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Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections
The DIAMOND Randomized Clinical Trial

Roy W. Beck, MD, PhD; Tonya Riddlesworth, PhD; Katrina Ruedy, MSPH; Andrew Ahmann, MD; Richard Bergenstal, MD; Stacie Haller, RD, LD, CDE; Craig Kollman, PhD; Davida Kruger, MSN, APN-BC; Janet B. McGill, MD; William Polonsky, PhD; Elena Toschi, MD; Howard Wolpert, MD; David Price, MD; for the DIAMOND Study Group

IMPORTANCE Previous clinical trials showing the benefit of continuous glucose monitoring (CGM) in the management of type 1 diabetes predominantly have included adults using insulin pumps, even though the majority of adults with type 1 diabetes administer insulin by injection.

OBJECTIVE To determine the effectiveness of CGM in adults with type 1 diabetes treated with insulin injections.

DESIGN, SETTING, AND PARTICIPANTS Randomized clinical trial conducted between October 2014 and May 2016 at 24 endocrinology practices in the United States that included 158 adults with type 1 diabetes who were using multiple daily insulin injections and had hemoglobin A_{1c} (HbA_{1c}) levels of 7.5% to 9.9%.

INTERVENTIONS Random assignment 2:1 to CGM (n = 105) or usual care (control group; n = 53).

MAIN OUTCOMES AND MEASURES Primary outcome measure was the difference in change in central-laboratory–measured HbA_{1c} level from baseline to 24 weeks. There were 18 secondary or exploratory end points, of which 15 are reported in this article, including duration of hypoglycemia at less than 70 mg/dL, measured with CGM for 7 days at 12 and 24 weeks.

RESULTS Among the 158 randomized participants (mean age, 48 years [SD, 13]; 44% women; mean baseline HbA_{1c} level, 8.6% [SD, 0.6%]; and median diabetes duration, 19 years [interquartile range, 10-31 years]), 155 (98%) completed the study. In the CGM group, 93% used CGM 6 d/wk or more in month 6. Mean HbA_{1c} reduction from baseline was 1.1% at 12 weeks and 1.0% at 24 weeks in the CGM group and 0.5% and 0.4%, respectively, in the control group (repeated-measures model $P < .001$). At 24 weeks, the adjusted treatment-group difference in mean change in HbA_{1c} level from baseline was −0.6% (95% CI, −0.8% to −0.3%; $P < .001$). Median duration of hypoglycemia at less than <70 mg/dL was 43 min/d (IQR, 27-69) in the CGM group vs 80 min/d (IQR, 36-111) in the control group ($P = .002$). Severe hypoglycemia events occurred in 2 participants in each group.

CONCLUSIONS AND RELEVANCE Among adults with type 1 diabetes who used multiple daily insulin injections, the use of CGM compared with usual care resulted in a greater decrease in HbA_{1c} level during 24 weeks. Further research is needed to assess longer-term effectiveness, as well as clinical outcomes and adverse effects.

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Author Affiliations: Jaeb Center for Health Research, Tampa, Florida (Beck, Riddlesworth, Ruedy, Kollman); Oregon Health & Science University, Portland (Ahmann); Park Nicollet Institute, International Diabetes Center, St Louis Park, Minnesota (Bergenstal); Diabetes & Glandular Disease Clinic, San Antonio, Texas (Haller); Division of Endocrinology, Henry Ford Medical Center, Detroit, Michigan (Kruger); Washington University in St Louis, St Louis, Missouri (McGill); Behavioral Diabetes Institute, San Diego, California (Polonsky); Joslin Diabetes Center, Boston, Massachusetts (Toschi, Wolpert); Dexcom Inc, San Diego, California (Price).

Group Information: The DIAMOND Study Group members are listed at the end of this article.

Corresponding Author: Roy W. Beck, MD, PhD, Jaeb Center for Health Research, 15310 Amberly Dr, Ste 350, Tampa, FL 33647 (rbeck@jaeb.org).

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Only approximately 30% of individuals with type 1 diabetes meet the American Diabetes Association goal of hemoglobin A_{1c} (HbA_{1c}) level of 7.5% (58 mmol/mol) for children (<18 years) and 7.0% (53 mmol/mol) for adults (≥18 years),[1] indicating the need for better approaches to diabetes management. Continuous glucose monitoring (CGM) with glucose measurements as often as every 5 minutes, plus low and high glucose level alerts and glucose trend information, has the capability of better informing diabetes management decisions than blood glucose meter testing performed several times a day. Randomized clinical trials have demonstrated the benefit of CGM in adults with type 1 diabetes, but not consistently in children, to improve glycemic control as measured by HbA_{1c} level and to reduce hypoglycemia.[2-6] These previous trials have either completely or predominantly included insulin pump users,[2,4,5] although the majority of adults with type 1 diabetes deliver insulin via injections.[7,8]

Only a small proportion of individuals with type 1 diabetes who inject insulin use CGM, although the limited available observational data suggest that the glycemic benefit may be comparable to that for pump users. In T1D Exchange registry 2015 data, mean HbA_{1c} level in the 410 adult insulin injecters using CGM was similar to that in 2316 pump users using CGM (7.6% vs 7.7%, respectively) and lower than mean HbA_{1c} level in the 6222 injection users not using CGM (7.6% vs 8.8%; $P < .001$).[9]

Whether individuals receiving insulin injections would be willing to regularly wear CGM sensors and would derive glycemic benefits from CGM needs investigation. Accordingly, this randomized multicenter clinical trial was conducted to evaluate the effect of CGM in adults with type 1 diabetes who have elevated HbA_{1c} levels and use multiple daily injections of insulin.

