

A Randomized Clinical Trial to Assess the Efficacy and Safety of Real-Time Continuous Glucose Monitoring in the Management of Type 1 Diabetes in Young Children Aged 4 to <10 Years

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OBJECTIVE—Continuous glucose monitoring (CGM) has been demonstrated to improve glycemic control in adults with type 1 diabetes but less so in children. We designed a study to assess CGM benefit in young children aged 4 to 9 years with type 1 diabetes.

RESEARCH DESIGN AND METHODS—After a run-in phase, 146 children with type 1 diabetes (mean age 7.5 ± 1.7 years, 64% on pumps, median diabetes duration 3.5 years) were randomly assigned to CGM or to usual care. The primary outcome was reduction in HbA_{1c} at 26 weeks by $\geq 0.5\%$ without the occurrence of severe hypoglycemia.

RESULTS—The primary outcome was achieved by 19% in the CGM group and 28% in the control group ($P = 0.17$). Mean change in HbA_{1c} was -0.1% in each group ($P = 0.79$). Severe hypoglycemia rates were similarly low in both groups. CGM wear decreased over time, with only 41% averaging at least 6 days/week at 26 weeks. There was no correlation between CGM use and change in HbA_{1c} ($r_s = -0.09$, $P = 0.44$). CGM wear was well tolerated, and parental satisfaction with CGM was high. However, parental fear of hypoglycemia was not reduced.

CONCLUSIONS—CGM in 4- to 9-year-olds did not improve glycemic control despite a high degree of parental satisfaction with CGM. We postulate that this finding may be related in part to limited use of the CGM glucose data in day-to-day management and to an unremitting fear of hypoglycemia. Overcoming the barriers that prevent integration of these critical glucose data into day-to-day management remains a challenge.

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Continuous glucose monitoring (CGM) has made it possible to assess the patterns and trends of blood glucose and the substantial variability in glucose

excursions in people with type 1 diabetes, even in those who are well controlled (1). The benefits of this technology are most apparent with near-continuous wear of

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*A complete list of members of the DirecNet Study Group can be found in the Appendix.

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the sensors, in which knowledge gained in identifying glycemic patterns, such as with meals and exercise, is incorporated into the day-to-day management of the individual's diabetes. The latter has proven to be more difficult to accomplish in children than in adults. In the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group randomized controlled trial (JDRF CGM RCT), only adults had a reduction in mean HbA_{1c} (2). However, in both children and adults, use of CGM for ≥ 6 days/week was associated with an HbA_{1c} reduction (3). Other studies report a similar association between the amount of CGM use and HbA_{1c} levels (4–8).

The use of CGM has been less well studied in younger children with type 1 diabetes, a group in whom parents, by necessity, are responsible for diabetes management, and parental fear of hypoglycemia often prevents better glycemic control (9–11). Therefore, we designed an RCT to evaluate the efficacy, safety, and effect of CGM on quality of life in younger children (aged 4 to 9 years).

RESEARCH DESIGN AND METHODS

The trial was conducted by the Diabetes Research in Children Network (DirecNet). The protocol was approved by the institutional review boards of the five participating sites. Written informed consent was obtained from the parents/guardians, and the child's assent was obtained when appropriate. The study is listed on www.clinicaltrials.gov (NCT00760526).

Study participants had a clinical diagnosis of type 1 diabetes and were using daily insulin therapy for at least 12 months. Eligibility criteria included age 4.0 to <10.0 years, HbA_{1c} $\geq 7.0\%$, and basal-bolus therapy using either an insulin pump or at least three multiple daily injections (MDIs) of insulin for the prior 3 months with no plans to switch the insulin modality within the next 6 months.

Exclusion criteria included 1) diagnosis of diabetes prior to 6 months of age; 2) use of a medication that could affect glycemic control, the performance of the CGM sensor, or completion of any aspect of the protocol; and 3) use of CGM during the prior 6 months.

After enrollment, participants had a run-in period for a minimum of 6 weeks to optimize glycemic control prior to CGM use. During the run-in period, a blinded CGM device was then used for 2 to 4 weeks to familiarize the participant and parent with its use and to obtain CGM data as a baseline assessment of glycemic control. To be randomized, participants had to wear the CGM for a minimum of 7 of 14 days; have no severe skin reaction at the insertion site; have at least 96 h of CGM values, including at least 24 h during 10 P.M. to 6 A.M.; and have performed a minimum of three blood glucose meter measurements per day. Participants meeting these criteria were randomly assigned to either the CGM group or the usual care control group, using a permuted-blocks design stratified by clinical center.

