version of the manuscript or any version derived from it by third parties. The definitive publisher-authenticated version will be available in a future issue of *Diabetes Care* in print and online at <http://care.diabetesjournals.org>.

*Objective:* The potential benefits of continuous glucose monitoring (CGM) in the management of adults and children with well controlled type 1 diabetes have not been examined.

*Research Design and Methods:* 129 adults and children with intensively-treated type 1 diabetes (age range 8 to 69 years) and HbA1c <7.0% were randomly assigned to either continuous or standard glucose monitoring for 26 weeks. The main study outcomes were time with glucose level  $\leq 70$  mg/dL, HbA1c level, and severe hypoglycemic events.

*Results:* At 26 weeks, biochemical hypoglycemia ( $\leq 70$  mg/dL) was less frequent in the CGM group than the control group (median 54 versus 91 minutes/day) but the difference was not statistically significant ( $P=0.16$ ). Median time with a glucose level  $\leq 60$  mg/dL was 18 versus 35 minutes/day, respectively ( $P=0.05$ ). Time out of range ( $\leq 70$  or  $>180$  mg/dL) was significantly lower in the CGM group than the control group (377 versus 491 minutes per day,  $P=0.003$ ). There was a significant treatment group difference favoring the CGM group in mean HbA1c at 26 weeks adjusted for baseline ( $P<0.001$ ). One or more severe hypoglycemic events occurred in 10% and 11% of the two groups, respectively ( $P=1.0$ ). Four outcome measures combining HbA1c and hypoglycemia data favored the CGM group in comparison with the control group ( $P<0.001$ , 0.007, 0.005, and 0.003).

*Conclusions:* Most outcomes, including those combining HbA1c and hypoglycemia, favored the CGM group. The weight of evidence suggests that CGM is beneficial for individuals with type 1 diabetes who have already achieved excellent control with HbA1c <7.0%.

Over the past 15 years, the use of rapid and long-acting insulin analogs, improvements in insulin pumps, and more frequent home blood glucose monitoring have had a positive impact on the ability to achieve target HbA1c levels in type 1 diabetes. However, the rates of severe hypoglycemia remain too high and the occurrence of such events is often followed by a decline in glycemic control due to fears of further hypoglycemic episodes.(1) Hypoglycemia remains the major limiting factor for achieving euglycemia in type 1 diabetes.(2)

The introduction of new real-time continuous glucose monitoring (CGM) systems has received great interest because these devices may have the potential to increase the proportion of patients who are able to maintain target HbA1c values while simultaneously limiting the risk of severe hypoglycemia. In a randomized trial of 322 adults and children with type 1 diabetes and baseline HbA1c level  $\geq 7.0\%$ , our Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group reported that CGM substantially improved HbA1c levels without increasing the frequency of hypoglycemia in adults  $\geq 25$  years of age, whereas the lowering of HbA1c levels in children and adolescents was more limited.(3) Like virtually every other study of a new drug or device in the treatment of type 1 diabetes, this study excluded individuals already reaching target HbA1c levels  $< 7.0\%$  because lowering of HbA1c was the primary outcome of interest. Consequently, our study group also conducted a separate, concurrent randomized trial to evaluate the efficacy and safety of CGM in adults and children with type 1 diabetes who already had successfully achieved HbA1c levels  $< 7.0\%$  with intensive insulin therapy.

## RESEARCH DESIGN AND METHODS

The protocol was approved by the institutional review boards of the 10 participating centers, which included academic, community, and managed care based practices. Written informed consent was obtained from adult subjects and parents/guardians of minor subjects. Minor subjects provided written assent. The study is listed on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT00406133). Study procedures were identical to those of a companion trial of individuals with type 1 diabetes and HbA1c  $\geq 7.0\%$ .(3, 4) Key aspects of the study protocol are described below.

**Study Design:** Major eligibility criteria included age  $\geq 8$  years, type 1 diabetes for at least one year, use of either an insulin pump or at least 3 daily insulin injections, and baseline HbA1c level  $< 7.0\%$ . Subjects who successfully completed a run-in phase of “blinded” CGM use (a modified device in which glucose values were recorded in the receiver but were not visible to the subject) were randomly assigned to either the CGM group or the control group, using a permuted-blocks design stratified by clinical center.

