Factors Predictive of Use and of Benefit From Continuous Glucose Monitoring in Type 1 Diabetes

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OBJECTIVE — To evaluate factors associated with successful use of continuous glucose monitoring (CGM) among participants with intensively treated type 1 diabetes in the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Randomized Clinical Trial.

RESEARCH DESIGN AND METHODS — The 232 participants randomly assigned to the CGM group (165 with baseline A1C ≥7.0% and 67 with A1C <7.0%) were asked to use CGM on a daily basis. The associations of baseline factors and early CGM use with CGM use ≥6 days/week in the 6th month and with change in A1C from baseline to 6 months were evaluated in regression models.

RESULTS — The only baseline factors found to be associated with greater CGM use in month 6 were age ≥25 years ($P < 0.001$) and more frequent self-reported prestudy blood glucose meter measurements per day ($P < 0.001$). CGM use and the percentage of CGM glucose values between 71 and 180 mg/dl during the 1st month were predictive of CGM use in month 6 ($P < 0.001$ and $P = 0.002$, respectively). More frequent CGM use was associated with a greater reduction in A1C from baseline to 6 months ($P < 0.001$), a finding present in all age-groups.

CONCLUSIONS — After 6 months, near-daily CGM use is more frequent in intensively treated adults with type 1 diabetes than in children and adolescents, although in all age-groups near-daily CGM use is associated with a similar reduction in A1C. Frequency of blood glucose meter monitoring and initial CGM use may help predict the likelihood of long-term CGM benefit in intensively treated patients with type 1 diabetes of all ages.

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D espite recent advances in insulin delivery and home blood glucose monitoring, many individuals with type 1 diabetes fail to achieve recommended A1C target levels (1,2). Further, hypoglycemia is a problem for many patients with type 1 diabetes (3) and can be a significant deterrent to achieving and maintaining tight glycemic control (4,5). Thus, the introduction of real-time continuous glucose monitoring (CGM) systems was received with great interest because these devices may have the potential to increase the proportion of patients who are able to maintain target A1C values while simultaneously limiting their risk of severe hypoglycemia. The first real-time CGM device, the GlucoWatch Biographer (6), was difficult to use, in large part because of skin reaction and frequent skipping of glucose measurements that prevented patients from using it as a tool for day-to-day diabetes management. More recently, several new real-time CGM systems have been introduced that have improved accuracy, functionality, and user tolerance.

In a multicenter randomized controlled trial, our Juvenile Diabetes Research Foundation (JDRF) Continuous Glucose Monitoring Study Group evaluated the effectiveness of CGM compared with standard blood glucose monitoring in 451 adults and children ≥8 years old with type 1 diabetes, 322 of whom had baseline A1C ≥7.0% and 129 of whom had baseline A1C <7.0% (7). Among subjects with baseline A1C level ≥7.0%, we found that CGM substantially improved A1C levels during 6 months of follow-up without increasing the frequency of hypoglycemia in adults ≥25 years of age. However, the efficacy of this device as a tool to help participants <25 years of age lower their A1C levels was much more limited (8). Among the subjects with baseline A1C <7.0%, we found that the CGM group had a reduction in hypoglycemia on most measures compared with the control group and was able to maintain mean A1C levels at 6.4%, whereas A1C increased in the control group (9). The present analyses were conducted to determine which demographic, clinical, and psychosocial factors were associated with successful CGM use and A1C improvement in the 232 CGM-group subjects.