Participants randomized to the CGM group were provided with an unblinded CGM device, sensors, and FreeStyle Flash (Abbott Diabetes Care, Inc., Alameda, CA) blood glucose meter and test strips. A FreeStyle Navigator (Abbott Diabetes Care, Inc.) was provided unless the participant was already using a Medtronic Paradigm insulin pump (Medtronic MiniMed, Inc., Northridge, CA), in which case a MiniMed MiniLink REAL-Time Transmitter (Medtronic MiniMed, Inc.) could be used. Parents were instructed on the use of the device and encouraged to use the sensor on a daily basis. They were instructed to continue testing with the home blood glucose meter ≥ 4 times each day and to verify the accuracy of the CGM glucose measurement with the home blood glucose meter before making management decisions. Participants in the control group were given a FreeStyle Flash blood glucose meter and test strips and asked to perform blood glucose monitoring at least four times daily.

Parents of participants in both the CGM and control groups were provided with detailed verbal and written instructions on how to use 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 (if a computer was available at home for downloading). The insulin

dose adjustment algorithms are available on the DirecNet public Web site (<http://direcnet.jaeb.org/Studies.aspx?RecID=162>). Target glucose values were 80–150 mg/dL before meals, <200 mg/dL after meals, 100–150 mg/dL at bedtime, and 80–150 mg/dL overnight.

The number of scheduled contacts was identical for both treatment groups. Visits were conducted at 1, 4, 8, 13, 19, and 26 weeks (± 1 week) postrandomization, with one scheduled phone contact between each visit, to review glucose data and adjust diabetes management, as indicated. After the 13- and 26-week visits, the control group wore a blinded CGM device to collect a minimum of 96 h of glucose values overall, with at least 24 h overnight.

Bayer DCA (Tarrytown, NY) point-of-care devices were used for HbA_{1c} measurements at each visit with the exception of the 1-week visit. A blood sample was collected at baseline, 13 weeks, and 26 weeks for measurement of HbA_{1c} at the University of Minnesota using the Tosoh A1c 2.2 Plus Glycohemoglobin Analyzer (Tosoh Medics, Foster City, CA) method (12). The parent completed the following questionnaires at baseline (prior to initiating use of the blinded CGM device) and at 26 weeks: Glucose Monitoring Survey (13), Pediatric Assessment In Diabetes Survey–Parent Version (PAID) (14), and Hypoglycemia Fear Survey (15–17). In addition, the CGM Satisfaction Scale (13,18) was completed by the parent for those in the CGM group at 26 weeks. Severe hypoglycemia was defined as an event requiring assistance of another person, as a result of altered consciousness, to administer carbohydrate, glucagon, or other resuscitative actions. For those developmentally too young to independently recognize and treat hypoglycemia, hypoglycemia was considered severe if there were associated signs or symptoms of neuroglycopenia, including temporary impairment of cognition; incoherent, disoriented, and/or combative behavior; seizure; or coma.

Statistical methods

The primary outcome was a binary variable, defined as a decrease in HbA_{1c} of $\geq 0.5\%$ from baseline to 26 weeks and no severe hypoglycemic events. A sample size of 140 was planned to have 90% power to detect an absolute difference in this outcome between treatment groups of 25%, assuming a control group rate of 10% (based on control group data

from the JDRF CGM RCT) (2), an α -level of 0.05, and $\leq 7.5\%$ losses to follow-up.

Analyses followed the intent-to-treat principle, with all participants analyzed in the group to which they were randomized regardless of actual sensor use. Treatment group comparisons of binary outcomes were performed with logistic regression models, adjusted for baseline HbA_{1c} level and clinical center. The comparisons of continuous outcomes, including HbA_{1c}, questionnaire data, and CGM glucose data, were made using ANCOVA models adjusted for their corresponding baseline values and clinical center. There was one outlier for HbA_{1c} (changed from 10.5% at baseline to 7.9% at 26 weeks), and the results were similar using a rank transformation (data not shown). In addition, CGM glucose data were transformed using van der Waerden normal scores, and the comparisons were adjusted for baseline HbA_{1c} level and type of CGM device. The percentages of participants with at least one severe hypoglycemic event in the two treatment groups were compared using Fisher exact test, and the incidences were compared using a permutation test.