Subjects randomized to the CGM group were provided with one of the following devices: the DexCom™ SEVEN® (DexCom, Inc., San Diego, CA), the MiniMed Paradigm® REAL-Time Insulin Pump and Continuous Glucose Monitoring System (Medtronic MiniMed, Inc., Northridge, CA), or the FreeStyle Navigator™ (Abbott Diabetes Care, Inc., Alameda, CA). Subjects were instructed to use the device on a daily basis and to verify the accuracy of the glucose measurement with a home blood glucose meter (provided by the study) before making management decisions (as per the regulatory labeling of the devices). Subjects in the control group were given blood glucose meters and test strips and asked to perform blood glucose monitoring at least four times daily.

Subjects in both the CGM and control groups were provided with written instructions on how to use the CGM and blood glucose meter data, respectively, to make real-time insulin dose adjustments and on using computer software to retrospectively review the glucose data to alter insulin dosing.(4, 5) Though not required, all subjects had a home computer.

The number of scheduled contacts was identical for both treatment groups. Visits were conducted at 1, 4, 8, 13, 19, and 26 weeks ( $\pm 1$  week), with one scheduled phone contact between each visit, to review glucose data and adjust diabetes management. For one week, following the 13 and 26-week visits, the control group used one of the three real-time CGM devices, modified such that the glucose values were recorded but not visible. An additional sensor was used if fewer than 96 hours of glucose values overall or 24 hours overnight were obtained. Central laboratory HbA1c was measured at baseline, 13 weeks, and 26 weeks at the University of Minnesota using the Tosoh A1c 2.2 Plus Glycohemoglobin Analyzer method.(6)

Reportable adverse events included severe hypoglycemia (defined as an event that required assistance from another person to administer carbohydrate, glucagon, or other resuscitative actions),(7) hyperglycemia resulting in ketoacidosis, unexpected study-related or device-related events, and serious adverse events regardless of causality.

## **STATISTICAL METHODS**

The primary outcome was the change in the time per day with glucose values  $\leq 70$  mg/dL comparing baseline sensor values with those obtained following the 26-week visit. A sample size of 120 subjects was planned to have 90% power to detect a difference in this outcome between treatment groups, assuming a population difference of 29 minutes per day, standard deviation of the 26-week values of 59 minutes per day, correlation between

baseline and 26-week values of 0.66 (based on data from a prior study (8)), an alpha level of 0.05, and no more than 15% losses to follow up.

Analyses followed the “intent-to-treat” principle. Percentage of values less than or greater than a given threshold were converted to minutes per day by multiplying by 1440. As a result of the skewness of the primary outcome data ( $P < 0.001$  with the Shapiro-Wilk test), a nonparametric approach was followed for the primary analysis using an analysis of covariance (ANCOVA) model based on ranks of the 26-week values using van der Waerden scores, adjusted for the baseline value, clinical center, and type of continuous glucose monitor. To assess for consistency, two other analytic approaches were used in ANCOVA models. In one, outlier values were truncated at 288 minutes per day (20% of the day) and in the other, a square root transformation was performed. Other outcomes based on the CGM data obtained in both groups at baseline and 26 weeks were analyzed similarly. Treatment group differences in the rate of CGM-based hypoglycemic events, defined as 20 minutes or more with a blood glucose of less than 54 mg/dL (3.0mmol/l),(9) were compared using the nonparametric approach that was used in the primary analysis.

Other preplanned secondary outcomes included change in HbA1c from baseline to 26 weeks in an ANCOVA model (adjusted for baseline HbA1c and clinical center) and 26-week binary HbA1c outcomes (decrease in HbA1c from baseline by  $\geq 0.3\%$ , increase in HbA1c from baseline by  $\geq 0.3\%$ , 26-week value  $< 7.0\%$ ) evaluated similarly in logistic regression models. The 0.3% change was selected because it exceeded the laboratory’s measurement error and was considered a clinically meaningful change for a HbA1c level  $< 7.0\%$ .

Analyses also were conducted to assess consistency of the treatment effect in subgroups based on age (8 to 14, 15 to 24,

and  $\geq 25$  years). Change in CGM use over time was evaluated with a repeated measurements regression model. The association of CGM use and age was evaluated with a Kruskal-Wallis test.

The proportions of subjects experiencing one or more severe hypoglycemic events in each treatment group were compared using Fisher's exact test. Incidences of hypoglycemic events were compared and confidence intervals for the treatment group difference calculated using permutation tests. Similar analyses were performed for the subset of hypoglycemic events associated with seizure or coma.