RESEARCH DESIGN AND METHODS — The randomized trial protocol has been described in detail (7–9). This report includes the 6-month follow-up of the 232 subjects in the CGM group, including both the ≥7.0% ($n = 165$) and <7.0% ($n = 67$) A1C cohorts. Major eligibility criteria for the trial included age ≥8 years, type 1 diabetes for at least 1 year, use of either an insulin pump or at least three insulin injections per day, and A1C level <10.0%. Randomization was stratified in three age-groups: ≥25, 15–24, and 8–14 years old. Subjects in

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the CGM group were instructed to use the CGM device on a daily basis and were provided with written instructions on how to use the CGM data to make real-time insulin dose adjustments and on using computer software (for those with a home computer) to retrospectively review the glucose data to alter future insulin dosing (7,10). Glucose data from the CGM devices were downloaded at each visit. A central laboratory-measured A1C level was obtained at baseline, 3 months, and 6 months at the University of Minnesota using the Tosoh A1C 2.2 Plus Glycohemoglobin Analyzer method (11).

Statistical methods

The amount of CGM use was determined from the information downloaded from the CGM devices. CGM was considered to be used on a day when there was at least one sensor glucose value; on 85% of days with at least one glucose value, there were at least 12 h of glucose values. Factors that were evaluated for association with CGM use included baseline demographic and clinical characteristics as well as psychosocial factors that included total and subscale scores from the Hypoglycemia Fear Survey (12), Blood Glucose Monitoring System Rating Questionnaire (developed for the study), and Problem Area in Diabetes Questionnaire (13,14).

Logistic regression analyses were used to evaluate the association between baseline demographic and clinical factors (listed in Table 1) and successful CGM use, which was defined as average use of ≥6.0 days/week during the 6th month of the trial. Baseline demographic and clinical factors were included in an initial model and then a backward elimination procedure was used to remove variables with $P > 0.05$. A forward selection process resulted in a similar model. Additional models evaluated the predictive value of CGM usage during the 1st month as well as CGM glucose indexes of the percentage of glucose values between 71 and 180, ≤70, and >180 mg/dl. The van der Waerden normal scores of the CGM usage were used in the models as a result of the skewed distribution of the data. A general linear model was used to evaluate demographic and clinical factors associated with a change in A1C from baseline to 6 months among subjects with a baseline A1C level ≥7.0%. The association between sensor use over the 6 months of the trial and change in A1C from baseline to 6 months also was evaluated with a general linear model.

Analyses were performed using SAS (version 9.1; SAS Institute, Cary, NC). All P values are two-sided. For models 1 and 2 in Table 1, missing values were imputed for covariates, and an indicator for missing values was added to the regression. One subject was missing sensor data for the 1st month because of a defective device from which information could not be downloaded and is excluded from Table 2.

RESULTS — The 232 subjects in the trial's CGM group ranged in age from 8 to 73 years, with 86 (37%) aged ≥25 years old, 72 (31%) aged 15–24 years old, and 74 (32%) aged 8–14 years old. Mean baseline A1C level was 7.4% ± 0.9%, with 165 (71%) at ≥7.0% and 67 (29%) at <7.0%. Insulin pump therapy was the treatment modality in 190 (82%) subjects, with the others being treated with multiple daily injections. The mean number of self-reported home blood glucose measurements per day was 6.6 ± 2.3 measurements. Additional baseline characteristics have been previously reported (8,9).

Factors associated with CGM use

CGM use averaged ≥6.0 days/week during month 6 of the study in 123 (53%) of the 232 subjects. As shown in Table 1, CGM use averaging ≥6.0 days/week in month 6 was associated with age (highest in adults, $P < 0.001$ in a multivariate model) and frequency of self-reported prestudy daily blood glucose meter measurements ($P < 0.001$). For the latter factor, the association was consistent across the three age-groups (Supplementary Table 1, available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc09-0889/DC1, shows the factors in Table 1 in three age-groups). There was a trend toward baseline A1C <7.0% being associated with greater CGM use in an unadjusted model but not after adjustment for age and frequency of prestudy daily blood glucose meter measurements. Other variables associated with CGM use that were confounded by age included race/ethnicity, duration of diabetes, educational level, and household income. When we examined the psychosocial measures, we found that none of the total or subscale scores were significantly associated with CGM use.

