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REPLACE-BG: A Randomized Trial Comparing Continuous Glucose Monitoring With and Without Routine Blood Glucose Monitoring in Adults With Well-Controlled Type 1 Diabetes

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Diabetes Care 2017;40:538–545 | DOI: 10.2337/dc16-2482

OBJECTIVE

To determine whether the use of continuous glucose monitoring (CGM) without confirmatory blood glucose monitoring (BGM) measurements is as safe and effective as using CGM adjunctive to BGM in adults with well-controlled type 1 diabetes (T1D).

RESEARCH DESIGN AND METHODS

A randomized noninferiority clinical trial was conducted at 14 sites in the T1D Exchange Clinic Network. Participants were ≥18 years of age (mean 44 ± 14 years), had T1D for ≥1 year (mean duration 24 ± 12 years), used an insulin pump, and had an HbA_{1c} ≤9.0% (≤75 mmol/mL) (mean 7.0 ± 0.7% [53 ± 7.7 mmol/mol]); prestudy, 47% were CGM users. Participants were randomly assigned 2:1 to the CGM-only (*n* = 149) or CGM+BGM (*n* = 77) group. The primary outcome was time in range (70–180 mg/dL) over the 26-week trial, with a prespecified noninferiority limit of 7.5%.

RESULTS

CGM use averaged 6.7 ± 0.5 and 6.8 ± 0.4 days/week in the CGM-only and CGM+BGM groups, respectively, over the 26-week trial. BGM tests per day (including the two required daily for CGM calibration) averaged 2.8 ± 0.9 and 5.4 ± 1.4 in the two groups, respectively ($P < 0.001$). Mean time in 70–180 mg/dL was 63 ± 13% at both baseline and 26 weeks in the CGM-only group and 65 ± 13% and 65 ± 11% in the CGM+BGM group (adjusted difference 0%; one-sided 95% CI −2%). No severe hypoglycemic events occurred in the CGM-only group, and one occurred in the CGM+BGM group.

CONCLUSIONS

Use of CGM without regular use of confirmatory BGM is as safe and effective as using CGM with BGM in adults with well-controlled T1D at low risk for severe hypoglycemia.

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Received 21 November 2016 and accepted 3 January 2017.

Clinical trial reg. no. NCT02258373, clinicaltrials.gov.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc16-2482/-/DC1.

**A complete list of members of the REPLACE-BG Study Group can be found in the Appendix.*

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In the past decade, continuous glucose monitoring (CGM) has evolved as an essential part of diabetes management for many people with type 1 diabetes (T1D) (1–3). This technology offers advantages to traditional self-monitoring of blood glucose by providing real-time information on high- and low-glucose patterns, directions and rate of glucose changes, and hypo/hyperglycemia alerts. Several multicenter randomized controlled trials have demonstrated the benefits of CGM in reducing HbA_{1c} and hypoglycemia, particularly in adults with T1D (2,4–11).

Before December 2016, the CGM systems commercially available in the U.S. were approved by the U.S. Food and Drug Administration (FDA) for use only as adjunctive devices to information obtained from standard home blood glucose monitoring (BGM). Therefore, according to the labeling of these CGM systems, a BGM measurement was required to confirm the CGM sensor glucose concentration before making an insulin dosing decision. This regulatory decision presumably was made because the accuracy of the CGM systems was considered to be inadequate for dosing insulin without BGM confirmation. However, with each new generation of sensors, accuracy has improved (12–17), suggesting that CGM may now be sufficiently accurate to be safely implemented as a stand-alone tool for glucose monitoring and therapeutic decisions. In December 2016, the FDA expanded the indications for the Dexcom G5 sensor (Dexcom, San Diego, CA) to allow for replacement of fingerstick blood glucose testing for diabetes treatment decisions.

Even when the FDA labeling limited CGM use to an adjunct-only tool, many CGM users were making insulin dosing decisions by CGM alone. Among adult participants in the T1D Exchange Clinic registry, only 26% of 999 surveyed CGM users indicated that they always confirmed the CGM glucose concentration with a BGM measurement before administering an insulin bolus, and 41% indicated that they dosed insulin based on CGM alone more than one-half of the time (R.W.B., unpublished data). In another survey of 222 CGM users, 50% of respondents indicated that during the night, they would treat a CGM low-glucose alert without a confirmatory fingerstick glucose, and 34% would dose insulin for hyperglycemia without a confirmatory BGM measurement (18).

To date, no clinical trials have confirmed the safety and effectiveness of CGM used without BGM to make therapeutic decisions in people with T1D. We conducted a multicenter randomized noninferiority clinical trial to determine whether the routine use of CGM without BGM confirmation is as safe and effective as CGM used as an adjunct to BGM in adults with T1D.