Among participants in the CGM group, change in the amount of CGM use over time was assessed using a repeated-measures regression model based on van der Waerden transformed scores. Spearman rank correlations between the amount of CGM use and age, baseline HbA_{1c}, and change in HbA_{1c} were computed. Changes in HbA_{1c} from baseline in the participants who wore CGM ≥ 6 days/week vs. <6 days/week were compared using least squares regression model adjusted for baseline HbA_{1c} level and clinical center.

Analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC). All *P* values are two-sided.

RESULTS—Between January 2009 and December 2010, the trial randomized 146 children aged 4.0–9.9 years (7.5 ± 1.7 years [mean \pm SD]) who had a median duration of type 1 diabetes of 3.5 years (interquartile range 2.2–5.2). The majority of participants was non-Hispanic white and was using insulin pumps. Baseline characteristics were well balanced between the two treatment groups (Table 1).

HbA_{1c} decreased by a mean of $0.2 \pm 0.7\%$ (measured with a DCA instrument) during the run-in phase. Mean HbA_{1c} at the time of randomization (measured by central laboratory) was $7.9 \pm 0.8\%$ in each treatment group. Total daily insulin dose averaged 0.8 ± 0.2 units/kg/day in

Table 1—Baseline characteristics of the participants

Characteristic	Overall (N = 146)	CGM (n = 74)	Control (n = 72)
Female sex	67 (46)	34 (46)	33 (46)
Age (years)	7.5 ± 1.7	7.5 ± 1.8	7.5 ± 1.7
4–5	35 (24)	19 (26)	16 (22)
6–7	45 (31)	22 (30)	23 (32)
8–9	66 (45)	33 (45)	33 (46)
Non-Hispanic white*	112 (77)	55 (74)	57 (80)
BMI percentile	75%	75%	76%
Median (25th, 75th percentile)	(53%, 87%)	(53%, 87%)	(54%, 86%)
Duration diabetes (years)			
Median (25th, 75th percentile)	3.5 (2.2, 5.2)	3.9 (2.8, 5.2)	2.9 (1.9, 5.6)
Insulin modality			
Pump	94 (64)	44 (59)	50 (69)
MDIs	52 (36)	30 (41)	22 (31)
Total daily insulin (units/kg)	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2
HbA _{1c} at randomization (%)†	7.9 ± 0.8	7.9 ± 0.8	7.9 ± 0.8
<8.0	86 (59)	44 (59)	42 (58)
≥8.0	60 (41)	30 (41)	30 (42)
CGM glucose values (mg/dL) (% median)‡			
71–180	47	46	47
>200	40	44	39
>250	22	23	22
≤70	2.2	2.5	2.0
≤60	0.9	1.0	0.7
≥1 severe hypoglycemia event			
in 6 months prior to enrollment§	9 (6)	5 (7)	4 (6)
Self-reported home blood glucose meter			
measurements at randomization (n per day)	7.0 ± 2.1	6.9 ± 1.9	7.2 ± 2.2
3–5	38 (26)	20 (27)	18 (25)
6–8	77 (53)	39 (53)	38 (53)
9+	31 (21)	15 (20)	16 (22)
Parent education level/college graduate	98 (67)	52 (70)	46 (64)
Quality of life measures			
Hypoglycemia Fear	46 ± 18	45 ± 17	47 ± 19
Blood Glucose Monitoring System			
Past month¶	2.4 ± 0.5	2.4 ± 0.5	2.3 ± 0.5
Change over 6 months prior to enrollment#	2.0 ± 0.2	2.0 ± 0.2	2.0 ± 0.2
PAID**	53 ± 16	52 ± 15	55 ± 16

Data are n (%) and mean ± SD unless otherwise noted. *Missing for one subject who did not self-report race/ethnicity. †From central laboratory measurement. ‡CGM glucose values obtained using a blinded CGM device prior to randomization. §Obtained from self-report. ||Scale 0–100. Higher score denotes more fear. ¶Scale 1–4. Higher score denotes fewer problems. #Scale 1–3. Higher score denotes improvement. **Scale 0–100. Higher score denotes worse condition.

both treatment groups at baseline and at 26 weeks.