Key Points

Question For adults with type 1 diabetes who are using multiple daily insulin injections, does continuous glucose monitoring improve hemoglobin A_{1c} (HbA_{1c}) levels compared with self-monitored blood glucose management?

Findings In a randomized clinical trial of 158 adults with type 1 diabetes, there was a significantly greater decrease in HbA_{1c} level during 24 weeks with continuous glucose monitoring vs usual care (−1.0% vs −0.4%).

Meaning Continuous glucose monitoring resulted in better glycemic control compared with usual care, but further research is needed to assess clinical outcomes, as well as effectiveness, in a typical clinical population.

Methods

The trial was conducted at 24 endocrinology practices in the United States (19 community-based and 5 academic centers). The protocol and Health Insurance Portability and Accountability Act–compliant informed consent forms were approved by institutional review boards (central commercial board for 17 sites and local boards for the other 7 sites). Written informed consent was obtained from each participant. The protocol is provided online and the statistical analysis plan is available in Supplement 1.

Study Participants

Major eligibility criteria included age 25 years or older, diagnosis of type 1 diabetes treated for at least 1 year with multiple daily insulin injections, central laboratory–measured HbA_{1c} level of 7.5% to 10.0%, no home use of a personal CGM device in the 3 months before the trial, and a negative pregnancy test for women of childbearing potential (eTable 1 in Supplement 2 has a complete listing of the inclusion and exclusion criteria).

Synopsis of Study Design

Each participant was required to complete a 2-week prerandomization phase using a CGM system that was configured to record glucose concentrations not visible to the participant (referred to as a "blinded" CGM). Eligibility required that the blinded CGM be worn on at least 85% of possible days, the CGM be calibrated at least 2 times per day, and blood glucose meter testing (with a study-provided meter and test strips) be performed at least 3 times daily. Fourteen participants did not meet these criteria and did not continue into the randomized trial (**Figure 1**). One participant had a sudden death during the prerandomization phase.

On the study website, after verification of eligibility from data entered, each participant was assigned randomly from a computer-generated sequence to either the CGM or control group in a 2:1 ratio, with a permuted block design (block sizes of 3 and 6) stratified by HbA_{1c} level (<8.5% and ≥8.5%). A 2:1 randomization was used rather than 1:1 to provide a larger sample size for a separate follow-on randomized trial assessing glycemic benefits of initiating pump therapy in CGM users using insulin injections.

Participants in the CGM group were provided with a CGM system (Dexcom G4 Platinum CGM System with an enhanced algorithm, software 505, Dexcom Inc) that measured glucose concentrations from interstitial fluid in the range of 40 to 400 mg/dL every 5 minutes for up to 7 days. Participants in both groups were provided with a Bayer Contour Next USB meter and test strips. The CGM group was instructed to use the CGM daily, calibrate the CGM twice daily, and verify the CGM glucose concentration with the blood glucose meter before injecting insulin (as per the regulatory labeling of the device at the time the trial was conducted). General guidelines were provided to participants about using CGM, and individualized recommendations were made by their clinician about incorporating CGM trend information into their diabetes management. The control group was asked to perform home blood glucose monitoring at least 4 times daily. Participants in both groups were provided general diabetes management education, and clinicians were encouraged to review downloaded glucose data at each visit to inform treatment recommendations, which were at clinician discretion and not prescriptive in the protocol. eTable 2 in Supplement 2 describes the participant education as well as guidelines for clinicians. CGM guidelines for participants are included in Supplement 1.

Follow-up visits for both treatment groups occurred after 4, 12, and 24 weeks. The CGM group had an additional visit 1 week after randomization. The control group had 2 additional visits 1 week before the 12- and 24-week visits, at which a CGM sensor in blinded mode was inserted to collect glucose data for 1 week. Telephone contacts for both groups occurred 2 and 3 weeks after randomization.

Hemoglobin A_{1c} level was measured at baseline, 12 weeks, and 24 weeks at the Northwest Lipid Research Laboratories, University of Washington, Seattle, with the Diabetes Control and Complications Trial standardized analyzer (TOSOH, Biosciences Inc).

Outcomes

The primary outcome was change in the central laboratory-measured HbA_{1c} level. Prespecified secondary outcomes included percentage of participants with HbA_{1c} level less than 7.0%; CGM-measured time in range (70-180 mg/dL), duration of hypoglycemia (<70 mg/dL, <60 mg/dL, and <50 mg/dL), duration of hyperglycemia (>180 mg/dL, >250 mg/dL, and >300 mg/dL), and glucose variability (coefficient of variation); change in hypoglycemia unawareness[10]; and change in frequency of blood glucose meter testing (longitudinal changes in blood glucose meter testing were not assessed). Prespecified exploratory outcomes included CGM-measured mean glucose concentration and the following binary HbA_{1c} outcomes to assist in translation of the primary HbA_{1c} analysis to a participant level: HbA_{1c} level less than 7.5% and relative HbA_{1c} reduction greater than or equal to 10%. Post hoc outcomes included HbA_{1c} reduction of 1% or more, HbA_{1c} level less than 7.0% or reduction of 1% or more, CGM-measured area above the curve 70 mg/dL and area under the curve 180 mg/dL, change in insulin dose, and change in body weight.

