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Effect of Continuous Glucose Monitoring on Hypoglycemia in Older Adults With Type 1 Diabetes
A Randomized Clinical Trial

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IMPORTANCE Continuous glucose monitoring (CGM) provides real-time assessment of glucose levels and may be beneficial in reducing hypoglycemia in older adults with type 1 diabetes.

OBJECTIVE To determine whether CGM is effective in reducing hypoglycemia compared with standard blood glucose monitoring (BGM) in older adults with type 1 diabetes.

DESIGN, SETTING, AND PARTICIPANTS Randomized clinical trial conducted at 22 endocrinology practices in the United States among 203 adults at least 60 years of age with type 1 diabetes.

INTERVENTIONS Participants were randomly assigned in a 1:1 ratio to use CGM (n = 103) or standard BGM (n = 100).

MAIN OUTCOMES AND MEASURES The primary outcome was CGM-measured percentage of time that sensor glucose values were less than 70 mg/dL during 6 months of follow-up. There were 31 prespecified secondary outcomes, including additional CGM metrics for hypoglycemia, hyperglycemia, and glucose control; hemoglobin A_{1c} (HbA_{1c}); and cognition and patient-reported outcomes, with adjustment for multiple comparisons to control for false-discovery rate.

RESULTS Of the 203 participants (median age, 68 [interquartile range {IQR}, 65-71] years; median type 1 diabetes duration, 36 [IQR, 25-48] years; 52% female; 53% insulin pump use; mean HbA_{1c}, 7.5% [SD, 0.9%]), 83% used CGM at least 6 days per week during month 6. Median time with glucose levels less than 70 mg/dL was 5.1% (73 minutes per day) at baseline and 2.7% (39 minutes per day) during follow-up in the CGM group vs 4.7% (68 minutes per day) and 4.9% (70 minutes per day), respectively, in the standard BGM group (adjusted treatment difference, −1.9% (−27 minutes per day); 95% CI, −2.8% to −1.1% [−40 to −16 minutes per day]; P <.001). Of the 31 prespecified secondary end points, there were statistically significant differences for all 9 CGM metrics, 6 of 7 HbA_{1c} outcomes, and none of the 15 cognitive and patient-reported outcomes. Mean HbA_{1c} decreased in the CGM group compared with the standard BGM group (adjusted group difference, −0.3%; 95% CI, −0.4% to −0.1%; P <.001). The most commonly reported adverse events using CGM and standard BGM, respectively, were severe hypoglycemia (1 and 10), fractures (5 and 1), falls (4 and 3), and emergency department visits (6 and 8).

CONCLUSIONS AND RELEVANCE Among adults aged 60 years or older with type 1 diabetes, continuous glucose monitoring compared with standard blood glucose monitoring resulted in a small but statistically significant improvement in hypoglycemia over 6 months. Further research is needed to understand the long-term clinical benefit.

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The population of older adults with type 1 diabetes is increasing because of advancements in diabetes care leading to longer life expectancy.[1] Older adults, particularly those with long-standing type 1 diabetes, are prone to hypoglycemia and hypoglycemia unawareness. In addition to acute changes in mental status, severe hypoglycemia can cause seizures, falls leading to fractures, cognitive impairment, and cardiac arrhythmias resulting in sudden death.[2,3] Consequently, treatment guidelines for older adults with type 1 diabetes emphasize minimizing hypoglycemia by having glucose levels less than 70 mg/dL less than 1% of the time, and allow for less stringent hemoglobin A_{1c} (HbA_{1c}) targets.[4] Despite this, severe hypoglycemia remains a common complication.[5]

Continuous glucose monitoring (CGM) measures interstitial glucose concentrations, allowing for near real-time assessment of glucose levels and trends. Continuous glucose monitors can provide alerts when glucose levels exceed low or high thresholds or are changing rapidly, allowing patients to adjust insulin dosing or consume carbohydrates to minimize the risk of hypoglycemia. The US Food and Drug Administration now allows certain continuous glucose monitors to be used in place of standard capillary blood glucose monitoring (BGM) for diabetes treatment decisions.[6] Several randomized trials have demonstrated the efficacy of CGM in adults with type 1 diabetes.[7-10] However, none have included a substantial number of older individuals,[7,11-14] and most have excluded patients with recent severe hypoglycemia or hypoglycemia unawareness. Thus, the benefits of CGM found in prior studies cannot be generalized to older adults with type 1 diabetes, who are at high risk of hypoglycemia and its complications. This trial was conducted with the primary goal of assessing whether CGM was effective in reducing hypoglycemia compared with standard BGM in older adults with type 1 diabetes.