The 26-week primary outcome visit was completed by 69 of 74 participants (93%) in the CGM group and 68 of 72 (94%) in the control group, with 5 and 4 participants in the two treatment groups, respectively, discontinuing study participation prior to completion of the 26-week visit (Supplementary Fig. A1). The overall completion rates for the six follow-up visits and the six protocol-specified phone calls were 93% and 94% in the CGM and control groups, respectively.

Among the 74 participants in the CGM group, 10 (14%) were provided with a Paradigm CGM device and 64 (86%) with a Navigator CGM device. No participants in the control group self-initiated CGM prior to completing the 26-week visit.

Glycemic control

The primary outcome of a decrease from randomization to 26 weeks in HbA_{1c} ≥0.5% with no severe hypoglycemic events occurred in 13 of 69 (19%) participants in the CGM group and 19 of 68 (28%) in the control group ($P = 0.17$).

Mean change in HbA_{1c} was similar between groups (-0.1 ± 0.6 in each group, $P = 0.79$) (Supplementary Fig. A2). Other HbA_{1c} outcomes at 26 weeks showed similar comparability between treatment groups (Table 2). Outcomes in subgroups based on age, sex, race/ethnicity, parent education level, insulin modality (pump vs. MDIs), baseline HbA_{1c}, or BMI also did not differ between groups and are shown in Supplementary Table A1.

Glycemic outcomes measured with CGM showed no significant differences between treatment groups (considering the multiple outcomes assessed) with respect to percent of values within, above, and below the target range (Table 2 and Supplementary Table A2). Participants in both groups had glucose values >250 mg/dL for >20% of the day.

Hypoglycemia and other adverse events

Three participants (4%, three total events) in the CGM group and five participants (7%, six total events) in the control group experienced at least one severe hypoglycemic event, with no significant differences comparing treatment groups (incidence rate = 8.6 and 17.6 per 100 person-years, respectively; $P = 0.80$) (Table 2). At 26 weeks, both groups had CGM glucose values ≤60 mg/dL for <1% of the day. There were no cases of diabetic ketoacidosis and no serious adverse events attributable to the study interventions, including no serious skin reactions.

Frequency of sensor use in the CGM group

A total of 63 (91%) of 69 participants who completed the 26-week visit were wearing a sensor on at least 1 day a week at the end of 26 weeks. The amount of CGM sensor wear decreased during the 26 weeks of the study ($P < 0.001$) (Fig. 1), with only 41% averaging at least 6 days/week of wear in month 6. The amount of sensor wear in month 6 did not vary with age overall ($r = -0.07$) and was not associated with baseline HbA_{1c} ($r = -0.02$).

There was no association between change in HbA_{1c} from baseline to 26 weeks and the overall amount of CGM sensor wear during the entire 26 weeks (Spearman $r_s = -0.09$, $P = 0.44$) or during month 6 (Spearman $r_s = -0.11$, $P = 0.37$). However, the 28 participants who wore a sensor ≥6 days/week during month 6 tended to have a slightly greater reduction in HbA_{1c} compared with the 41 participants who wore a sensor less frequently

Table 2—Outcomes at 26 weeks*

Outcome	CGM	Control	P value
HbA _{1c}	n = 69	n = 68	
Decrease $\geq 0.5\%$ with no severe hypoglycemic event†	13 (19)	19 (28)	0.17‡
Level (%)	7.8 \pm 0.8	7.8 \pm 0.7	
Change from baseline to 26 weeks§	-0.1 \pm 0.6	-0.1 \pm 0.6	0.79
Drop $\geq 0.5\%$	14 (20)	20 (29)	0.17‡
Increase $\geq 0.5\%$	11 (16)	15 (22)	0.28‡
Level <7.0%	11 (16)	10 (15)	0.75‡
CGM glucose values (mg/dL) (% median)	n = 62	n = 67	
71 to 180	48	49	0.60
>200	39	41	0.72
>250	20	22	0.18
≤ 70	1.5	2.1	0.78
≤ 60	0.4	0.6	0.31
Severe hypoglycemic events¶	n = 73	n = 71	
n	3	6	
Subjects with at least 1 event	3 (4)	5 (7)	0.49
Incidence rate (per 100 person-years)	8.6	17.6	0.80
Quality of life questionnaires	n = 69	n = 68	
Hypoglycemia Fear#	38 \pm 17	42 \pm 19	0.38
Blood Glucose Monitoring System			
Past month**	2.7 \pm 0.5	2.4 \pm 0.5	0.001
Change over past 6 months††	2.3 \pm 0.3	2.0 \pm 0.2	<0.001
PAID‡‡	44 \pm 17	49 \pm 16	0.42