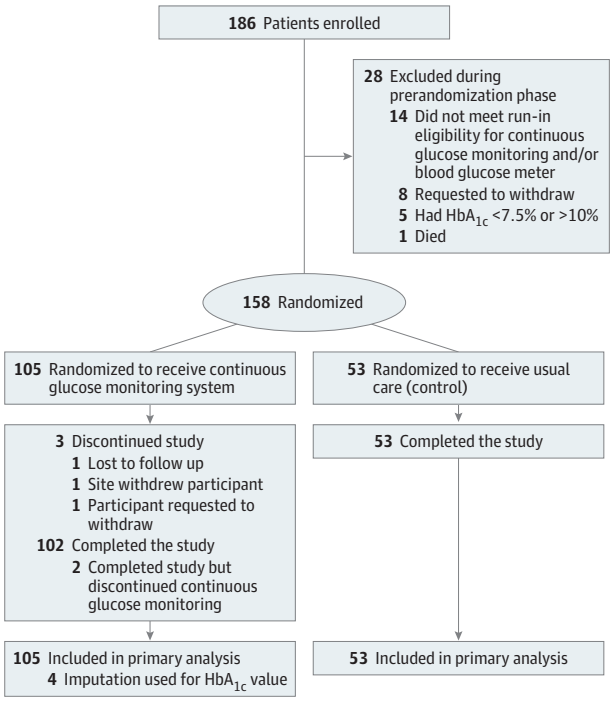
Satisfaction with CGM was assessed by completion at 24 weeks of the CGM Satisfaction Survey (44 items on a 1-5 Likert scale, with the computed score representing the mean of the 44 items and subscales of benefits and lack of hassles).[11] Quality-of-life and health economic outcomes will be reported in separate articles.

Safety outcomes included severe hypoglycemia (defined as an event that required assistance from another person to administer carbohydrate, glucagon, or other resuscitative actions), diabetic ketoacidosis, and serious adverse events regardless of causality.

Statistical Methods

A sample size of 147 for the 2:1 randomization was calculated to have 90% power to detect a difference in mean HbA_{1c} level between treatment groups, assuming a population difference of 0.4%, standard deviation of the 24-week values of 0.7 adjusted for the correlation between baseline and 24-week values (based on data from the Juvenile Diabetes Research Foundation CGM randomized trial[5]), and a 2-sided α level of .05. Sample size initially was increased to 169 to account for potential loss to follow-up. When it was recognized by the coordinating center that the trial completion rate was higher than anticipated, the recruitment goal was changed to a minimum of 150, with the approval of the steering committee and the sponsor.

Figure 1. Flowchart of Continuous Glucose Monitoring Study Completion



All enrolled participants started the run-in phase; 28 did not proceed to randomization for the reasons indicated in the figure. The number eligible for screening who did not sign the informed consent form was not recorded.

Analyses followed the intent-to-treat principle. The following change was made from the protocol and statistical analysis plan before the data lock: the primary analysis was a treatment group comparison of the change in HbA_{1c} level from baseline to 24 weeks, adjusted for baseline HbA_{1c} level and clinical site as a random effect, in a repeated-measures linear model in the protocol and with analysis of covariance in the statistical analysis plan; both are reported in this article. Confounding was assessed by repeating the analysis, including potential confounding variables as covariates. The Rubin method was used to impute for missing data.[12] Exploratory analyses were conducted to assess for interaction between the treatment effect on the change in HbA_{1c} level from baseline to 24 weeks and baseline factors by including interaction terms in analysis of covariance models. The following changes were made from the protocol and statistical analysis plan during the peer-review process: in post hoc analyses, binary HbA_{1c} outcomes were evaluated with propensity scores[13] instead of logistic regression, adjusted for baseline HbA_{1c} level and clinical site; and for secondary, exploratory, and post hoc analyses, 99% CIs instead of 95% CIs are reported.

For CGM outcomes, treatment group comparisons using the CGM data collected in each group for 7 days at 12 and 24 weeks were made with analysis of covariance models based on ranks using van der Waerden scores if the metric was

Table 1. Baseline Participant Characteristics

	Group, No. (%)	
	CGM (n = 105)	Control (n = 53)
Age, y		
25-<45	53 (50)	16 (30)
45-<60	32 (30)	23 (43)
≥60	20 (19)	14 (26)
Mean (SD) [range]	46 (14) [26-72]	51 (11) [26-73]
Diabetes duration, median (IQR), y	19 (9-29)	19 (11-35)
Female sex	47 (45)	23 (43)
Highest education[a]		
<Bachelor's degree	47 (47)	22 (43)
Bachelor's degree	43 (43)	19 (37)
Graduate degree	10 (10)	10 (20)
BMI, mean (SD)	28 (6)	27 (5)
Weight, mean (SD), kg	84 (20)	81 (18)
HbA_{1c}, %		
7.5-<8.5	47 (45)	24 (45)
8.5-≤9.9	58 (55)	29 (55)
Mean (SD) [range]	8.6 (0.7) [7.5-9.9]	8.6 (0.6) [7.5-9.9]
Self-reported No. of self-monitoring blood glucose tests per day, mean (SD)	3.9 (1.3)	4.1 (1.6)
Event in previous 12 mo		
≥1 Severe hypoglycemia	8 (8)	9 (17)
≥1 Diabetic ketoacidosis	1 (<1)	1 (2)
Use of noninsulin glucose-lowering medication	8 (8)	4 (8)
Total daily insulin dose, median (IQR), U/kg/d	0.7 (0.5-0.9)	0.6 (0.5-0.9)
No. of long-acting insulin injections per day		
1	78 (74)	34 (64)
2	26 (25)	19 (36)
3	1 (<1)	0
No. of rapid-acting insulin injections per day		
2	0	1 (2)
3	71 (68)	32 (60)
4	23 (22)	15 (28)
≥5	11 (10)	5 (9)
CGM use previously	17 (16)	9 (17)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CGM, continuous glucose monitoring; HbA_{1c}, hemoglobin A_{1c}; IQR, interquartile range.