Key Points

Question Is continuous glucose monitoring effective in reducing hypoglycemia compared with standard blood glucose monitoring in older adults with type 1 diabetes?

Findings In this randomized clinical trial that included 203 adults aged 60 years or older with type 1 diabetes, treatment for 6 months with continuous glucose monitoring compared with standard blood glucose monitoring resulted in a significantly lower percentage of glucose values less than 70 mg/dL (adjusted difference, 1.9%).

Meaning Among older adults with type 1 diabetes, continuous glucose monitoring resulted in a small but statistically significant improvement in hypoglycemia over 6 months.

Methods

Trial Design and Oversight

This randomized clinical trial was conducted at 22 endocrinology practices in the United States. The protocol and informed consent forms were approved by institutional review boards. Written informed consent was obtained from each participant prior to enrollment. An independent data and safety monitoring board provided trial oversight reviewing unmasked safety data during the conduct of the study. The final protocol and statistical analysis plan are available in Supplement 1.

Participants

Major eligibility criteria included a clinical diagnosis of type 1 diabetes, age of at least 60 years, no use of real-time CGM in the 3 months prior to enrollment, and an HbA_{1c} of less than 10.0%. Participants were required to be using either an insulin pump or multiple daily insulin injections, and an enrollment target was set to include at least 40% of participants using each mode of insulin delivery. A complete list of the inclusion and exclusion criteria is available in eTable 1 in Supplement 2.

Each participant completed a 2-week prerandomization period using a masked CGM on which sensor glucose concentrations were not visible to participants. To be eligible for randomization, participants were required to have at least 10 of 14 days (240 hours) of data available with an average of at least 1.8 calibrations per day using the study-provided blood glucose meter (Bayer Contour Next USB; Ascensia Diabetes Care).

Intervention and Procedures

Eligible participants were randomly assigned in a 1:1 ratio via a computer-generated sequence to use of CGM (Dexcom G5, Dexcom) with a study blood glucose meter as needed or to use the study blood glucose meter without CGM, using a permuted block design (block sizes of 2 and 4), stratified by site.

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 at their discretion. The standard BGM group was asked to perform home BGM at least 4 times daily. The CGM group was instructed to use the continuous glucose monitor daily, to calibrate the monitor twice daily, and to set the low alert (recommended to be set at 70 mg/dL). The continuous glucose monitor includes an urgent low alert at 55 mg/dL that cannot be turned off. General guidelines were provided to participants about using CGM. Additional instructions were provided on using CGM trend arrows to adjust insulin dosing based on guidelines specific to an at-risk older adult population (eAppendix in Supplement 2).[15]

Both groups had clinic visits 4, 8, 16, and 26 weeks following randomization. In addition, the standard BGM group was seen in clinic at weeks 7, 15, and 25 for placement of a masked CGM (same algorithm as the CGM group's real-time CGM), which was worn for 1 week.

Hemoglobin A_{1c} was measured at randomization, 16 weeks, and 26 weeks at the University of Minnesota using the Tosoh A_{1c} 2.2 Plus Glycohemoglobin Analyzer. Participants completed patient-reported outcome and cognitive assessments at the randomization and 26-week clinic visits.

Data Collection and Outcomes

Participant sociodemographic data, including fixed categories for race/ethnicity, were collected from medical records and

confirmed by participants to better describe the study cohort and to address generalizability.