Data are n (%) and mean \pm SD unless otherwise noted. *Excludes five subjects in the CGM group and four in the control group who dropped out prior to the 26-week visit; for one subject who was missing central laboratory HbA_{1c} values at randomization and one at 26 weeks, the DCA value measured at the site was used to impute values using repeated-measures regression models. †Primary outcome. ‡P value from logistic regression, adjusted for baseline HbA_{1c} and site. §Negative difference denotes lower HbA_{1c} at 26 weeks compared with baseline. ||CGM glucose values obtained using a blinded CGM device in the control group and unblinded device in the CGM group after the 26-week visit. Glucose indices were calculated for subjects with at least 24 h of glucose. Seven subjects in the CGM group and one subject in the control group who completed the 26-week visit were missing 26-week CGM data. ¶Excludes one subject in the CGM group and one subject in the control group who dropped out of the study immediately after randomization. Two events in the CGM group and three in the control group were seizure/loss of consciousness. #Scale 0–100 with higher score denoting more fear. **Scale 1–4. Higher score denotes fewer problems in the past month. ††Scale 1–3. Higher score denotes improvement in last 6 months. ‡‡Scale 0–100. Higher score denotes worse condition.

(mean change from baseline to 26 weeks $-0.3 \pm 0.7\%$ vs. $0.0 \pm 0.5\%$, $P = 0.01$; 25 vs. 15% with a reduction in HbA_{1c} $\geq 0.5\%$ without a severe hypoglycemia event, $P = 0.33$). Among those wearing a sensor ≥ 6 days/week in month 6, the median percentage of glucose values in the target range of 71–180 mg/dL was 51%, with 38% >200 mg/dL, 16% >250 mg/dL, and 0.3% ≤ 60 mg/dL compared with 43, 44, 23, and 0.4%, respectively, in those wearing a sensor less frequently.

Quality of life assessments

At 26 weeks, there were no significant differences between treatment groups on the Hypoglycemia Fear or the PAID questionnaire survey scores (Table 2 and Supplementary Tables A3 and A6). However, scores on the Blood Glucose Monitoring System Rating Scale were indicative of fewer problems/concerns perceived by the CGM group compared with the

control group (Table 2 and Supplementary Table A5).

On the CGM Satisfaction Scale at 26 weeks (Table 3 and Supplementary Table A4), parents generally reported a high degree of satisfaction with CGM, with an average item score of 3.9 and 86% of scores ≥ 3.5 (on a 5-point Likert-type scale, with 3 being neutral). Mean item scores were more favorable than neutral (>3.0) on all 43 items. Scores on the Benefits of CGM subscale tended to be slightly higher than scores on the Lack of Hassles of CGM subscale (mean 4.1 ± 0.4 vs. 3.9 ± 0.6 , respectively). It is particularly noteworthy that >90% of parents responded that use of CGM makes adjusting insulin easier, shows patterns in blood glucose not seen before, and makes them feel safer knowing that they will be warned about low blood glucose before it happens. No one responded that he or she would not recommend

CGM for other children with type 1 diabetes.

CONCLUSIONS—In this RCT in preschool- and school-aged children with type 1 diabetes, we found no benefit of wearing a CGM sensor on glycemic control after a 26-week follow-up period, despite high parental satisfaction with CGM. The incidence of severe hypoglycemia was low and comparable between the two groups, similar to published results in older children and adults in other trials (1,2,4,6,8). There were no other serious adverse events, including no serious skin issues.