On a subject level, a reduction in time  $\leq 70$  mg/dL was defined as a decrease from baseline of  $\geq 43$  minutes a day (3% of the day) and an increase likewise was defined as an increase from baseline of  $\geq 43$  minutes a day (representing approximately a 50% change from the average baseline level). Four outcome measures were created by combining HbA1c and hypoglycemia data (as defined in the legend for figure 1) and compared between treatment groups, using a logistic regression model adjusting for baseline HbA1c.

Analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC). All P values are 2-sided. Adjusting for imbalances between baseline factors and imputing for missing data using Rubin's method (10) did not alter the results (data not shown).

## RESULTS

Between February and December, 2007, the trial randomized 129 children and adults with type 1 diabetes; 67 were assigned to the CGM group and 62 to the control group. Baseline characteristics are summarized in Table 1.

The visit completion rate was  $>99\%$  in the CGM group and  $98\%$  in the control group (see Figure A1 in the online appendix, available at

<http://diabetescare.diabetesjournals.org>) and the phone contact completion rates were  $98\%$  and  $95\%$ , respectively. The 26-week visit was completed by all CGM subjects and all but two subjects in the control group. No subjects in the CGM group discontinued sensor use prior to the 26-week visit and no subjects in the control group self-initiated CGM use prior to completing the 26-week visit.

Self-reported home glucose meter use was  $7.3 \pm 2.4$  measurements per day prior to study entry and  $7.1 \pm 3.5$  measurements per day at 26 weeks in the CGM group compared with  $6.8 \pm 2.4$  and  $6.4 \pm 2.4$  respectively in the control group.

**Glycemic Control:** Median time per day with a glucose level  $\leq 70$  mg/dL (as measured with CGM) decreased from 91 minutes at baseline to 54 minutes at 26 weeks in the CGM group ( $P=0.002$ ) and from 96 minutes to 91 minutes in the control group ( $P=0.43$ ) ( $P=0.16$  using ranks,  $P=0.04$  truncating outliers, and  $P=0.06$  using square root transformation). As seen in table 2, there was stronger statistical evidence of a treatment group difference favoring the CGM group for other definitions of hypoglycemia (time  $\leq 60$  mg/dL, time  $\leq 50$  mg/dL, area under the curve for 70 mg/dL) and when the CGM data collected following the 13-week and 26-week visits were pooled to provide a better indication of glycemic control over the 6 months than either time point alone. A more complete indication of the treatment group difference can be seen in the cumulative distribution curves in the appendix (Online appendix figures A3 and A4). The CGM-based hypoglycemia event rate ( $\geq 20$  minutes with glucose level  $< 54$  mg/dL [ $3.0$  mmol/l], using the CGM data collected during the week following the 13-week and 26-week visits) was  $0.25 \pm 0.40$  events per 24 hours in the CGM group and  $0.47 \pm 0.68$  events per 24 hours in the control group ( $P=0.07$ ).

There was a significant difference between treatment groups in the mean HbA1c level at 26 weeks adjusted for baseline ( $P < 0.001$ , Table 3). Compared with the control group, more subjects in the CGM group had an improvement in HbA1c of  $\geq 0.3\%$  (31% versus 5%,  $P < 0.001$ ), fewer had a worsening of HbA1c  $\geq 0.3\%$  (28% versus 52%,  $P = 0.002$ ), and more had a HbA1c level below 7.0% at 26 weeks (88% versus 63%,  $P < 0.001$ ).

In three prespecified age groups ( $\geq 25$  years, 15 to 24 years, and 8 to 14 years), results of treatment group comparisons generally were similar to the overall analysis for the amount of time per day  $\leq 70$  mg/dL. Results also appeared similar in subjects using multiple daily insulin injections and in those using an insulin pump, but the number of injection subjects was too small for a meaningful comparison.

**Severe Hypoglycemia and Other Adverse Events:** Seven subjects (10%) in the CGM group and seven (11%) in the control group experienced at least one severe hypoglycemic event, with no significant differences comparing treatment groups (Online Appendix, Table A1). Likewise, there were no significant differences comparing the incidence rate of severe hypoglycemic events between treatment groups. There were no serious adverse events attributable to the study interventions.