SI Conversions: to convert HbA_{1c} to the SI units of mmol/mol, multiply the HbA_{1c} percentage value × 10.93 and subtract 23.5 from the product.

[a] Education data missing for 5 in the CGM group and 2 in the control group.

skewed, adjusted for the corresponding baseline value, baseline HbA_{1c} level, and clinical site as a random effect. Similar analyses were performed separately for daytime and nighttime. Frequency of blood glucose monitoring was compared between groups with an analysis of covariance model, adjusted for the baseline frequency and clinical site as a random effect.

Statistical methods for other analyses are described in table footnotes. Standard deviations are reported for means and interquartile ranges (IQRs) for medians where applicable. Reported point estimates are unadjusted unless otherwise noted. Analyses were conducted with SAS version 9.4. All *P* values are 2 sided. $P < .05$ was considered significant for the primary analysis and $P < .01$ for all other analyses to account for multiple comparisons (with 99% CIs accordingly provided).

SI Unit Conversions

Throughout, to convert HbA_{1c} to the SI units of mmol/mol, multiply the HbA_{1c} percentage value × 10.93 and subtract 23.5 from the product. For example, an HbA_{1c} value of 7.0% corresponds to 53 mmol/mol. To convert glucose to mmol/L, multiply the values × 0.0555.

Results

Between October 2014 and December 2015, 158 participants were assigned to the CGM group (n = 105) or control group (n = 53). Mean age was 48 years (SD, 13) (range, 26-73 years, with 34 participants [22%] ≥60 years); 44% were women. Median diabetes duration was 19 years (IQR, 10-31 years), and mean baseline HbA_{1c} level was 8.6% (SD, 0.6%; range, 7.5%-9.9%). Participant characteristics according to randomized group are shown in **Table 1.**

The 24-week primary study outcome visit was completed by 102 participants (97%) in the CGM group and all 53 (100%) in the control group (Figure 1). Overall visit completion was 99% and 98%, respectively. Three participants in the CGM group (4 total visits) and 3 in the control group (3 total visits) had additional visits, not required in the protocol, for diabetes management.

Among the 102 participants in the CGM group who completed the trial, median CGM use was 7.0 d/wk (IQR, 7.0-7.0) at 4, 12, and 24 weeks; only 2 (2%) discontinued CGM before the 24-week visit. During month 6 (weeks 21-24), CGM use was 6 or more d/wk for 93% of the 102 participants (eTable 3 in Supplement 2). No participant in the control group initiated unblinded CGM use before the primary outcome.

According to meter downloads, mean blood glucose self-monitoring was 5.1 tests per day (SD, 1.8) in the CGM group and 5.1 tests per day (SD, 1.4) in the control group during the baseline period of blinded CGM wear and 3.6 tests per day (SD, 1.6) and 4.6 tests per day (SD, 1.6), respectively, at 24 weeks (adjusted mean difference for the change, -1.0; 99% CI, -1.7 to -0.4; $P < .001$).

Glycemic Control and Other Outcomes

Primary Outcome

Mean reduction in HbA_{1c} level from baseline was 1.1% at 12 weeks and 1.0% at 24 weeks in the CGM group and 0.5% and 0.4%, respectively, in the control group (primary analysis repeated-measures $P < .001$). At 24 weeks, the adjusted treatment group difference in mean change in HbA_{1c} level was -0.6% (95% CI, -0.8% to -0.3%; $P < .001$) (**Table 2**). For each treatment group, baseline and 24-week HbA_{1c} values for each

Table 2. Primary Outcome and Hemoglobin A_{1c} Outcomes at 12 and 24 Weeks[a]

	12 Weeks		24 Weeks			
	CGM Group (n = 103)	Control Group (n = 52)	CGM Group (n = 105)[b]	Control Group (n = 53)	Between-Group Difference[c,d]	*P* Value[c,d]
Primary outcome, mean (SD), %					Mean adjusted difference, % (95% CI)	
HbA_{1c}	7.6 (0.7)	8.1 (0.7)	7.7 (0.8)	8.2 (0.8)		
Change in HbA_{1c} from baseline	−1.1 (0.7)	−0.5 (0.7)	−1.0 (0.8)	−0.4 (0.7)	−0.6 (−0.8 to −0.3)	<.001
Prespecified secondary outcome, No. (%)					Mean adjusted difference, % (99% CI)	
HbA_{1c} <7.0%	14 (14)	2 (4)	18 (18)	2 (4)	15 (0 to 30)	.01
Prespecified exploratory outcomes, No. (%)						
HbA_{1c} <7.5%	49 (48)	6 (12)	39 (38)	6 (11)	31 (12 to 51)	<.001
Relative reduction in HbA_{1c} ≥10%	62 (60)	12 (23)	58 (57)	10 (19)	37 (16 to 58)	<.001
Post hoc outcomes, No. (%)						
Reduction in HbA_{1c} ≥1%	55 (53)	12 (23)	53 (52)	10 (19)	33 (11 to 54)	<.001
Reduction in HbA_{1c} ≥1% or HbA_{1c} <7.0%	57 (55)	12 (23)	53 (52)	11 (21)	31 (9 to 52)	<.001

Abbreviations: CGM, continuous glucose monitoring; HbA_{1c}, hemoglobin A_{1c}.