RESEARCH DESIGN AND METHODS

The trial was conducted at 14 endocrinology practices in the U.S. of which 4 were community-based and 10 were academic centers. The protocol and Health Insurance Portability and Accountability Act–compliant informed consent forms were approved by institutional review boards. Written informed consent was obtained from each participant. The study is listed on ClinicalTrials.gov under identifier NCT02258373. An investigational device exemption was obtained from the FDA to conduct the trial. The full protocol is available at http://t1dexchange.org/pages/resources/clinic-network/studies and is summarized below.

Study Participants

Major eligibility criteria were age ≥18 years, T1D for ≥1 year being treated with an insulin pump for at least 3 months (and not currently using a low-glucose-suspend function), and point of care HbA_{1c} ≤9.0% (≤75 mmol/mol). Exclusion criteria included the occurrence of a severe hypoglycemic event resulting in seizure or loss of consciousness in the past 3 years or an event without seizure or loss of consciousness requiring the assistance of another individual in the past 12 months, significant hypoglycemia unawareness based on the Clarke Hypoglycemia Unawareness Survey (19), >10.0% of baseline CGM glucose concentrations <60 mg/dL, more than one episode of diabetic ketoacidosis (DKA) in the past year, history of seizures other than those due to hypoglycemia, current use of a threshold-suspend pump feature, myocardial infarction or stroke in the past 6 months, estimated glomerular filtration rate <30 mL/min/1.73 m^2, abnormal thyroid function, use of a systemic β-blocker, regular use of oral corticosteroids, initiation of a noninsulin drug for glucose control during the past 3 months, pregnancy, inpatient psychiatric treatment in the past 6 months, and presence of a contraindicated medical condition or medication, including ongoing use of acetaminophen. (Supplementary Table 1 provides a complete list of the inclusion and exclusion criteria.)

Synopsis of Study Design

A run-in phase of 2–10 weeks preceded the 6-month randomized trial. After successful completion of the run-in phase and after verification of eligibility from data entered on the study website, each participant was randomly assigned from a computer-generated sequence to the CGM-only or CGM+BGM group in a 2:1 ratio on the basis of a permuted block design with stratification by clinical site. Both groups used a Dexcom G4 Platinum CGM System with an enhanced algorithm (Software 505) (referred to as the study CGM), which measures glucose concentrations from interstitial fluid in the range of 40–400 mg/dL every 5 min for up to 7 days. The study BGM was the CONTOUR NEXT (Ascensia Diabetes Care US, Parsippany, NJ). The Abbott Precision Xtra (Abbott Diabetes Care, Alameda, CA) was used to measure blood ketone levels (β-hydroxybutyrate).

Run-in Phase

Informed consent was signed by 295 individuals, 19 of whom did not pass the screening assessment. The run-in phase, which was initiated by 276 participants, lasted for 2–10 weeks, depending on whether the participant was a CGM user at the time of study entry. There were two parts of the run-in phase of which participants completed various portions, depending on whether they were using CGM at study entry: *1*) Dexcom CGM system configured to record glucose concentrations not visible to the participant (referred to as a blinded CGM) for 14 days to collect baseline data and *2*) standard CGM for 2–8 weeks for CGM training. In both phases, the participant's willingness and ability to use the study CGM and BGM were assessed. Participants who used a Dexcom CGM for at least 21 of the 28 days before study enrollment skipped the blinded CGM phase and were required to have only 2 weeks of unblinded study CGM

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use. Participants who used a Medtronic CGM for at least 21 of the 28 days before enrollment skipped the blinded CGM phase and were required to have at least 4 weeks of unblinded study CGM use. All other participants completed the 14-day blinded phase and 8 weeks of unblinded CGM use. Successful completion of the blinded phase required study CGM wear on a minimum of 11 of 14 days and an average of three blood glucose measurements per day by the study BGM. Successful completion of the unblinded CGM phase required CGM use on ≥21 days during the past 28 days and an average of four or more BGM measurements on at least 90% of days; for participants whose run-in phase was shortened, the number of days of CGM use were reduced accordingly. Of 276 participants who entered the run-in phase, 50 did not enter the randomized trial for the following reasons: 24 did not meet the BGM criterion, 6 had >10% of CGM readings of <60 mg/dL, and 20 were withdrawn for a variety of other reasons (Supplementary Figs. 1 and 2).

Randomized Trial

After randomization, participants in both groups were instructed to calibrate the study CGM per Dexcom specifications and to use it daily. Both groups also were instructed to perform a BGM measurement when the fasting CGM glucose concentration was >300 mg/dL or when the CGM glucose concentration during the day was >300 mg/dL for 1 h. In both instances, if the BGM measurement confirmed that the glucose level was >300 mg/dL, the participant was instructed to perform a blood ketone measurement with the study ketone meter.