As shown in Table 2, CGM use during the 1st month of the trial was predictive of use in month 6 ($P < 0.001$, after adjust-ment for age and baseline frequency of daily blood glucose measurements). Subjects who used the CGM device on at least 27 of the 28 days during the 1st month were more than three times more likely to be using the device ≥6 days/week in month 6 than were subjects who used the device fewer than 21 of the first 28 days. Results according to age-group are shown in supplementary Table 2 (available in an online appendix).

In addition to the amount of use during the 1st month, a higher percentage of CGM glucose values between 71 and 180 mg/dl during month 1 was predictive of greater CGM use during month 6 ($P = 0.002$ adjusted for age, baseline frequency of daily blood glucose meter measurements, and sensor use during the first 4 weeks) (Table 2). In similar models, a lower percentage of glucose values >180 in the 1st month was associated with greater use in month 6 ($P = 0.006$), but a lower percentage of glucose values ≤70 mg/dl was not ($P = 0.91$). The percentage of glucose values >180 mg/dl was associated with baseline A1C ($P < 0.001$). The significant associations were still present after adjusting for the respective values obtained during blinded CGM use before randomization.

Factors associated with a reduction in A1C

In a multivariate model that included subjects with a baseline A1C level ≥7.0%, improvement in A1C from baseline to 6 months was associated with higher baseline A1C level ($P < 0.001$) and greater CGM use over the 6 months of the study ($P < 0.001$) (Table 3). The Spearman correlation between change in A1C from baseline to 6 months and average CGM use over the 6 months of the study was −0.46 (supplementary Fig. 1, available in an online appendix). None of the psychosocial measures were predictive of change in A1C. Age-group was associated with the change in A1C in a multivariate analysis including baseline factors ($P = 0.004$) but after adjustment for the amount of CGM use, the association was no longer significant ($P = 0.70$). The main reason was that in all three age-groups, greater CGM use was associated with a similar reduction in A1C. As can be seen in Fig. 1, in each age-group, subjects averaging at least 6 days/week of CGM use had substantially greater improvement in A1C than those who used CGM less often ($P = 0.02$ in the ≥25 year age-group, $P = 0.002$ in the 15–24 year age-group, and $P < 0.001$ in the 8–14 year age-group).

Table 1—*Baseline factors predictive of sensor use ≥6 days per week during month 6 of the trial*

	n overall (age-groups*)	% ≥6 days/week in month 6 overall (age-groups*)	P†	Model 1‡		Model 2§†	
				OR (95% CI)	P	OR (95% CI)	P
Total	232	53					
Age (years)			<0.001/NA		<0.001		<0.001
8–<15	74	46		1.00		1.00	
15–<25	72	29		0.60 (0.28, 1.26)		0.60 (0.29, 1.26)	
≥25	86	79		5.35 (2.48, 11.53)		5.90 (2.78, 12.52)	
Sex			0.32/0.39				
Female	123 (37, 38, 48)	56 (57, 29, 77)					
Male	109 (37, 34, 38)	50 (35, 29, 82)					
Race/ethnicity			0.02/0.37				
Nonwhite	19 (7, 12, 0)	26 (43, 33, 67)					
White, Non-Hispanic	213 (67, 60, 86)	55 (46, 32, 79)					
Duration of diabetes (years)‖			<0.001/0.87				
<5	48 (30, 15, 3)	42 (43, 33, 67)					
5–<10	70 (35, 27, 8)	47 (49, 30, 100)					
10–<20	61 (9, 30, 22)	44 (44, 27, 68)					
≥20	53 (0, 0, 53)	81 (0, 0, 81)					
Baseline insulin modality			0.006/0.06				
Multiple daily injection	42 (10, 22, 10)	33 (30, 23, 60)		1.00	0.45		
Pump	190 (64, 50, 76)	57 (48, 32, 82)		1.20 (0.51, 2.84)			
Baseline A1C (%)‖			0.002/0.10		0.28		
≥8.0	63 (27, 26, 10)	38 (44, 23, 60)		1.00			
7.0–<8.0	102 (29, 31, 42)	53 (45, 23, 81)		1.23 (0.57, 2.65)			
<7.0	67 (18, 15, 34)	67 (50, 53, 82)		1.69 (0.72, 4.01)			
Severe hypoglycemia in last 6 months			0.39/0.64				
None	211 (71, 65, 75)	52 (48, 28, 77)					
≥1 episode	21 (3, 7, 11)	62 (0, 43, 91)					
Self-reported home blood glucose meter measurements per day‖¶			<0.001/0.002		0.005		0.002
3–5	68 (16, 31, 21)	28 (13, 16, 57)		1.00		1.00	
6–8	104 (34, 26, 44)	61 (53, 27, 86)		3.64 (1.69, 7.84)		4.00 (1.89, 8.47)	
≥9	31 (12, 4, 15)	68 (50, 50, 87)		4.16 (1.45, 11.96)		4.82 (1.72, 13.55)	
Education level‖#			0.04/0.40				
≤12	26 (2, 22, 2)	19 (50, 14, 50)					
Associate	23 (8, 6, 9)	57 (38, 50, 78)					
Bachelor	90 (32, 21, 37)	61 (53, 38, 81)					
Master	65 (21, 14, 30)	55 (38, 36, 77)					
Professional	28 (11, 9, 8)	50 (45, 22, 88)					
Household income‖**			0.04/0.26				
≤$25,000	16 (2, 12, 2)	25 (50, 17, 50)					
$25,001–$50,000	27 (3, 13, 11)	48 (67, 46, 45)					
$50,001–$100,000	74 (24, 14, 36)	65 (58, 43, 78)					
>$100,000	95 (37, 24, 34)	53 (35, 25, 91)					