**Combined Outcome Measures:** More subjects in the CGM group than the control group had a decrease in HbA1c of  $\geq 0.3\%$  without experiencing a severe hypoglycemic event (28% versus 5%,  $P < 0.001$ ). As seen in figure 1 (and online appendix figure A4), more subjects in the CGM group than the control group also had a decrease in HbA1c of  $\geq 0.3\%$  without an increase of  $\geq 43$  minutes a day (3% of the day) in CGM-measured glucose values  $\leq 70$  mg/dL (18% versus 2%,  $P = 0.007$ ), and more had a  $\geq 43$  minutes a day decrease in the time

per day with the glucose level  $\leq 70$  mg/dL without an increase in HbA1c of  $\geq 0.3\%$  (29% versus 15%,  $P = 0.005$ ).

**Frequency of Sensor Use in the CGM Group:** In the CGM group, all subjects were using CGM at the end of the 26 weeks of the study. The amount of CGM use decreased slightly over the 26 weeks of the study ( $P < 0.001$ ), but was still quite high after 26 weeks. During the first 13 weeks of the study, 78% of subjects averaged at least 6 days per week of CGM use compared with 67% during the final 4 weeks. Only 13% of subjects averaged  $< 4$  days a week during the final 4 weeks. Over the 26 weeks of the study, median CGM use was 6.8 days/week in subjects  $\geq 25$  years old, 6.2 days/week in the 15 to 24 year olds, and 6.4 days/week in the 8 to 14 year olds ( $P = 0.07$ ), averaging  $\geq 6$  days/week in 79%, 53%, and 61%, respectively.

## CONCLUSIONS

In this randomized trial, we evaluated the effect of CGM on glycemic control in adults and children with well controlled type 1 diabetes using conventional blood glucose monitoring, as evidenced by a baseline HbA1c level  $< 7.0\%$ . For the primary outcome, the median time per day  $\leq 70$  mg/dL as measured with CGM was 37 minutes lower in the CGM group than in the control group after 6 months of intervention. Although the prespecified primary analysis method failed to reach statistical significance, other methods accounting for the skewness of the data had smaller p values and significant differences between groups were seen with almost all other CGM-measured biochemical hypoglycemic and hyperglycemic outcomes as well as for HbA1c outcomes and outcomes combining HbA1c and hypoglycemia.

In planning this study, the change in HbA1c was not selected as the primary outcome measure because we did not anticipate being able to lower HbA1c levels in

the CGM group in view of their exquisite level of control on entry in the study.(4) Indeed, we expected that there might even be small and clinically insignificant increases in HbA1c values in the CGM group if we were able to reduce the frequency of glucose levels  $\leq 70$  mg/dl. Instead, the CGM group was able to maintain HbA1c levels at baseline values with less biochemical hypoglycemia, whereas HbA1c levels rose over time in the control group. Moreover, all of the other HbA1c outcomes favored the CGM over the control group. The increases in HbA1c in the control group might have been expected due to regression to the mean from the effective floor on the HbA1c level of around 6.0% for most patients and from the 6.9% HbA1c cut off point required for eligibility as well as the difficulties in maintaining a near-normal HbA1c level.

Lower HbA1c values in the CGM group than in the control group were not associated with an increased frequency of severe hypoglycemic events, although the trial was not formally powered to assess for a treatment group difference in the rate of severe hypoglycemia. It also is noteworthy that the rates of severe hypoglycemia in both the CGM and control group in this study were less than half those reported by the DCCT, which may reflect the benefits of insulin analogs and greater frequency of use of insulin pumps in our population.(7, 11)

This study included a unique population of children, adolescents, and adults with type 1 diabetes noted by their entry HbA1c levels being  $< 7.0\%$  and their attention to intensive diabetes management principles with frequent blood glucose monitoring at baseline averaging about seven times per day. Consistent with pre-study management behaviors, adherence to CGM use was high during this study in subjects of all ages, though slightly higher in adults than children and adolescents. This contrasts with the results of our randomized trial evaluating

CGM in patients with type 1 diabetes and baseline HbA1c level  $\geq 7.0\%$ . In that trial, CGM use was substantially higher in adults than children, and as a presumed consequence, the benefit of CGM in lowering HbA1c was greater in adults than children.(3)

In summary, almost all analyses, though not the method preselected for the primary analysis, including the time per day  $\leq 60$  mg/dL, time per day between 71 and 180 mg/dL, and those involving HbA1c coupled with hypoglycemia, favored the CGM group compared with the control group. Based on the weight of evidence, CGM is beneficial for adults and children with type 1 diabetes who already have achieved excellent control with home glucose monitoring.