The CGM+BGM group was instructed to perform a BGM measurement with the study meter for CGM calibrations whenever an insulin bolus was administered, when treating or attempting to prevent hypoglycemia, and before going to bed. The CGM-only group was instructed to dose insulin and make management decisions on the basis of the CGM sensor glucose concentration, except in the following circumstances that required BGM testing: *1*) for 12 h after insertion of a new sensor, *2*) on a sick day (e.g., nausea, vomiting), *3*) for 4 h after taking acetaminophen, *4*) for symptoms suggestive of hypoglycemia but the CGM sensor glucose concentration was not hypoglycemic or dropping rapidly, *5*) for 20 min after treating a low CGM sensor glucose concentration if the CGM sensor glucose level had not begun to rise, *6*) before administering an insulin bolus when the CGM sensor glucose concentration was >250 mg/dL, and *7*) for a fasting CGM glucose >300 mg/dL or CGM glucose concentration during the day >300 mg/dL for 1 h. If a CGM calibration measurement coincided with a meal, the participant was instructed to base the meal bolus on the CGM sensor value and then perform a BGM measurement to calibrate the CGM.

Follow-up visits for both groups occurred at 3, 6, 13, 19, and 26 weeks, with a ±1-week window. Data were uploaded from the study CGM and BGM devices and the participant's personal insulin pump by using the Tidepool platform (http://tidepool.org). For insulin pumps that were unable to be uploaded to the Tidepool platform, the data were obtained by using Diasend (Chicago, IL) software. At each visit, compliance with CGM and BGM use was assessed, and additional training was given as needed. Glucose and pump data were reviewed to determine whether changes were indicated in diabetes management.

HbA_{1c} was measured at baseline, 13 weeks, and 26 weeks at the Northwest Lipid Research Laboratories, University of Washington, by using the Diabetes Control and Complications Trial standardized analyzer (Tosoh Bioscience, South San Francisco, CA). The following questionnaires were completed at baseline and 26 weeks: the Diabetes Technology Questionnaire, which consists of 30 questions about diabetes self-treatment practices and the impact of living with diabetes on the individual (20), and the Hypoglycemia Fear Survey, which consists of 23 questions about the effect of or worry about hypoglycemia on the individual with diabetes (21).

Study Outcomes

The primary outcome was CGM-measured time in the range of 70–180 mg/dL over the entire 26-week trial. To be included in the primary and secondary analyses of CGM metrics, the participant had to have at least 200 h of CGM data during the 26 weeks of the trial. Secondary outcomes included CGM measures of mean glucose, glycemic variability (coefficient of variation), hypoglycemia (time <70 mg/dL, 60 mg/dL, and 50 mg/dL; area above curve 70 mg/dL; and percentage of days with ≥20 consecutive min of glucose concentrations <60 mg/dL), hyperglycemia (time >180 mg/dL, 250 mg/dL, 300 mg/dL; area under the curve 180 mg/dL; and percentage of days with ≥20 consecutive min of glucose concentrations >300 mg/dL), change in HbA_{1c}, and proportion of participants with both no worsening of HbA_{1c} by >0.3% (3.3 mmol/mol) and no severe hypoglycemic event. Safety outcomes were severe hypoglycemia (defined as an event that required assistance from another person to administer carbohydrate, glucagon, or other resuscitative actions); DKA; hyperglycemia not meeting the definition of DKA for which emergency evaluation or treatment was obtained from a health care provider or blood ketone levels ≥0.6 or ≥1.0 mmol/L; and other occurrences meeting the regulatory definition of a serious adverse event.

Statistical Methods

Sample size was determined for a noninferiority limit of 7.5% for the difference between treatment groups in the time in the range of 70–180 mg/dL over the course of 26 weeks. For 90% power, a one-sided α of 0.05, and assuming an SD of 14% with correlation of 0.48 between the baseline and outcome time in range (based on data from the JDRF CGM randomized trial [8]), the required sample size was estimated to be 122. However, to better assess CGM-only safety, the sample size was selected to be 225 participants randomly assigned 2:1 to the CGM only group or CGM+BGM group.

Analyses followed the intention-to-treat principle. The primary analysis was a treatment group comparison of time in range (70–180 mg/dL) during the 26-week trial by using an ANCOVA model adjusted for baseline time in range and site as a random effect. Confounding was assessed by repeating the analysis with the inclusion of potential confounding variables as covariates. Prespecified exploratory analyses were conducted to assess for interaction between the treatment effect on the

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time in range (70–180 mg/dL) during the 26-week trial and baseline factors by including interaction terms in the ANCOVA models. For the remaining CGM outcomes, treatment group comparisons were made by using ANCOVA models based on van der Waerden score rankings if the metric was skewed and adjusted for the corresponding baseline value and clinical site as a random effect.