*Age-groups are 8–14, 15–24, and ≥25 years. †P values are unadjusted/adjusted for age-group. ‡The multivariate logistic regression model includes all variables having age-adjusted P < 0.20. §Multivariate logistic regression model using backward selection keeping those variables with P < 0.05. ‖P value obtained by treating as continuous variable. Education level and income category analyzed as ordinal variables. ¶Collected on randomization form, as assessed by clinic personnel over the last 7 days. Question was added to the case report form after study initialization, and data were missing for 29 subjects in the real-time CGM group. #Education level is for parent/guardian for subjects <15 years old and for subjects aged ≥25 years. For subjects in the 15–24 year age-group, education level is that of the subject for 28, of the subject's spouse for 1, and of the subject's parent for 43. **Twenty subjects did not provide household income data. In the 15–24 year age-group, household income reflects that of the subject for 35 and that of the parent for 37. NA, not applicable.

Table 2—*CGM use and sensor glucose values during 1st month as predictors of month 6 CGM use*

	n^*	Sensor use ≥6 days/week during month 6	Odds ratio (95% CI)	P†
Sensor use during first 7 days				0.14
0–5‡	8	2 (25)	1.00	
6	19	7 (37)	1.70 (0.23–12.63)	
7	204	114 (56)	3.13 (0.55–17.71)	
Sensor use during first 14 days				0.03
4–8	13	4 (31)	1.00	
9–11	14	4 (29)	2.22 (0.34–14.53)	
12–13	26	11 (42)	2.83 (0.56–14.26)	
14	178	104 (58)	4.26 (1.08–16.84)	
Sensor use during first 21 days				<0.001
7–13	14	3 (21)	1.00	
14–17	13	6 (46)	9.93 (1.48–66.83)	
18–20	53	18 (34)	3.35 (0.70–16.05)	
21	151	96 (64)	8.86 (2.03–38.63)	
Sensor use during first 28 days				<0.001
7–20	20	4 (20)	1.00	
21–23	19	7 (37)	4.52 (0.90–22.63)	
24–26	34	10 (29)	2.43 (0.55–10.72)	
27–28	158	102 (65)	7.19 (2.04–25.37)	
Sensor use during 15–28 days				<0.001
0–10	28	7 (25)	1.00	
11–13	57	19 (33)	1.57 (0.50–4.89)	
14	146	97 (66)	4.80 (1.72–13.37)	
% of day 71–180 mg/dl during 1st month§				0.002
20–<55	64	13 (20)	1.00	
55–<70	94	56 (60)	3.39 (1.50–7.66)	
70–95	73	54 (74)	3.82 (1.52–9.57)	
% of day ≤70 mg/dl during 1st month§				0.91
5–31	77	38 (49)	1.00	
2–<5	77	43 (56)	1.71 (0.79–3.74)	
0–<2	77	42 (55)	1.43 (0.64–3.19)	
% of day >180 mg/dl during 1st month§				0.006
40–79	68	18 (26)	1.00	
25–<40	86	50 (58)	2.09 (0.95–4.63)	
1–<25	77	55 (71)	2.42 (1.01–5.85)	