#### **ACKNOWLEDGEMENT**

The Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group would like to recognize the efforts of the subjects and their families and thank them for their participation.

**Disclosure:** Financial support: Study funding was provided by the Juvenile Diabetes Research Foundation, Inc. (grant numbers 22-2006-1107, 22-2006-1117, 22-2006-1112, 22-2006-1123, and 01-2006-8031).

Continuous glucose monitors and sensors were purchased at a bulk discount price from DexCom, Inc. (San Diego, CA), Medtronic MiniMed, Inc. (Northridge, CA), and Abbott Diabetes Care, Inc. (Alameda, CA.). Home glucose meters and test strips were provided to the study by LifeScan, Inc. and Abbott Diabetes Care, Inc. The companies had no involvement in the design, conduct, or analysis of the trial or the manuscript preparation.

Below is a listing of relationships of the investigators with companies that make products relevant to the manuscript between July 1, 2006 and June 30, 2008. Research funds where listed below were provided to the

legal entity that employs the individual and not directly to the individual.

Dr. Bode reports having received consulting fees, honoraria, travel reimbursement, and research funds from Abbott Diabetes Care, Inc., and Medtronic MiniMed, Inc., and grant support from DexCom, Inc.; Dr. Buckingham reports having received a speaker honorarium and research funding from Abbott Diabetes Care, Inc., a fee for serving on a medical advisory board for Lifescan, Inc., a speaker honorarium, consulting fees, and research funding from Medtronic MiniMed, Inc., and a consulting fee from Novo Nordisk, Inc.; Dr. Chase reports having received a speaker honorarium from Abbott Diabetes Care, Inc. and Sanofi-Aventis, and grant support from Symlin; Dr. Fiallo-Scharerer reports having received supplies for research from Abbott Diabetes Care, Inc. and Medtronic MiniMed, Inc.; Dr. Fox reports having received supplies for research from Abbott Diabetes Care, Inc. and Smiths Medical; Dr. Hirsch reports having received consulting fees and travel reimbursement from Abbott Diabetes Care, Inc., and grant support from Medtronic MiniMed, Inc.; Dr. Laffel reports having

received consulting fees from Lifescan, Inc., consulting fees and a speaker honorarium from Abbott Diabetes Care, Inc., consulting fees and research funding from Medtronic MiniMed, Inc., and consulting and speaker fees from Roche; Dr. Mauras reports having received grant support from Medtronic MiniMed, Inc.; Dr. Tamborlane reports having received consulting fees from Abbott Diabetes Care, Inc. and Lifescan, Inc. and consulting fees, a speaker honorarium, and research funding from Medtronic MiniMed, Inc.; Dr. Weinzimer reports having received research support, a speaker honorarium and travel reimbursement from Medtronic MiniMed, Inc., and a speaker honorarium from Animas Corp / Lifescan, Inc.; Dr. Wolpert reports having received consulting fees from Abbott Diabetes Care, Inc. and research funding from Medtronic MiniMed, Inc.; Dr. Wilson reports having received equipment and software from Abbott Diabetes Care, Inc. and Medtronic MiniMed, Inc. and research support from Medtronic MiniMed, Inc. and The Elizabeth Glaser Pediatric AIDS Foundation.

## **REFERENCES**

1. Irvine AA, Cox D, Gonder-Frederick L. Fear of hypoglycemia: relationship to physical and psychological symptoms in patients with insulin-dependent diabetes mellitus. *Health Psychol.* 1992;11:135-138
2. Cryer PE. Banting Lecture. Hypoglycemia: the limiting factor in the management of IDDM. *Diabetes.* 1994;43:1378-1389
3. The Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med.* 2008;359:1464-1476
4. JDRF CGM Study Group. JDRF randomized clinical trial to assess the efficacy of real-time continuous glucose monitoring in the management of type 1 diabetes: research design and methods. *Diabetes Technol Ther.* 2008;10:310-321
5. Diabetes Research in Children Network (DirecNet) Study Group. Use of the DirecNet Applied Treatment Algorithm (DATA) for diabetes management with a real-time continuous glucose monitor (the Freestyle Navigator). *Pediatric Diabetes* 2008;9:142-147
6. Gibb I, Parnham A, Fonfrede M, Lecoek F. Multicenter evaluation of Tosoh glycohemoglobin analyzer. *Clin Chem.* 1999;45:1833-1841
7. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Eng J Med.* 1993;329:977-986
8. Diabetes Research in Children Network Study Group. Continuous glucose monitoring in children with type 1 diabetes. *J Pediatr.* 2007;151:388-393
9. UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. *Diabetologia.* 2007;50:1140-1147
10. Little RJA, Rubin DB. *Statistical analysis with missing data.* New York: John Wiley & Sons; 1987
11. The Diabetes Control and Complications Trial Research Group. Hypoglycemia in the Diabetes Control and Complications Trial. *Diabetes.* 1997;46:271-286