In the CGM group, sensor wear decreased over the 26 weeks, with only 41% averaging at least 6 days/week of wear in month 6. The amount of sensor wear did not vary significantly with age or HbA_{1c} level. This decrease over time is similar to what was observed in the 8- to 14-year-olds in the JDRF CGM RCT (3). However, in the current trial, even when the CGM sensor was worn ≥ 6 days/week during the 6th month of the trial, improvement in HbA_{1c} was modest and less than the mean HbA_{1c} improvement seen in the 8- to 14-year-olds who used CGM regularly in the JDRF CGM RCT (0.3 vs. 0.8%).

Because parental responses on the Lack of Hassles of CGM subscale did not indicate major problems with the use of CGM, problems with the insertion and maintenance of a sensor do not appear to have been primary impediments to improving glycemic control in this age group. Accuracy of the CGM sensor was also not stated as a concern. It also seems unlikely that the lack of improvement was related to inadequate training and instructions on insulin dosing because the subjects were contacted and data reviewed on the same frequent schedule that was used in the JDRF CGM RCT, in which frequent CGM wear was associated with greater improvement in HbA_{1c}. The parents of the study participants generally were well educated, representing a selected population interested in using CGM as part of their child's diabetes management. Therefore, it seems unlikely that parent education level or lack of motivation contributed to the lack of benefit on glycemic control.

Why then was parental report that CGM helped with management not reflected in better HbA_{1c} levels? Several factors may have played a role. The target blood glucose levels were those recommended by the American Diabetes

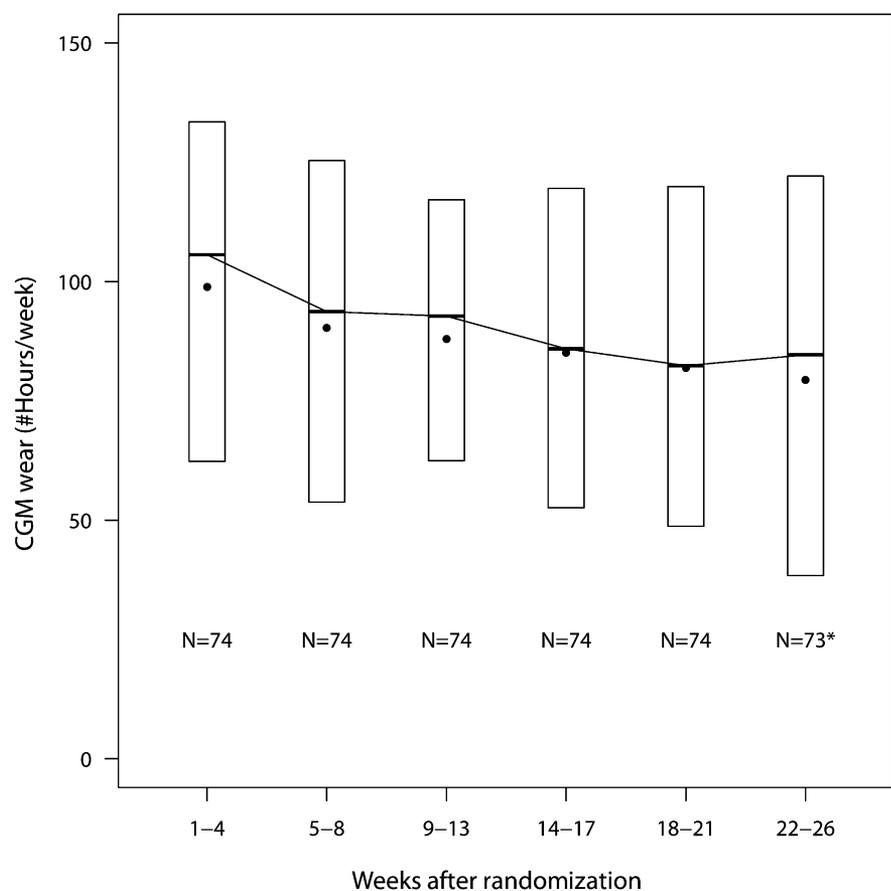


Figure 1—Sensor use during the 26 weeks of the trial. Each box represents the number of hours per week of CGM sensor glucose data averaged over 4 weeks. The top and bottom of the boxes represent the 75th and 25th percentiles, respectively; the horizontal line within each box represents the median; and the black dot represents the mean. For participants who dropped from the trial, sensor use was considered to be zero after the day of dropout. Data were considered missing when downloaded glucose data were not available for a 4-week period. *Sensor download was unavailable due to device issue for one subject in 22–26 weeks.