Change in HbA_{1c} from baseline was compared between groups by using an ANCOVA model adjusted for baseline HbA_{1c} and site as a random effect. The proportions of participants with both no worsening of HbA_{1c} by >0.3% (3.3 mmol/mol) and no severe hypoglycemic event were compared between treatment groups by using a logistic regression model adjusted for baseline HbA_{1c} and site as a random effect. The percentages of subjects with at least one blood ketone level ≥0.6 mmol/L (and ≥1.0 mmol/L) were compared between treatment groups by using a logistic regression model adjusted for site as a random effect. The mean scores on the Diabetes Technology Questionnaire were compared between treatment groups by using ANCOVA models adjusted for site as a random effect. For the Hypoglycemia Fear Survey, the overall total score, the total score for the low–blood glucose questions (1–10), and the total score for the worrying questions (11–23) were each compared between treatment groups by using an ANCOVA model adjusted for the baseline value and site as a random effect.

Analyses were conducted with SAS 9.4 software (SAS Institute, Cary, NC). All *P* values are two-sided.

Table 1—Participant characteristics at enrollment (*N* = 226 randomized)

	CGM-only group (*n* = 149)	CGM+BGM group (*n* = 77)
Age (years)	44 ± 14	45 ± 13
Range	19–78	25–69
Diabetes duration (years)	23 ± 12	25 ± 12
Range	2–64	4–58
BMI (kg/m^2)	27.7 ± 4.1	26.5 ± 4.9
Female sex	71 (48)	41 (53)
Race/ethnicity		
White non-Hispanic	139 (93)	68 (88)
Hispanic or Latino	4 (3)	5 (6)
Black/African American	4 (3)	1 (1)
Asian	2 (1)	2 (3)
Other/unknown	0 (0)	1 (1)
Annual household income ($)*		
<50,000	18 (16)	7 (12)
>50,000–100,000	39 (35)	17 (30)
≥100,000	54 (49)	33 (58)
Highest education*		
Less than bachelor's degree	35 (24)	12 (16)
Bachelor's degree	75 (51)	35 (48)
Postbachelor's degree	38 (26)	26 (36)
Insurance*		
Private	132 (89)	66 (88)
Other	15 (10)	7 (9)
None	2 (1)	2 (3)
CGM use before study		
Never used CGM	26 (17)	14 (18)
In past, but not current	54 (36)	25 (32)
Current Dexcom CGM user	49 (33)	28 (36)
Current Medtronic CGM user	20 (13)	10 (13)
Central laboratory HbA_{1c} value†		
<7.0% (53 mmol/mol)	59 (40)	39 (51)
7.0–8.0% (53–64 mmol/mol)	79 (53)	31 (40)
≥8.0% (64 mmol/mol)	11 (7)	7 (9)
% (mmol/mol)	7.1 ± 0.7 (54 ± 7.7)	7.0 ± 0.7 (53 ± 7.7)
Self-reported BGM testing times/day	5.2 ± 2.1	4.9 ± 1.9
Clarke Hypoglycemia Unawareness Survey total score		
0	100 (67)	53 (69)
1	34 (23)	14 (18)
2	15 (10)	10 (13)

Data are mean ± SD or *n* (%) unless otherwise indicated. *Missing data for CGM-only and CGM+BGM groups: annual income for 38 and 20, education for 1 and 4, and insurance for 0 and 2, respectively; †The local laboratory HbA_{1c} value was used for one participant in the CGM+BGM group whose central laboratory value was unavailable.

RESULTS

Between 22 May 2015 and 11 March 2016, 226 participants were assigned to either the CGM-only group (*n* = 149) or the CGM+BGM group (*n* = 77). Mean age was 44 ± 14 years (35 [15%] ≥60 years old), mean diabetes duration was 24 ± 12 years, and mean baseline HbA_{1c} was 7.0 ± 0.7% (53 ± 7.7 mmol/mol); 107 (47%) were CGM users, and 119 (53%) were not using CGM when enrolled. Participant characteristics according to treatment group are listed in Table 1.

One participant in the CGM-only group was determined after randomization to have been ineligible (percentage of time <60 mg/dL during blinded baseline CGM wear was >10%). Seven participants in the CGM-only group and two in the CGM+BGM group withdrew from the trial. Thus, the trial was completed by 142 (95%) of the CGM-only group participants and by 75 (97%) of the CGM+BGM group participants (Supplementary Figs. 2 and 3).