The primary outcome was CGM-measured percentage of time spent with a glucose value less than 70 mg/dL during follow-up using data pooled from approximately 7 days prior to the 8, 16, and 26-week visits. (To convert glucose values to millimoles per liter, multiply by 0.0555.) Prespecified secondary hypoglycemia outcomes included percentage of time with a glucose value less than 54 mg/dL, percentage of time with a glucose value less than 60 mg/dL, and rate of hypoglycemia events per week (with an event defined as 15 consecutive minutes with a sensor glucose value <54 mg/dL). Prespecified secondary hyperglycemia outcomes included percentages of time with glucose values greater than 180 mg/dL, greater than 250 mg/dL, and greater than 300 mg/dL. Prespecified glycemic control outcomes included percentage of time with glucose values in the range of 70 to 180 mg/dL, mean glucose, and glycemic variability (coefficient of variation, defined as ratio of the standard deviation to the mean). Prespecified secondary HbA_{1c} outcomes included mean change from baseline, percentage with HbA_{1c} less than 7.0%, percentage with HbA_{1c} less than 7.5%, percentage with relative reduction in HbA_{1c} of at least 10%, percentage with absolute reduction in HbA_{1c} of at least 0.5%, percentage with absolute reduction in HbA_{1c} of at least 1%, and percentage with absolute reduction in HbA_{1c} of at least 0.5% or HbA_{1c} less than 7.0%.

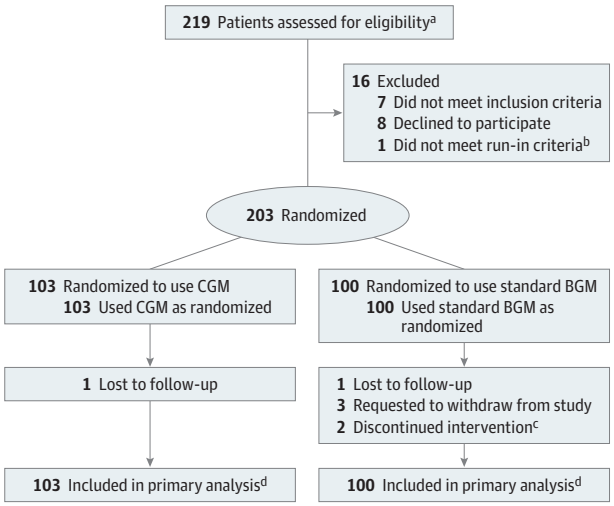
Additional prespecified secondary participant-reported outcomes included general quality of life (PROMIS Global Health Short Form; National Institutes of Health [NIH] Toolbox [http://www.nihtoolbox.org] Emotion Battery), hypoglycemia awareness (Clarke Survey[16]), hypoglycemia fear (Hypoglycemia Fear Survey II-Worry subscale[17]), and diabetes distress (Type 1 Diabetes Distress Scale[18]). Descriptions of these outcomes, scoring, and clinically relevant change (when known) are shown in eTable 2 in Supplement 2. Cognitive performance also was assessed at baseline and 26 weeks using the NIH Toolbox Cognition Battery; specifics on this measure and training of study personnel are also described in eTable 2.

Reportable adverse events included severe hypoglycemia (defined as an event that required assistance from another person because of altered consciousness), hyperglycemia resulting in treatment at a health care facility or that involved diabetic ketoacidosis (as defined by the Diabetes Control and Complications Trial[19]), device-related events with potential effect on participant safety, falls, fractures, emergency department visits, and all serious adverse events regardless of causality.

Statistical Analysis

A sample size of 200 participants was determined to have at least 90% power to detect a reduction in percentage of time spent with a glucose value less than 70 mg/dL for the overall cohort and a minimum of 80% power for an a priori subgroup analysis by insulin delivery method, assuming a population relative treatment reduction of 50% from a percentage of time spent with a glucose value less than 70 mg/dL of 6%, a standard deviation of 5%, a type I error rate (2-sided) of 5%, and 10% missing follow-up data.

Figure 1. Flow of Participants in the Wireless Innovation for Seniors With Diabetes Mellitus (WISDM) Study



Enrollment took place from September 2017 to May 2018, and study follow-up for the randomized trial continued through December 2018. BGM indicates blood glucose monitoring; CGM, continuous glucose monitoring.

[a] Information on patients screened but not enrolled was not collected.

[b] One patient was excluded for having both a history of at least 1 severe hypoglycemia event in the past 6 months and spending more than 10% of time with CGM glucose levels less than 54 mg/dL during the blinded prerandomization phase.