SI Conversion: to convert HbA_{1c} to the SI units of mmol/mol, multiply the HbA_{1c} percentage value × 10.93 and subtract 23.5 from the product.

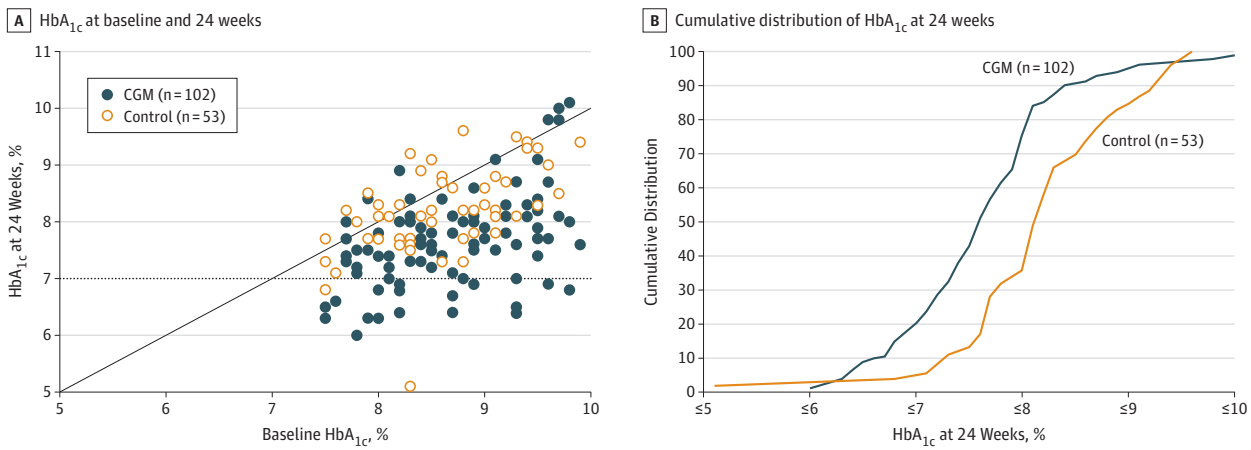
[a] Mean baseline HbA_{1c} level was 8.6% in each group. For all analyses, missing HbA_{1c} values in which the central laboratory value was missing but the local laboratory value was known were imputed with a regression line based on the site's local HbA_{1c} measurements (CGM/control: 1/0 at 12 weeks; 1/0 at 24 weeks).

[b] For the 24-week primary outcome only, the Rubin method was used to impute missing HbA_{1c} values when both the central and local laboratory values were missing (3 in the CGM group and 0 in the control group). For the secondary, exploratory, and post hoc analyses, n = 102.

[c] For the primary analysis, treatment group comparisons were made with analysis of covariance models, adjusted for baseline HbA_{1c} level and clinical site as a random effect. Model residuals were verified to have an approximate normal distribution.

[d] For the secondary, exploratory, and post hoc outcomes, treatment group comparisons were made with propensity scores, adjusted for baseline HbA_{1c} level and clinical site. $P < .01$ was considered significant to account for multiple comparisons (with 99% CIs accordingly provided).

Figure 2. Hemoglobin A_{1c} Values at Baseline and 24 Weeks, by Group



A, Scatterplot of 24-week hemoglobin A_{1c} (HbA_{1c}) levels by baseline HbA_{1c} level. The horizontal line at 7.0% represents the American Diabetes Association HbA_{1c} goal for adults with type 1 diabetes. Points below the diagonal line represent cases in which the 24-week HbA_{1c} level was lower than the baseline HbA_{1c} level, points above the diagonal line represent cases in which the 24-week HbA_{1c} level was higher than the baseline HbA_{1c} level, and points on the diagonal line represent cases in which the 24-week and baseline HbA_{1c} values were the same. B, Cumulative distribution of 24-week HbA_{1c} values. For any given 24-week HbA_{1c} level, the percentage of cases in each treatment group with an HbA_{1c} value at that level or lower can be determined from the figure. To convert HbA_{1c} to the SI units of mmol/mol, multiply the HbA_{1c} percentage value × 10.93 and subtract 23.5 from the product.

participant are shown in **Figure 2**A, and the cumulative distribution of the 24-week HbA_{1c} values is shown in Figure 2B.

Secondary, Exploratory, and Post Hoc HbA_{1c} Outcomes

The greater HbA_{1c} improvement in the CGM group also was reflected in multiple participant-level secondary, exploratory, and post hoc HbA_{1c} outcomes (Table 2). There was no significant interaction of the effect of treatment on 24-week HbA_{1c} level according to baseline HbA_{1c}, age, education level, or type of site (eTable 4 in Supplement 2).