Among participants completing the trial, all in both groups were using CGM in month 6. CGM use averaged 6.7 ± 0.5 and 6.8 ± 0.4 days/week in the CGM-only and CGM+BGM groups, respectively, over the 26-week trial (Table 2), with 91% and 95% averaging ≥6 days/week. All participants in the CGM+BGM group and all but one in the CGM-only group averaged ≥5 days/week over the entire 26 weeks. Among participants ≥60 years old who completed the study, 95% in the CGM-only group (*n* = 21) and 92% in the CGM+BGM group (*n* = 13) averaged ≥6 days/week, and among participants <60 years old, 90% (*n* = 121) and 95% (*n* = 62) averaged ≥6 days/week. Among the

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Table 2—CGM use over the 26-week study period in participants completing the trial

CGM use (days/week)	CGM-only group (n = 142)	CGM+BGM group (n = 75)
Median (interquartile range)	7.0 (6.5–7.0)	7.0 (6.7–7.0)
Mean ± SD	6.7 ± 0.5	6.8 ± 0.4
3 to <4	1 (<1)	0
4 to <5	0	0
5 to <6	12 (8)	4 (5)
6 to <7	55 (39)	34 (45)
7	74 (52)	37 (49)
<6	13 (9)	4 (5)
≥6	129 (91)	71 (95)

Data are n (%) unless otherwise indicated.

completers of the trial, BGM tests per day from meter downloads (including the two required daily BGM tests) averaged 2.8 ± 0.9 in the CGM-only group and 5.4 ± 1.4 in the CGM+BGM group ($P < 0.001$).

Glycemic Control and Other Outcomes

Mean time spent in the range of 70–180 mg/dL was 63 ± 13% at both baseline and 26 weeks in the CGM-only group and 65 ± 13% and 65 ± 11%, respectively, in the CGM+BGM group (adjusted difference 0%; one-sided 95% CI −2%). Other CGM metrics of glucose control for mean glucose, hyperglycemia, hypoglycemia, and glycemic variability also showed little change from baseline to 26 weeks and no significant differences between groups (Table 3). Mean change in HbA_{1c} was 0.0% (0.0 mmol/mol) in each group (P = 0.41) (Table 3). Results were similar in subgroups based on age, duration, education, CGM use before study enrollment, baseline HbA_{1c}, and baseline time in

Table 3—Study outcomes

	CGM-only group		CGM+BGM group		
CGM results	Baseline (n = 149)	26-week study period (n = 148)*	Baseline (n = 77)	26-week study period (n = 76)*	P value†
Hours of CGM data	640 (620–650)	4,007 (3,709–4,166)	641 (619–651)	4,021 (3,725–4,136)	
Range	306–663	467–4,399	270–684	811–4,535	
% Time in range (70–180 mg/dL)	63 ± 13	63 ± 13	65 ± 13	65 ± 11	0.81
Mean glucose (mg/dL)	162 ± 22	162 ± 23	158 ± 22	158 ± 20	>0.99
Coefficient of variation (%)	36 (33–41)	37 (34–41)	37 (33–40)	37 (34–40)	0.58
Hypoglycemia‡					
% Time <70 mg/dL	2.9 (1.5–4.5)	3.0 (1.6–5.1)	3.6 (1.9–4.8)	3.7 (1.9–4.9)	0.95
% Time <60 mg/dL	1.1 (0.6–1.9)	1.3 (0.5–2.4)	1.4 (0.6–2.3)	1.6 (0.6–2.2)	0.57
% Time <50 mg/dL	0.3 (0.1–0.6)	0.4 (0.2–0.8)	0.4 (0.2–0.7)	0.5 (0.2–0.8)	0.75
Area above curve 70 mg/dL	0.3 (0.2–0.5)	0.3 (0.1–0.6)	0.4 (0.2–0.6)	0.4 (0.2–0.5)	0.76
% Days with ≥20 consecutive min glucose values <60 mg/dL	25 (15–43)	28 (13–42)	33 (15–43)	32 (16–46)	0.68
Hyperglycemia‡					
% Time >180 mg/dL	33 (25–43)	35 (25–41)	31 (22–40)	31 (24–38)	0.88
% Time >250 mg/dL	8 (4–15)	9 (5–13)	7 (3–11)	7 (4–11)	0.65
% Time >300 mg/dL	2 (1–5)	2 (1–4)	2 (1–4)	2 (1–3)	0.72
Area under curve 180 mg/dL	17 (10–25)	17 (10–23)	14 (8–22)	15 (9–21)	0.90
% Days with ≥20 consecutive min of glucose values >300 mg/dL	25 (12–48)	27 (14–40)	20 (8–36)	20 (10–37)	0.72
HbA_{1c} results	Baseline (n = 149)	Week 26 visit (n = 142)	Baseline (n = 77)	Week 26 visit (n = 75)	P value†
HbA_{1c}					
%	7.1 ± 0.7	7.1 ± 0.7	7.0 ± 0.7	7.0 ± 0.6	
mmol/mol	54 ± 7.7	54 ± 7.7	53 ± 7.7	53 ± 6.6	
Change in HbA_{1c} from baseline					0.41
%		0.0 ± 0.5		0.0 ± 0.5	
mmol/mol		0.0 ± 5.5		0.0 ± 5.5	
No worsening of HbA_{1c} by >0.3% (3.3 mmol/mol) and no severe hypoglycemic event		115 (81)		54 (72)	0.15