[c] Two participants in the standard BGM group initiated real-time CGM before completing the 26-week visit.

[d] One participant in the CGM group and 6 participants in the standard BGM group were missing CGM data at follow-up. Missing data were handled using direct likelihood. Baseline data for these participants were included in the model.

Participants were analyzed according to their randomization group, and all participants were included in the primary analysis. For the primary analysis, the difference in percentage of time spent with a glucose value less than 70 mg/dL at follow-up between the 2 treatment groups was assessed in a longitudinal linear regression model including baseline and follow-up data and clinical center as a random effect. Missing data were handled by direct likelihood, which maximizes the likelihood function integrated over possible values of the missing data.[20] The analyses for the secondary continuous outcomes paralleled those for the primary outcome. Binary HbA_{1c} outcomes were compared between treatment groups using available cases only in a logistic regression model adjusting for baseline HbA_{1c} and clinical center as a random effect.

Modification of the treatment effect by baseline variables was assessed by including an interaction term in the primary model. Sensitivity analyses were performed as described in the statistical analysis plan (adjustment for potential confounding of baseline imbalances and including only participants meeting per-protocol criteria) (Supplement 1).

Analysis of all outcomes was repeated separately among insulin pump and injection users and paralleled the overall

Table 1. Baseline Characteristics of Study Participants

Characteristics	Continuous glucose monitoring (n = 103)	Blood glucose monitoring (n = 100)
Age, y		
No. (%)		
<70	70 (68)	67 (67)
≥70	33 (32)	33 (33)
Median (IQR) [range]	68 (65-72) [60-83]	67 (64-71) [60-86]
Diabetes duration, median (IQR) [range], y	39 (24-49) [0.9-64.7]	36 (25-47) [0.2-70.7]
Age at diagnosis, median (IQR), y	30 (19-47)	31 (19-43)
Sex, No. (%)		
Female	61 (59)	44 (44)
Male	42 (41)	56 (56)
Race/ethnicity, No. (%)	n = 101	n = 100
White, non-Hispanic	93 (92)	94 (94)
Black, non-Hispanic	4 (4)	2 (2)
Hispanic or Latino	1 (<1)	4 (4)
Asian	1 (<1)	0
>1 Race	2 (2)	0
Annual household income, $, No. (%)	n = 70	n = 72
<50 000	14 (20)	25 (35)
50 000 to <100 000	34 (49)	27 (38)
≥100 000	22 (31)	20 (28)
Highest education, No. (%)	n = 101	n = 100
Less than a bachelor's degree	31 (31)	46 (46)
Bachelor's degree	35 (35)	28 (28)
Graduate or professional degree	35 (35)	26 (26)
Health insurance, No. (%)		
Private	30 (29)	27 (27)
Private and Medicare	37 (36)	33 (33)
Medicare/other	36 (35)	40 (40)
Continuous glucose monitor use, No. (%)		
Past but not current	53 (51)	40 (40)
Never	50 (49)	60 (60)
Insulin pump use, No. (%)	58 (56)	50 (50)
Screening HbA_{1c}, mean (SD) [range], %[a]	7.6 (1.0) [5.4-10.0]	7.5 (0.9) [5.7-9.8]
HbA_{1c} at randomization, %[b]	n = 100	n = 97
No. (%)		
<8.0	72 (72)	71 (73)
≥8.0	28 (28)	26 (27)
Mean (SD) [range]	7.6 (0.9) [5.6-10.8]	7.5 (0.8) [5.7-9.6]
Detectable C-peptide, No. (%)[c]	24 (23)	22 (22)
Total daily insulin doses per kg, median (IQR)	0.5 (0.4-0.6) [n = 97]	0.5 (0.4-0.7) [n = 95]
≥1 Severe hypoglycemia event in the past 12 mo, No. (%)[d]	20 (19)	10 (10)
≥1 Diabetic ketoacidosis event in the past 12 mo, No. (%)[e]	5 (5)	3 (3)
Functional Activities Questionnaire score, No. (%)[f]	n = 100	n = 96
<8	98 (98)	86 (90)
≥8	2 (2)	10 (10)
NIH Toolbox Cognition Battery age-corrected fluid composite score, mean (SD) [range][g]	96 (13) [67-122] [n = 100]	94 (14) [64-137] [n = 97]
Cognition status measured by NIH Toolbox Cognition Battery, No. (%)[g]	n = 100	n = 97
No cognitive impairment	84 (84)	81 (84)
Clinically significant cognitive impairment	16 (16)	16 (16)