Data are n (%) or OR (95% CI). $*n = 231$. One subject is missing sensor data for the 1st month because of a defective device that could not be downloaded. †P values are from logistic regression model treating CGM use as a continuous variable, adjusting for age and baseline number of blood glucose meter measurements/day. Categories were created for presentation purposes. ‡One subject had zero use, 1 subject had 1 day of use, 4 subjects had 4 days of use, and 2 subjects had 5 days of use. §Logistic regression models adjusted for age, baseline number of blood glucose meter measurements/day, and sensor use during the 1st month.

CONCLUSIONS — The goal of the JDRF CGM randomized clinical trial was to have subjects use a CGM device every day and incorporate the real-time glucose information into their daily diabetes management to reduce the frequency of high and low glucose values. Before entering the study, the subjects were being intensively treated with either an insulin pump or multiple daily insulin injections and were performing frequent blood glucose monitoring (mean 6.6 measurements/ day). We defined successful use of CGM as an average of ≥6 days/week to allow for the possibility of issues such as device inoperability, exhausted sensor supply, or other problems that might prevent daily use for a few days.

As reported previously, among subjects with baseline A1C ≥7.0%, nearly daily use after 6 months was strongly associated with age, with 83% of subjects ≥25 years sustaining CGM use ≥6 days/ week compared with 30% of subjects 15–24 years and 50% of subjects 8–14 years (8). After adjustment for age, the only other baseline factor associated with successful use after 6 months was the frequency of self-reported prestudy daily blood glucose meter measurements. Subjects in all age-groups who performed ≥6 meter measurements/day were more likely to use CGM on a near-daily basis than those who were monitoring fewer times a day. One possible explanation is that those subjects who were monitoring their blood glucose frequently were using these multiple glucose measurements to self-manage their diabetes and as a result could more readily incorporate information from CGM into their already intensive diabetes management. In addition, more frequent home blood glucose monitoring may be a marker for patients who are more engaged in their diabetes self-management and who are therefore more likely to adhere to a daily CGM regimen as used in this trial.

Notably, none of our surveys, which were geared to assess baseline psychosocial variables such as fear of hypoglycemia and perceived diabetes-associated burden, were predictive of CGM use, suggesting that additional research is needed to identify salient patient beliefs and expectations regarding CGM use. We did not formally evaluate subject expectations for CGM at study entry, and such an assessment might prove to be a predictor of sustained long-term use.

CGM use in the 1st month was very high, with >90% of subjects using CGM on at least 21 of the first 28 days. Subjects who used the CGM device at least 27 of 28 days in the 1st month were more likely to sustain near-daily use through month 6 than those who used CGM less often. However, because of the overall high degree of use, the study had limited ability to evaluate whether CGM use in the 1st month could be used to predict the likelihood of long-term CGM use. This high degree of early use could reflect in part the fact that successful use of a blinded CGM device during a prerandomization run-in period was required for study entry.