Data are median (interquartile range), mean ± SD, or n (%) unless otherwise indicated. *One participant in the CGM-only group and one in the CGM+BGM group never came in for a follow-up visit and therefore had no CGM data; †two-sided P value for the CGM metrics and change in HbA_{1c} are from ANCOVA models adjusted for the corresponding baseline value and site as a random effect. Because of the skewed distributions for the CGM coefficient of variation, as well as the CGM hypoglycemia and hyperglycemia metrics, these models were based on van der Waerden score rankings. The P value for the HbA_{1c}/severe hypoglycemia combined outcome is from a logistic regression model adjusted for baseline HbA_{1c} and site as a random effect. Results were similar for the % time in range when also adjusting for education; ‡1% time equals 14.4 min/day.

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Table 4—Percent time in range (70–180 mg/dL) by group according to baseline factors

	CGM-only group (n = 148)*			CGM+BGM group (n = 76)*			
	n	Baseline	26-Week study period	n	Baseline	26-Week study period	P value for interaction†
Age							0.08
<50 years	94	60 ± 13	60 ± 13	45	65 ± 13	65 ± 13	
≥50 years	54	68 ± 12	67 ± 12	31	64 ± 11	65 ± 9	
Diabetes duration							0.74
<25 years	87	62 ± 13	63 ± 12	41	67 ± 12	66 ± 11	
≥25 years	61	63 ± 14	63 ± 14	35	62 ± 13	63 ± 12	
Education‡							0.71
Less than bachelor's degree	34	59 ± 14	59 ± 13	12	65 ± 9	63 ± 11	
Bachelor's degree or higher	113	64 ± 13	64 ± 13	61	66 ± 13	65 ± 11	
CGM use before study							
Never used	25	64 ± 12	65 ± 10	14	65 ± 10	63 ± 13	0.26
In past, but not current	54	58 ± 13	57 ± 14	24	62 ± 14	63 ± 13	
Current Dexcom user	49	67 ± 12	67 ± 12	28	69 ± 12	68 ± 10	
Current Medtronic user	20	64 ± 13	63 ± 11	10	59 ± 8	61 ± 7	
Baseline HbA_{1c}							0.20
<7.5% (58 mmol/mol)	108	67 ± 11	66 ± 11	60	69 ± 10	68 ± 9	
≥7.5% (58 mmol/mol)	40	51 ± 10	52 ± 12	16	50 ± 9	52 ± 10	
Baseline time in range (70–180 mg/dL)							0.39
<60%	61	50 ± 8	53 ± 11	24	51 ± 7	54 ± 9	
≥60%	87	72 ± 8	69 ± 10	52	72 ± 8	69 ± 9	

Data are mean ± SD unless otherwise noted. *One participant in the CGM-only group and one in the CGM+BGM group never came in for a follow-up visit and therefore had no CGM data; †P values obtained by including an interaction term in each ANCOVA model adjusted for baseline value and site as a random effect. Continuous variable used in the models for age, duration, HbA_{1c}, and baseline time in range; ‡education missing for one participant in the CGM-only group and three participants in the CGM+BGM group.

range (Table 4). CGM and HbA_{1c} results also were similar between groups in the subset ≥60 years old (Supplementary Table 2).

Severe Hypoglycemia and Other Adverse Events

No severe hypoglycemic events occurred in the CGM-only group, and one occurred in the CGM+BGM group. No occurrences of DKA occurred in either group. Other serious adverse events, unrelated to the study intervention, occurred in four (3%) participants in the CGM-only group and three (4%) in the CGM+BGM group (Supplementary Table 3). A blood ketone level ≥0.6 mmol/L occurred at least once in 48 (32%) participants in the CGM-only group and 26 (34%) in the CGM+BGM group (P = 0.79); the ketone level was ≥1.0 mmol/L at least once in 27 (18%) and 15 (19%) participants, respectively (P = 0.84).

Questionnaires

Mean scores on the Diabetes Technology Questionnaire were 3.6 ± 0.6 in the CGM-only group and 3.8 ± 0.6 in the CGM+BGM group at baseline and 3.6 ± 0.6 in each group at 26 weeks (P = 0.58). There also was no significant difference between groups on the section of the questionnaire inquiring about change from prestudy (P = 0.28) (Supplementary Table 4). On the Hypoglycemia Fear Survey, total scores were 29 ± 11 in the CGM-only group and 28 ± 9 in the CGM+BGM group at baseline and 32 ± 11 and 31 ± 11 at 26 weeks, respectively (P = 0.88) (Supplementary Table 5).