**Table 1** Baseline Characteristics of Study Subjects by Treatment Group

	Treatment Group	
	CGM N=67	Control N=62
<b>Gender:</b> female <i>no. (%)</i>	36 (54)	32 (52)
<b>Age</b> <i>Mean ± SD (years)</i>	29.3 ± 16.3	32.0 ± 17.7
≥25 years old <i>no. (%)</i>	34 (51)	33 (53)
15 to 24 years old <i>no. (%)</i>	15 (22)	18 (29)
8 to 14 years old <i>no. (%)</i>	18 (27)	11 (18)
<b>Race:</b> Non-Hispanic White <i>no. (%)</i>	63 (94)	58 (94)
<b>Duration of diabetes by age group</b> <i>years mean ± SD (years)</i>		
≥25 years old	25.6 ± 16.6	28.6 ± 12.7
15 to 24 years old	8.7 ± 5.3	8.1 ± 4.5
8 to 14 years old	4.9 ± 2.6	4.4 ± 3.2
<b>Insulin modality</b> <i>no. (%)</i>		
Pump	62 (93)	49 (79)
Multiple daily injections	5 (7)	13 (21)
<b>Total daily dose of insulin by age group</b> <i>units/kg mean ± SD (years)</i>		
≥25 years old	0.5 ± 0.1	0.5 ± 0.1
15 to 24 years old	0.7 ± 0.2	0.8 ± 0.2
8 to 14 years old	0.8 ± 0.1	0.8 ± 0.3
<b>HbA1c</b> <i>(%) mean ± SD</i>	6.4 ± 0.5	6.5 ± 0.3
<b>One or more severe hypoglycemia events* in last six months</b> <i>no. (%)</i>	7 (10)	7 (11)
<b>Home glucose meter readings per day</b> <sup>†</sup> <i>mean ± SD</i>	7.3 ± 2.4	6.8 ± 2.4
<b>College graduate (subject or primary care giver)</b> <i>no. (%)</i>	58 (87)	55 (89)

\*A severe hypoglycemia event was defined as an event that required assistance from another person to administer carbohydrate, glucagon, or other resuscitative actions.

<sup>†</sup> Data were missing for 6 subjects in CGM group and 4 in control group.