Association to mitigate the risks of hypoglycemia in young children with type 1 diabetes (19); thus, it is possible that the insulin-adjusting algorithms that were used in this study may have contributed to the failure to substantially lower HbA_{1c} levels in our subjects by setting higher target levels to minimize hypoglycemia. We also speculate that avoidance of hypoglycemia might have been so important to the parents of these young children that they were reluctant to tighten glycemic control and increase the risk of hypoglycemia. Although responses on the CGM Satisfaction Scale indicated a strong perceived benefit of CGM in warning about hypoglycemia, no significant treatment group differences were found on the Hypoglycemia Fear Survey at 26 weeks. We conjecture that this apparent discordance may be explained by the fact that even though wearing a sensor provided parental reassurance and comfort on a daily basis (as measured on the CGM

Satisfaction Scale), sensor wear might not alter an underlying deep-rooted fear of hypoglycemia (as measured on the Hypoglycemia Fear Survey). In fact, for some parents, it is possible that observing downward trends of the CGM glucose levels actually might have made them even less aggressive in trying to achieve tighter glycaemic control because of their fear of hypoglycemia. At 26 weeks, the amount of time the glucose level was ≤ 60 mg/dL was extremely small (median 6 min/day), whereas glucose levels were high for a substantial portion of the day: >200 mg/dL for ~ 10 h/day (median) even when a sensor was being worn ≥ 6 days/week.

In summary, CGM in 4- to 9-year-olds did not improve glycaemic control, despite a high degree of parental satisfaction with CGM. We postulate that this may be related to limited use of CGM glucose data in the day-to-day management of diabetes, target glucose levels that are too high,

and a persistent, unremitting fear of hypoglycemia in the parents of these young children. Overcoming the barriers that prevent the integration of these glucose data into day-to-day management of pediatric diabetes remains a substantial challenge.

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N.M. researched data, contributed to discussion, and wrote, reviewed, and edited the manuscript. R.B. contributed to discussion and wrote, reviewed, and edited the manuscript. D.X. researched data and wrote, reviewed, and edited the manuscript. K.R., B.B., M.T., N.H.W., S.A.W., and W.T. researched data, contributed to discussion, and reviewed and edited the manuscript. C.K. researched data and reviewed and edited the manuscript.

R.B. is the guarantor of the study.

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APPENDIX—The DirecNet Study Group: Clinical Centers (listed in alphabetical order with clinical center name, city, and state; personnel listed as [PI] for Principal Investigator, [I] for co-Investigator, and [C] for

Table 3—CGM Satisfaction Scale scores* at 26 weeks (N = 69)

	Mean score	Percentage							
		<3	≥3.5	≥4.0	Negative§		Neutral	Favorable§	
					1	2	3	4	5
Overall	3.9 ± 0.5	4	86	45	—	—	—	—	—
Benefits of CGM subscale†	4.1 ± 0.4	0	88	61	—	—	—	—	—
Lack of Hassles of CGM subscale†	3.9 ± 0.6	9	80	45	—	—	—	—	—
Responses on selected items‡:									
Using the continuous monitor:									
Makes me feel safer knowing that I will be warned about low blood glucose before it happens	4.6	—	—	—	0	1	3	33	62
I want to use this device when it is approved for sale	4.4	—	—	—	0	4	6	30	59
Makes adjusting insulin easier	4.3	—	—	—	0	3	6	51	41
Shows patterns in blood sugars that we didn't see before	4.3	—	—	—	1	0	6	55	38
Helps me to relax, knowing that unwanted changes in blood glucose will be detected quickly	4.2	—	—	—	1	0	9	55	35
Helps me to be sure about making diabetes decisions	4.2	—	—	—	0	3	9	58	30
Has made me worry less about having low blood sugars	4.1	—	—	—	1	9	4	46	39
Helps to keep low blood sugars from happening	4.1	—	—	—	1	6	7	51	35
Teaches me how eating affects blood glucose	4.0	—	—	—	0	1	20	58	20
Has helped to adjust premeal insulin doses	3.9	—	—	—	1	4	16	64	14
Has helped me to learn how to treat low sugars better	3.8	—	—	—	1	7	13	68	10
Has helped to control diabetes better even when not wearing it	3.5	—	—	—	0	14	35	41	10

*Scoring on a 5-point Likert-type scale with a higher value denoting more favorable response toward CGM use. †The CGM Satisfaction Scale has two subscales: Benefits of CGM and Lack of Hassles of CGM (13). For both subscales, a higher value denotes more satisfaction (more perceived benefits or fewer hassles). ‡Supplementary Table A4 contains all items. §Favorable denotes agree/strongly agree with a positively worded statement or disagree/strongly disagree with a negatively worded statement. Negative denotes vice versa.