A higher percentage of CGM glucose values in the range of 71 to 180 mg/dl during the 1st month (with fewer values >180 mg/dl) were predictive of greater use in month 6 even after adjustment for the amount of CGM use. This could re-

Table 3—*Baseline factors predictive of change in A1C from baseline to 6 months in subjects with baseline A1C ≥7.0%*

| | | | | P | |
| | | | Univariate models | Model 1† | Model 2‡ |
	n	Mean*			
Total	162	−0.35			
Sex			0.55		
Female	86	−0.32			
Male	76	−0.38			
Age-group			0.08	0.004	0.70
8–<15 years	56	−0.37			
15–<25 years	56	−0.18			
≥25 years	50	−0.50			
Race/ethnicity			0.69		
White, Non-Hispanic	148	−0.35			
Nonwhite	14	−0.27			
Baseline insulin modality			0.51		
Multiple daily injection	35	−0.27			
Pump	127	−0.37			
Baseline A1C§			<0.001	<0.001	<0.001
7.0–<7.5%	47	−0.11			
>7.5–<8.0%	53	−0.36			
≥8.0%	62	−0.52			
Severe hypoglycemia in last 6 months			0.76		
None	149	−0.34			
≥1 episode	13	−0.41			
Self-reported home blood glucose per day§‖			0.27		
3–5	55	−0.16			
6–8	69	−0.36			
≥9	15	−0.34			
Education level of primary caregiver§¶			0.78		
≤12	20	−0.38			
Associate	19	−0.21			
Bachelor	58	−0.43			
Master	45	−0.32			
Professional	20	−0.26			
Household income§#			0.89		
≤$25,000	13	−0.25			
$25,001–$50,000	17	−0.47			
$50,001–$100,000	49	−0.39			
>$100,000	67	−0.33			
No. days per week of sensor use during 6 months			<0.001		<0.001
<4 days	18	+0.02			
4–<6 days	56	−0.10			
≥6 days	88	−0.58			

*Negative change denotes improvement and positive change is worsening. †Includes all baseline variables with univariate P ≤0.20 (does not include sensor use). ‡Includes all variables in model 1 plus CGM use. §P value obtained by treating as a continuous variable. Education level and income category analyzed as ordinal variables. ‖Collected on randomization form, as assessed by clinic personnel over the last 7 days. Question was added to the case report form after study initialization and data were missing for 29 subjects in the real-time CGM group. ¶Education level is for parent/guardian for subjects <15 years old and for subjects aged ≥25 years. For subjects in the 15–24 age-group, education level is that of the subject for 28, of the subject's spouse for 1, and of the subject's parent for 43. #20 subjects did not provide household income data. In the 15–24 year age-group, household income reflects that of the subject in 35 and that of the parent in 37.

flect the fact that those who observed the most benefit early in their usage of CGM were more likely to recognize the advantages of sustained use of CGM. Conversely, individuals with more values >180 mg/dl may have felt discouraged and therefore less inclined to use the device. Alternatively, frequent sensor values >180 mg/dl may be a marker for persons less attentive or too busy to attend to diabetes management and the additional effort that CGM usage entails. Ongoing education and support may assist these patients in achieving equivalent CGM benefit.

We also analyzed the benefit of CGM as measured by A1C in those whose baseline A1C was ≥7.0%. The amount of CGM use was strongly associated with change in A1C, similar to what was seen in other trials (15). In all three age-groups, near-daily use of CGM was associated with similar improvements in A1C. In fact, the association between age and CGM use accounted for the association between age and change in A1C. Higher baseline A1C was associated with a greater A1C drop from baseline to 6 months but not greater CGM use. This probably is related to a floor effect in those who started with lower A1C levels. Less time with glucose values >180 mg/dl during the 1st month was associated with greater CGM use in month 6.