Secondary and Exploratory CGM Outcomes

As secondary outcomes, CGM metrics for time in the range of 70 to 180 mg/dL, hyperglycemia, hypoglycemia, and glycemic

Table 3. Continuous Glucose Monitoring Metrics

	Baseline		12 and 24 Weeks Pooled[a]			
	CGM Group (n = 105)	Control Group (n = 53)	CGM Group (n = 103)	Control Group (n = 53)	Mean Adjusted Difference (99% CI)[b]	*P* Value[b]
Hours of data, mean (SD)	322 (50)	325 (51)	301 (41)	301 (54)		
Prespecified secondary outcomes						
Glucose variability: coefficient of variation, mean (SD), %	42 (7)	42 (7)	38 (6)	42 (7)	−4 (−6 to −2)	<.001
Minutes per day in range 70-180 mg/dL, mean (SD)	660 (179)	650 (170)	736 (206)	650 (194)	77 (6 to 147)	.005
Hypoglycemia, median (IQR)						
Minutes per day <70 mg/dL	65 (33 to 103)	72 (35 to 136)	43 (27 to 69)	80 (36 to 111)		.002
Minutes per day <60 mg/dL	32 (15 to 61)	39 (15 to 78)	20 (9 to 30)	40 (16 to 68)		.002
Minutes per day <50 mg/dL	13 (5 to 29)	18 (4 to 39)	6 (2 to 12)	20 (4 to 42)		.001
Hyperglycemia, median (IQR)						
Minutes per day >180 mg/dL	687 (554 to 810)	725 (537 to 798)	638 (503 to 807)	740 (625 to 854)		.03
Minutes per day >250 mg/dL	301 (190 to 401)	269 (184 to 383)	223 (128 to 351)	347 (241 to 429)		<.001
Minutes per day >300 mg/dL	129 (66 to 201)	109 (71 to 204)	78 (36 to 142)	167 (89 to 226)		<.001
Prespecified exploratory outcome						
Mean glucose, mean (SD), mg/dL	187 (27)	186 (30)	180 (27)	189 (25)	−9 (−19 to 0)	.01
Post hoc outcomes, median (IQR)[c]						
Area above curve 70 mg/dL	0.5 (0.3 to 1.1)	0.7 (0.2 to 1.4)	0.3 (0.2 to 0.5)	0.7 (0.2 to 1.3)		<.001
Area under curve 180 mg/dL	34 (25 to 46)	33 (26 to 45)	27 (17 to 40)	40 (31 to 51)		<.001

Abbreviations: CGM, continuous glucose monitoring; IQR, interquartile range.

SI Conversion: to convert glucose to mmol/L, multiply the values × 0.0555.

[a] Excludes 2 participants in the CGM group with less than 72 hours of data (a prespecified condition).

[b] Treatment group comparisons made with analysis of covariance models, adjusted for the corresponding baseline value, baseline hemoglobin A_{1c} level, and clinical site as a random effect, using pooled data from 12 and 24 weeks. Because of skewed distributions for the hypoglycemia and hyperglycemia metrics (including area above the curve 70 mg/dL and area below the curve 180 mg/dL), these models were based on ranks using van der Waerden scores. $P < .01$ was considered significant to account for multiple comparisons (with 99% CI accordingly provided for the metrics that are approximately normally distributed).

[c] Area above (the glucose) curve 70 mg/dL reflects both percentage and severity of glucose values in the hypoglycemic range. Area under (the glucose) curve 180 mg/dL is the analogous measure for hyperglycemia.

variability favored the CGM group compared with the control group (**Table 3**, eTable 5 in Supplement 2). In exploratory analyses, hypoglycemia treatment group differences favored the CGM group during both daytime and nighttime, but hyperglycemia treatment group differences favoring the CGM group were present only during the daytime (eTables 6 and 7 in Supplement 2).

Other Analyses

At 24 weeks, in post hoc analyses there were no significant differences between the CGM group and control group in median change in total daily insulin dose per kilogram of body weight (-0.02 vs 0.03 U/kg; $P = .23$), median ratio of long-acting to rapid-acting daily insulin dose (0.9 vs 1.0; $P = .54$), proportion of participants with an increase in number of injections of rapid-acting insulin per day (26% vs 26%; $P = .90$), or mean change in body weight (1.7 vs 0.7 kg; mean difference, 1.0 kg; 99% CI, -0.7 to 2.8; $P = .12$) (eTable 8 in Supplement 2). Clarke Hypoglycemia Unawareness scores did not differ between groups (mean difference, -0.1; 99% CI, -0.7 to 0.5; $P = .64$).

Severe Hypoglycemia and Other Adverse Events

Severe hypoglycemic events occurred in 2 participants in each group ($P = .67$). There were no occurrences of diabetic ketoacidosis. Other serious adverse events, unrelated to the study intervention, occurred in 2 participants in the CGM group and none in the control group (eTable 9 in Supplement 2).

CGM Satisfaction

In the CGM group, satisfaction with use of CGM was high, as indicated by the mean (SD) score of 4.2 (0.4) on the CGM Satisfaction Survey, with mean (SD) scores of 4.2 (0.5) on the benefits subscale and 4.3 (0.5) on the subscale for lack of hassles (eTable 10 in Supplement 2).