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References

1. Beck RW, Hirsch IB, Laffel L, et al.; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. The effect of continuous glucose monitoring in well-controlled type 1 diabetes. *Diabetes Care* 2009;32:1378–1383
2. Tamborlane WV, Beck RW, Bode BW, et al.; 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
3. Beck RW, Buckingham B, Miller K, et al.; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Factors predictive of use and of benefit from continuous glucose monitoring in type 1 diabetes. *Diabetes Care* 2009;32:1947–1953
4. Bergenstal RM, Tamborlane WV, Ahmann A, et al.; STAR 3 Study Group. Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. *N Engl J Med* 2010;363:311–320
5. Hirsch IB, Abelson J, Bode BW, et al. Sensor-augmented insulin pump therapy: results of the first randomized treat-to-target study. *Diabetes Technol Ther* 2008;10:377–383
6. O'Connell MA, Donath S, O'Neal DN, et al. Glycaemic impact of patient-led use of sensor-guided pump therapy in type 1 diabetes: a randomised controlled trial. *Diabetologia* 2009;52:1250–1257
7. Pickup JC, Freeman SC, Sutton AJ. Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data. *BMJ* 2011;343:d3805
8. Raccach D, Sulmont V, Reznik Y, et al. Incremental value of continuous glucose monitoring when starting pump therapy in patients with poorly controlled type 1 diabetes: the RealTrend study. *Diabetes Care* 2009;32:2245–2250
9. Barnard K, Thomas S, Royle P, Noyes K, Waugh N. Fear of hypoglycaemia in parents

- of young children with type 1 diabetes: a systematic review. *BMC Pediatr* 2010;10:50
10. Haugstvedt A, Wentzel-Larsen T, Graue M, Søvik O, Rokne B. Fear of hypoglycaemia in mothers and fathers of children with Type 1 diabetes is associated with poor glycaemic control and parental emotional distress: a population-based study. *Diabet Med* 2010;27:72–78
 11. Patton SR, Dolan LM, Henry R, Powers SW. Fear of hypoglycemia in parents of young children with type 1 diabetes mellitus. *J Clin Psychol Med Settings* 2008;15:252–259
 12. Gibb I, Parnham A, Fonfrède M, Lecock F. Multicenter evaluation of Tosoh glycohemoglobin analyzer. *Clin Chem* 1999;45:1833–1841
 13. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Validation of measures of satisfaction with and impact of continuous and conventional glucose monitoring. *Diabetes Technol Ther* 2010;12:679–684
 14. Antisdell JE. Diabetes-specific distress among parents of youth with type 1 diabetes (Abstract). *Dissertation Abstracts International* 2001;61:6123
 15. Clarke WL, Gonder-Frederick A, Snyder AL, Cox DJ. Maternal fear of hypoglycemia in their children with insulin dependent diabetes mellitus. *J Pediatr Endocrinol Metab* 1998;11(Suppl. 1):189–194
 16. Cox DJ, Irvine A, Gonder-Frederick L, Nowacek G, Butterfield J. Fear of hypoglycemia: quantification, validation, and utilization. *Diabetes Care* 1987;10:617–621
 17. Green LB, Wysocki T, Reineck BM. Fear of hypoglycemia in children and adolescents with diabetes. *J Pediatr Psychol* 1990;15:633–641
 18. Diabetes Research in Children Network (DirecNet) Study Group. Youth and parent satisfaction with clinical use of the GlucoWatch G2 Biographer in the management of pediatric type 1 diabetes. *Diabetes Care* 2005;28:1929–1935
 19. American Diabetes Association. Standards of medical care in diabetes—2008. *Diabetes Care* 2008;31(Suppl. 1):S12–S54