**Table 2** CGM-measured Outcomes by Treatment Group\*

	CGM Group	CGM Group	CGM Group	Control Group	Control Group	Control Group	P Values‡	P Values‡
	Baseline	13 Weeks	26 Weeks†	Baseline	13 Weeks	26 Weeks ‡	26 weeks	13 & 26 weeks combined
	N=67	N=67	N=66	N=62	N=58	N=60		
Glucose Level <i>minutes/day</i>								
<i>Median</i>								
<i>(interquartile range)</i>								
≤70 mg/dL	91 (40, 147)	61 (24, 118)	54 (28, 108)	96 (37, 225)	89 (33, 198)	91 (27, 188)	0.16/0.04/0.06	0.05/0.03/0.03
≤60 mg/dL	40 (9, 73)	21 (3, 52)	18 (5, 40)	40 (9, 130)	37 (12, 100)	35 (7, 116)	0.05/0.02/0.02	0.01/0.007/0.008
≤50 mg/dL	7 (0, 38)	3 (0, 18)	4 (0, 15)	9 (0, 45)	7 (0, 51)	8 (0, 55)	0.12/0.05/0.04	0.05/0.03/0.01
71-180 mg/dL	1063 (921, 1174)	1092 (947, 1200)	1063 (948, 1185)	972 (809, 1089)	951 (778, 1079)	949 (784, 1106)	0.003/0.002/0.004	<0.001/<0.001/0.001
>180 mg/dL	255 (151, 420)	268 (179, 410)	283 (173, 423)	331 (206, 489)	362 (221, 527)	341 (232, 502)	0.10/0.09/0.13	0.03/0.03/0.04
>250 mg/dL	40 (10, 101)	42 (8, 77)	48 (11, 103)	63 (27, 118)	76 (29, 173)	82 (22, 149)	0.12/0.05/0.10	0.005/0.003/0.006
Area Under the Curve (70 mg/dL)								
<i>Median</i>	0.64	0.32	0.26	0.60	0.48	0.49	0.09/0.02/0.02	0.03/0.01/0.008
<i>(interquartile range)</i>	(0.19, 1.24)	(0.09,0.80)	(0.11, 0.64)	(0.18, 1.88)	(0.17, 1.80)	(0.13, 1.73)		
Standard Deviation of Values								
<i>Median</i>	48	49	50	56	58	60	0.17/0.13/0.21	0.008/0.02/0.03
<i>(interquartile range)</i>	(42, 58)	(40, 58)	(41, 63)	(48, 67)	(48, 69)	(46, 67)		
MAGE <sup>£</sup> <i>Median</i>	93	95	96	106	103	108	0.77/0.78/0.87	0.26/0.27/0.31
<i>(interquartile range)</i>	(80, 110)	(82, 111)	(84, 113)	(84, 130)	(90, 129)	(86, 126)		
Absolute rate of change								
<i>mg/dL/min median</i>	0.60	0.65	0.66	0.65	0.63	0.66	0.35/0.51/0.51	0.39/0.63/0.57
<i>(interquartile range)</i>	(0.50, 0.71)	(0.50, 0.73)	(0.53, 0.76)	(0.56, 0.80)	(0.54, 0.79)	(0.54, 0.87)		

\* CGM glucose data were obtained following completion of the 13-week and 26-week visits with the CGM group using an unblinded device and the control group using a blinded device.

† One subject in CGM group was missing sensor data.

‡ Two subjects in control group dropped out before the 26-week visit.

§ p-values were from three methods described in Methods section: ANCOVA model based on van der Waerden scores, ANCOVA model with truncation of outliers, and ANCOVA model with square root transformation.

£ The mean amplitude of glucose excursion.

**Table 3** HbA1c at 26 Weeks by Treatment Group

	Treatment Group		P value
	CGM N=67	Control N=62	
<b>HbA1c *</b>			
Baseline (%) <i>mean ± SD</i>	6.4 ± 0.5	6.5 ± 0.3	
26 weeks (%) <i>mean ± SD</i>	6.4 ± 0.5	6.8 ± 0.5	
Change from baseline to 26 weeks (%) <i>mean ± SD</i>	+0.02 ± 0.45	+0.33 ± 0.43	
Treatment group difference (95% CI) (%) †	-0.34 (-0.49 to -0.20)		<0.001
Decrease by ≥0.3% from baseline to 26 weeks <i>no. (%)</i>	21 (31)	3 (5)	<0.001
Increase by ≥0.3% from baseline to 26 weeks <i>no. (%)</i>	19 (28)	31 (52)	0.002
Subjects who maintained HbA1c <7.0 at 26 weeks <i>no. (%)</i>	59 (88)	38 (63)	<0.001

\*26-week HbA1c data were not available for 2 subjects in control group.

† ANCOVA model adjusted for baseline A1c and site. Negative value denotes lower A1c in CGM group compared with control group.

**Figure 1** Combined HbA1c and hypoglycemia outcomes. Four outcomes are shown. ‘A’ represents the combined outcome of HbA1c improved by  $\geq 0.3\%$  from baseline to 26 weeks and no severe hypoglycemic events. ‘B’ represents the combined outcome of HbA1c improved by  $\geq 0.3\%$  from baseline to 26 weeks and CGM-measured hypoglycemia ( $\leq 70$  mg/dL) not increased from baseline to 26 weeks by  $\geq 43$  minutes a day (3% of the day). ‘C’ represents the combined outcome of HbA1c not worse by  $\geq 0.3\%$  and CGM-measured hypoglycemia ( $\leq 70$  mg/dL) decreased from baseline to 26 weeks by  $\geq 43$  minutes a day (3% of the day). ‘D’ represents the combined outcome of either ‘B’ or ‘C’.