Discussion

Among adults with type 1 diabetes using multiple daily insulin injections, the use of CGM compared with usual care resulted in a greater decrease in HbA_{1c} level during 24 weeks. The HbA_{1c} benefit in the CGM group was consistently present across the age range of 26 to 73 years, the baseline HbA_{1c} level range of 7.5% to 9.9%, and all education levels. In addition, CGM use was associated with a high degree of participant satisfaction with CGM, increased time with glucose concentrations between 70 and 180 mg/dL, decreased time with glucose concentrations less than 70 mg/dL, and decreased glycemic variability, measured with the coefficient

of variation. The trial was not designed to demonstrate a benefit in reducing clinical severe hypoglycemia events, and the low event rate in the control group precluded a meaningful analysis. However, less biochemical hypoglycemia, as was observed in the trial, has been associated with a lower risk for subsequent severe hypoglycemic events[14,15] and improved quality of life.[16-18]

The amount of CGM use by the participants was high (median CGM use 7 d/wk in month 6) despite a protocol approximating usual practice, with only 1 visit after week 4 and no visits or other protocol-specified contacts between 12 and 24 weeks. The amount of use was similar to or greater than the frequency of use in pump-using adults with type 1 diabetes in previous trials and observational studies,[2-5,19] which could be related to CGM accuracy being significantly improved from the generation of sensors in previous trials.[20-22] The observed benefits of CGM occurred despite the CGM group's having significantly less blood glucose meter testing per day than the control group.

The magnitude of benefit of CGM on HbA_{1c} levels relative to control in this trial of insulin injection users is comparable to the magnitude of benefit of CGM observed in pump users in previous randomized trials.[2,4,5] This finding was not a foregone conclusion. Insulin injection users have less flexibility in adjusting their insulin delivery in response to CGM glucose concentrations and trends than do pump users. Basal insulin delivery for pump users is continuous, can be programmed to vary at different times of the day, and can be temporarily changed in response to decreasing or increasing glucose concentrations or planned activities such as exercise. In contrast, injection users have fixed basal insulin based on the absorption of their long-acting insulin and can make adjustments only to rapid-acting insulin boluses.

The strengths of the trial included a high retention rate, high adherence to treatment group assignment, central laboratory measurement of HbA_{1c} level, a protocol approximating usual clinical practice, and participation in the trial by both community-based and academic sites. Assignment to the CGM and control groups could not be blinded because of the nature of the intervention; however, the groups had a similar number of visits. The 0.4% mean improvement in HbA_{1c} level in the control group likely reflects both a study effect related to clinical trial participation and more structured training in using blood glucose monitoring in adjusting insulin regimens than was occurring for these individuals before the study.

This study also had several limitations. In light of the eligibility criteria, the results may not apply to individuals with type 1 diabetes who are younger than 26 years or have HbA_{1c} levels outside the range of 7.5% to 9.9% and should not be applied to individuals with type 2 diabetes who receive multiple daily injections of insulin. The informed consent process and the run-in phase had the potential to exclude individuals who might be less adherent with CGM than the cohort that was studied.

Conclusions

Among adults with type 1 diabetes who use multiple daily insulin injections, the use of CGM compared with usual care resulted in a greater decrease in HbA_{1c} level during 24 weeks. Further research is needed to assess longer-term effectiveness, as well as clinical outcomes and adverse effects.

ARTICLE INFORMATION

Author Contributions: Dr Beck had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Beck, Riddlesworth.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Riddlesworth, Kollman.
Obtained funding: Price.
Administrative, technical, or material support: All authors.
Supervision: All authors.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dexcom Inc provided funding for the trial to each investigator's institution. Dr Beck reports receiving a study grant from Dexcom and that his institution received supplies for research from Dexcom and Abbott Diabetes Care for other studies. Dr Ahmann reports receiving grants for the study and consulting for Dexcom Inc; receiving grants for research support from Medtronic, Novo Nordisk, Lexicon, and Sanofi; consulting for Novo Nordisk, Sanofi, and AstraZeneca; and serving on advisory boards for Lilly, Janssen, and AstraZeneca. Dr Bergenstal reports receiving a study grant from Dexcom and NIH; reports serving on the advisory boards for and/or receiving study funding from Abbott Diabetes Care, AstraZeneca, Becton Dickinson, Boehringer Ingelheim, Calibra, Eli Lilly, Halozyme, Hygieia, Johnson & Johnson, Medtronic, Novo Nordisk, Roche, Sanofi, and Takeda; and reports holding stock in Merck. Ms Kruger reports holding stock in Dexcom. Dr McGill reports receiving grant funding from Novartis, Novo Nordisk, Lexicon, Bristol-Myers Squibb, and Dexcom; and consulting fees from Boehringer Ingelheim, Dexcom, Lilly, Merck, Novo Nordisk, Intarcia, Dynavax, Valeritas, Janssen, and Calibra. Dr Polonsky reports consulting for Dexcom. Dr Wolpert reports receiving grant funding from Abbott Diabetes Care. Dr Price is an employee of Dexcom, Inc and reports holding stock in the company. No other disclosures were reported.