CONCLUSIONS

This multicenter randomized trial was conducted to determine whether using CGM alone to make insulin dosing decisions is as safe and effective as using CGM as an adjunct to BGM. For the primary outcome of CGM-measured time in the glucose range of 70–180 mg/dL, use of CGM alone was shown to be noninferior to using CGM and BGM together. For this metric and all other efficacy outcomes for CGM-measured hyperglycemia, hypoglycemia, and glucose variability, results in the CGM-only and CGM+BGM groups were virtually identical as were the HbA_{1c} results. Scores obtained from the Diabetes Technology Questionnaire and Hypoglycemia Fear Survey also were similar in the two groups. From a safety perspective, no DKA events or severe hypoglycemic episodes occurred in the CGM-only group. Comparable results were found in participants who were experienced CGM users at study entry, in those who were CGM naive, in older versus younger participants, and in those with higher and lower education levels. In both treatment groups, mean time in range was similar at baseline and during follow-up, likely reflecting the excellent glycemic control of most participants entering the trial.

To our knowledge, this randomized trial is the first to assess the effectiveness and safety of insulin dosing by using CGM alone in adults with T1D. In addition to randomization and multiple center participation, the strengths of this study include a high degree of participant retention, CGM use, and treatment group adherence. Notably, there was good separation between the treatment groups in the number of BGM tests per day, particularly when recognizing that two of the BGM measurements per day were required for CGM calibration and that according to the protocol, the calibrations were performed at times such

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that they would not influence insulin bolusing.

The major limitation of the trial relates to the generalizability of the results based on the participant inclusion and exclusion criteria. The trial cohort included adults with T1D who used an insulin pump and were well controlled (mean HbA_{1c} 7.0% [53 mmol/mol]) and likely to adhere to the study protocol and excluded individuals with significant hypoglycemia unawareness or a substantial amount of CGM-measured hypoglycemia. Although the trial only included pump users to be able to document when an insulin bolus was given, it seems reasonable to apply the results to individuals who use multiple daily injections of insulin who otherwise fit the profile of the study participants because the impact of sensor inaccuracy in determining the amount of a bolus should be similar in pump users and injection users (8,22). The results of this study support the need for future studies to assess the safety of CGM used without routine BGM testing in youth and in less-compliant adults than those included in this study, such as individuals with higher HbA_{1c} levels, who perform BGM testing fewer than four times a day, and with hypoglycemia unawareness (23).

The application of this trial's results to clinical practice can benefit people with T1D by reducing their burden of multiple daily fingersticks when using CGM and can enhance the cost-effectiveness of CGM therapy by reducing the number of daily BGM test strips. Furthermore, the demonstration that insulin dosing based on CGM alone is safe has applicability to assessing risk involved with artificial pancreas systems that automate insulin delivery based on CGM sensor glucose measurements.

In conclusion, in adults with well-controlled T1D meeting the eligibility criteria for this trial, use of CGM without regular use of confirmatory BGM is as safe and effective as using CGM with a confirmatory BGM measurement for insulin dosing.

Funding. Funding was provided by the Leona M. and Harry B. Helmsley Charitable Trust. Dexcom provided the CGM systems used in the trial.