Our results need to be interpreted within the context of the enrollment criteria for the study, which required intensive diabetes management with an insulin pump or multiple daily injections, frequent home blood glucose monitoring, and successful completion of a run-in period of blinded CGM use. For such patients, our results have shown that long-term consistent CGM use is more frequent in adults than in children or adolescents, but a similar benefit on A1C is seen in patients of all ages who regularly use CGM. CGM use in the 1st month may help predict the likelihood of long-term benefit, and our results suggest that a trial of CGM use for several weeks may help predict long-term use and consequent benefit. Because regular use of CGM is not observed in all patients with type 1 diabetes, particularly children and adolescents, further research is needed to better understand and overcome the barriers to daily CGM use.
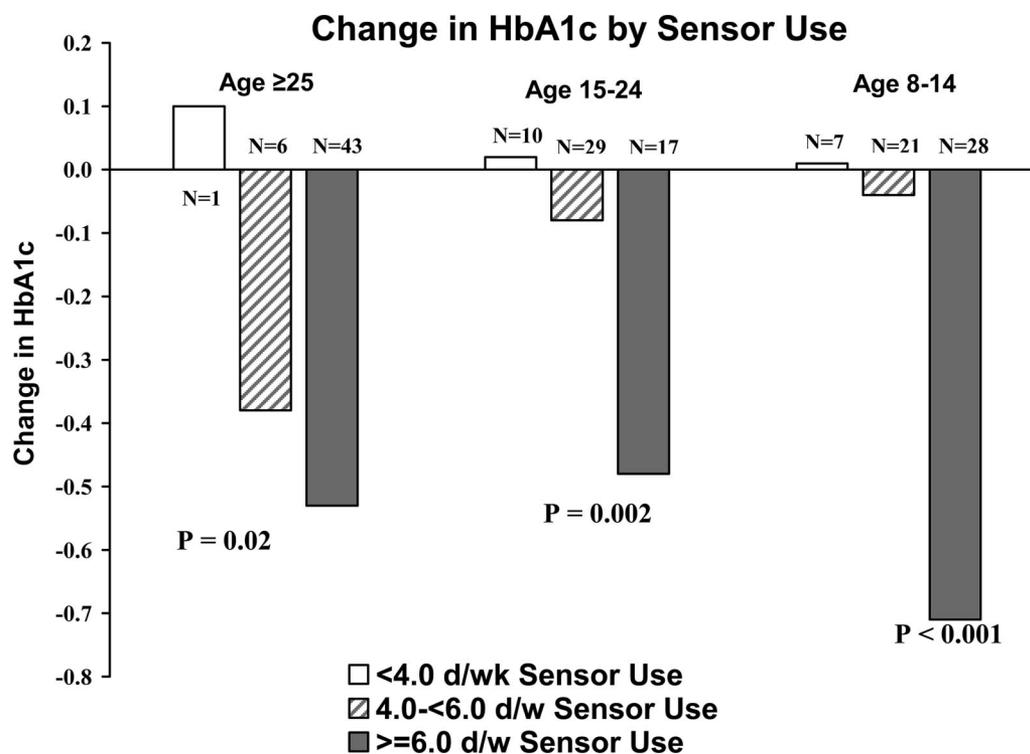
Figure 1—*Change in A1C from baseline to 6 months in subjects with baseline A1C ≥7.0% according to average amount of CGM use over the 6-month period. The Ns refer to the number of subjects in each CGM use category. The P values are for the association between sensor use over the 6 months and change in A1C from baseline to 26 weeks, evaluated in a general linear model with sensor use as continuous variable adjusted for baseline A1C.*

APPENDIX — Members of the Writing Committee are the following: lead authors: Roy W. Beck, MD, PhD; Bruce Buckingham, MD; Kellee Miller, MPH; Howard Wolpert, MD; and Dongyuan Xing, MPH. Additional members of the Writing Committee (alphabetical) include Jennifer M. Block, RN, CDE; H. Peter Chase, MD; Irl Hirsch, MD; Craig Kollman, PhD; Lori Laffel, MD, MPH; Jean M. Lawrence, ScD, MPH, MSSA; Kerry Milaszewski, RN, CDE; Katrina J. Ruedy, MSPH; and William V. Tamborlane, MD.

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