DIAMOND Participating Clinical Sites: Personnel are listed as (I) for study investigator and (C) for study coordinator. Sites are listed in order by number of participants randomized in the study. The number of participants randomized is noted in parentheses, preceded by the site location and site name. *Joslin Diabetes Center*, Boston, MA (24): Elena Toschi (I); Howard Wolpert (I); Astrid Atakov-Castillo (C); Edvina Markovic (C). *Research Institute of Dallas*, Dallas, TX (17): Stephen Aronoff (I); Satanya Brooks (C); Gloria Martinez (C); Angela Mendez (C); Theresa Dunnam (C). *Iowa Diabetes & Endocrinology Research Center*, Des Moines, IA (13): Anuj Bhargava (I); Kathy Fitzgerald (I); Diana Wright (I); Teck Khoo (I); Pierre Theuma (I); Tara Herrold (C); Debra Thomsen (C). *International Diabetes Center – HealthPartners Institute*, Minneapolis, MN (13): Richard Bergenstal (I); Marcia Madden (I); Kathleen McCann (C); Arlene Monk (C), Char Ashanti (C). *Rocky Mountain Diabetes and Osteoporosis Center*, Idaho Falls, ID (12): David Liljenquist (I); Heather Judge (C); Jean Halford (C). *Henry Ford Medical Center Division of Endocrinology*, Detroit, MI (10): Davida Kruger (I); Shiri Levy (I); Arti Bhan (I); Terra Cushman (C); Heather Remtema (C). *Washington University in St Louis*, St Louis, MO (10): Janet McGill (I); Olivia Jordan (C); Carol Recklein (C). *Portland Diabetes & Endocrinology Center*, Portland, OR (8): Fawn Wolf (I); James Neifing (I); Jennifer Murdoch (I); Susan Staat (C); Tamara Mayfield (C). *Diabetes & Glandular Disease Clinic*, San Antonio, TX (7): Mark Kipnes (I); Stacie Haller (C); Terri Ryan (C). *Atlanta Diabetes Associates*, Atlanta, GA (5): Bruce Bode (I); Jennifer Boyd (I); Joseph Johnson (I); Nitin Rastogi (C); Katherine Lindmark (C). *Oregon Health & Science University*, Portland, OR (5): Andrew Ahmann (I); Bethany Klopfenstein (I); Farahnaz Joarder (I); Kathy Hanavan (I); Jessica Castle (I); Diana Aby-Daniel (I); Victoria Morimoto (I); Donald DeFrang (C); Bethany Wollam (C). *Amarillo Medical Specialists LLP*, Amarillo, TX (5): William Biggs (I);

Lorena Sandoval (C); Robin Eifert (C); Becky Cota (C). *Accent Clinical Trials*, Las Vegas, NV (4): Quang Nguyen (I); Alejandra Martinez (C); Cathy Duran (C). *Columbus Regional Research Institute, Endocrine Consultants PC*, Columbus, GA (4): Steven Leichter (I); Emily Evans (C). *East Coast Institute for Research LLC*, Jacksonville, FL (4): Scott Segel (I); David Sutton (I); Miguel Roura (I); Rebecca Rosenwasser (C); Jennifer McElveen (C); Emily Knisely (C); Anne Johnson (C). *Mountain Diabetes and Endocrine Center*, Asheville, NC (4): Wendy Lane (I); Stephen Weinrib (I); Kaitlin Ramsey (C); Lynley Farmer (C); Mindy Buford (C). *Diabetes & Endocrine Associates PC*, Omaha, NE (3): Sarah Konigsberg (I); Jennifer Rahman (C). *Physicians Research Associates LLC*, Lawrenceville, GA (2): A. Ola Odugbesan (I); Karla Wardell (C); Carolyn Paulus (C). *Consano Clinical Research*, San Antonio, TX (2): Michelle Welch (I); Daniel Katselnik (I); Greg Danet (C). *Marin Endocrine Care & Research Inc*, Greenbrae, CA (2): Linda Gaudiani (I); Natalie Woods (C); Jesse Cardozo (C). *Coastal Metabolic Research Centre*, Ventura, CA (1): Ronald Chochinov (I); Graciela Hernandez (I); Gabriel Garcia (C); Jessica Rios-Santiago (C). *Laureate Medical Group at Northside, LLC*, Atlanta, GA (1): Kate Wheeler (I); Jennifer Kane (C); Terri Eubanks (C). *Granger Medical Clinic*, West Valley, UT (1): Michelle Litchman (I); Kim Martin (C); Heather Holtman (C); Carrie Briscoe (C). *Advanced Research Institute*, Ogden, UT (1): Jack Wahlen (I); Jon Winkfield (I); Hilary Wahlen (C); Emily Hepworth (C); David Winkfield (C); Sue Owens (C).

Coordinating Center: Jaeb Center for Health Research, Tampa, FL: Katrina Ruedy; Roy W. Beck; Craig Kollman; Tonya Riddlesworth; Thomas Mouse. **Sponsor:** Dexcom Inc, San Diego, CA: David Price; Eileen Casal; Claudia Graham. **Quality-of-Life Collaborator:** University of California, San Diego, La Jolla, CA: William Polonsky.

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Role of the Funder/Sponsor: Dr Price, a Dexcom employee, participated in the steering committee, which was responsible for designing the study, writing the protocol, reviewing and approving the manuscript, and interpreting the data. Dexcom did not participate in collection, management, analysis, and interpretation of the data; or, except for the role of Dr Price as a coauthor, in the preparation or revision of the manuscript or in the decision to submit the manuscript for publication. Dexcom staff participated in onsite audit visits. All other monitoring was performed by staff of the Jaeb Center for Health Research.

Meeting Presentation: The trial results were presented at the American Diabetes Association meeting, June 12, 2016, New Orleans, Louisiana.

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