Duality of Interest. G.A. has served on a scientific advisory board for Diasend and Novo Nordisk and received consultancy payments from Dexcom. G.A.'s employer has received research support from Novo Nordisk and Bristol-Myers Squibb/AstraZeneca with no personal income to G.A. D.F.K. has served on a scientific advisory board for Novo Nordisk, Abbott, Eli Lilly, Sanofi, and Janssen. D.F.K. has received speaker fees from Janssen, Valeritas, AstraZeneca, Eli Lilly, Novo Nordisk, and Dexcom. D.F.K.'s employer has received research support from AstraZeneca, Eli Lilly, Novo Nordisk, Dexcom, and Lexicon. D.F.K. holds stock in Dexcom. A.L.P. has served on a scientific advisory board and consulted for Abbott, Becton Dickinson, Bigfoot Biomedical, Boehringer Ingelheim, Eli Lilly, AstraZeneca, Intarcia, Janssen, Lexicon, Medtronic-MiniMed, Merck, Novo Nordisk, Omada Health, OptumRx, Sanofi, and UnitedHealthcare and received editorial fees from Medscape. A.L.P.'s employer has received research support from Dexcom. I.H. has received consultancy fees from Abbott Diabetes Care, Roche, and Intarcia. R.M.B. has served on a scientific advisory board and received consultancy fees from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb/AstraZeneca, Dexcom, Eli Lilly, Halozyme, Johnson & Johnson, Medtronic, Novo Nordisk, Roche, Sanofi, and Takeda. R.M.B.'s employer has contracts with the following companies for his services with no personal income to R.M.B.: Abbott, Boehringer Ingelheim, Bristol-Myers Squibb/AstraZeneca, Dexcom, Eli Lilly, Halozyme, Johnson & Johnson, Medtronic, Novo Nordisk, Roche, Sanofi, Takeda, and Merck. R.M.B. has inherited Merck stock. A.J.A. has received consultancy fees from Dexcom, Lexicon, Medtronic, and Novo Nordisk. A.J.A.'s nonprofit employer has received research support from Dexcom, Lexicon, Medtronic, and Novo Nordisk with no personal compensation to A.J.A. V.N.S. has received speaking fees from Dexcom. A.P.-T. has served on a scientific advisory board and received consultancy fees from Boehringer Ingelheim, Bristol-Myers Squibb/AstraZeneca, Dexcom, Eli Lilly, Halozyme, Lexicon, Merck, Medtronic, Mylan, Novo Nordisk, and Sanofi. A.P.-T.'s employer has contracts with the following companies for her services with no personal income to A.P.T.: Boehringer Ingelheim, Bristol-Myers Squibb/AstraZeneca, Dexcom, Eli Lilly, Halozyme, Lexicon, Merck, Medtronic, Mylan, Novo Nordisk, and Sanofi. H.R. has served on a scientific advisory board for Elli Lilly, Merck, Novartis, and Novo Nordisk. H.R. received research grant support from Bristol-Myers Squibb, Daiichi Sankyo, and Lexicon. H.R.'s employer has received research support from Medtronic and Merck. A.B. has served on a scientific advisory board for Abbott and Janssen and received speaker fees from AstraZeneca and Sanofi. A.B. has received research grant support from Novo Nordisk, Eli Lilly, AbbVie, MannKind Corporation, Orexigen Therapeutics, Inc., Sanofi, Jaeb, Merck, GlaxoSmithKline, University of Oxford, Bristol-Myers Squibb, Boehringer Ingelheim, Duke University Medical Center, Medtronic, AstraZeneca, and Halozyme. R.W.B.'s employer has received research support and study supplies from Dexcom and Abbott Diabetes Care. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. G.A., K.J.R., and R.W.B. contributed to the data interpretation and wrote and edited the manuscript. T.D.R. performed statistical analyses and wrote and edited the manuscript. D.F.K., A.L.P., I.H., R.M.B., E.T., A.J.A., V.N.S., M.R.R., B.W.B., A.P.-T., R.P.-B., H.R., E.E., A.B., and C.K. contributed to the data interpretation and reviewed and edited the manuscript. R.W.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Appendix

Participating REPLACE-BG Study Group sites from the T1D Exchange Clinic Network with the principal investigator (PI), co-investigator (I), and coordinator (C) in order by the number of participants randomized per site as of 4 November 2016. Detroit, Michigan, Henry Ford Health System (*n* = 27), Davida Kruger (PI), Terra Cushman (C); Los Angeles, California, University of Southern California Community Diabetes Initiatives (*n* = 19), Anne Peters (PI), Mark Harmel (C); Seattle, Washington, University of Washington Diabetes Care Center (*n* = 19), Irl Hirsch (PI), Dori Khakpour (C); Minneapolis, Minnesota, Park Nicollet International Diabetes Center Adult Endocrinology (*n* = 18), Richard Bergenstal (PI), Beth Olson (C); Chicago, Illinois, Northwestern University (*n* = 18), Grazia Aleppo (PI), Elaine Massaro (C), Teresa Pollack (C); Boston, Massachusetts, Joslin Diabetes Center Adult Diabetes (*n* = 16), Elena Toschi (PI), Astrid Atakov-Castillo (C); Portland, Oregon, Harold Schnitzer Diabetes Health Center at Oregon Health & Science University (*n* = 15), Andrew Ahmann (PI), Kristin Jahnke (C); Aurora, Colorado, University of Colorado/Denver, Barbara Davis Center for Childhood Diabetes (*n* = 15), Viral N. Shah (PI), Terra Thompson (C); Philadelphia, Pennsylvania, University of Pennsylvania Perelman School of Medicine Penn Rodebaugh Diabetes Center (*n* = 15), Michael Rickels (PI), Amy Peleckis (I), Shannon O'Brien (I), Cornelia Dalton-Bakes (C); Atlanta, Georgia, Atlanta Diabetes Associates (*n* = 14), Bruce Bode (PI), Siana Tyler (C); San Diego, California, Scripps Whittier Diabetes Institute (*n* = 14), Athena Philis-Tsimikas (PI), Rosario Rosal (C); Ann Arbor, Michigan, University of Michigan (*n* = 13), Rodica Pop-Busui (PI), Cynthia Plunkett (C); Tampa, Florida, University of South Florida Diabetes Center (*n* = 12), Henry Rodriguez (PI), Emily Eyth (C); Des Moines, Iowa, Iowa Diabetes and Endocrinology Research Center (*n* = 8), Anuj Bhargava (PI), Lisa Borg (C).

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