(continued)

Table 1. Baseline Characteristics of Study Participants (continued)

Characteristics	Continuous glucose monitoring (n = 103)	Blood glucose monitoring (n = 100)
Reduced hypoglycemia awareness, No. (%)[h]	n = 100	n = 99
Yes (Clarke Survey score ≥4)	32 (32)	29 (29)
No (Clarke Survey score ≤3)	68 (68)	70 (71)
Wearing hearing aids regularly, No. (%)	8 (8)	12 (12)
Near vision card (corrected) last line read worse than 20/40, No. (%)	10 (10)	12 (12)

Abbreviations: HbA_{1c}, hemoglobin A_{1c}; IQR, interquartile range; NIH, National Institutes of Health.

[a] Screening HbA_{1c} measured by point-of-care device or at local laboratory and used to determine eligibility.

[b] Randomization HbA_{1c} measured by central laboratory.

[c] Random C-peptide measured by central laboratory. The detection limit of the assay was 0.003 nmol/L. The presence of detectable C-peptide is an indicator that the pancreas is capable of at least some insulin production.

[d] Severe hypoglycemia was defined as an event that required the assistance of another person to administer carbohydrate, glucagon, or other resuscitative actions because of altered consciousness.

[e] A diabetic ketoacidosis event was defined as an episode in which a participant had ketosis that necessitated treatment in a health care facility.

[f] Score ranges from 0 to 30, with higher scores reflecting greater dependence in instrumental activities of daily living (<8 is indicative of dementia based on Juva et al[26]).

[g] Clinically significant cognitive impairment was defined as 2 or more age-corrected scores of 80 or lower on the following NIH Toolbox Cognition Battery instruments: Flanker Inhibitory Control and Attention, List Sorting Working Memory, Dimensional Change Card Sort, Pattern Comparison Processing Speed, and Picture Sequence Memory.[27]

[h] The Clarke method of assessing hypoglycemia awareness ranges from 0 to 8, with higher scores reflecting lower awareness.[16]

analysis described above. Additional analyses also were performed for data collected through 16 weeks and data collected separately during daytime (6:00 AM to 11:59 PM) and nighttime (12:00 AM to 5:59 AM) hours for CGM outcomes.

For all secondary analyses, 2-sided *P* values and 95% confidence intervals were adjusted for multiple comparisons to control the false-discovery rate using the adaptive Benjamini-Hochberg procedure[21] (eTable 3 in Supplement 2). Analyses were conducted with SAS software version 9.4 (SAS Institute Inc).

Results

Between October 2017 and June 2018, 203 participants were randomly assigned to the CGM group (n = 103) or the standard BGM group (n = 100). Sixteen patients who provided consent and were screened for the study did not proceed into the randomized clinical trial (**Figure 1**). Participant characteristics overall and according to randomization group are shown in **Table 1** and additionally stratified by insulin delivery method in eTable 4 in Supplement 2. Participant comorbidities and medications are reported in eTables 5 and 6 and in Supplement 2, respectively.

The 26-week visit was completed by 102 participants in the CGM group (99%) and by 96 participants in the standard BGM group (96%) (Figure 1 and eFigure 1 in Supplement 2). Unscheduled visits and contacts are reported in eTable 7 in Supplement 2.

In the CGM group, CGM use was high throughout the study (eTable 8 in Supplement 2). In the 4 weeks prior to the 26-week visit, 81% were wearing the device 7 days per week and 89% 5 or more days per week; 6% had zero use, which included 1 participant who had dropped out. Use of CGM was similar between those who used a pump and those who used injections for insulin delivery (eTable 9 in Supplement 2). Two participants in the standard BGM group initiated real-time CGM use during the trial.

Blood glucose self-monitoring, measured as the median of individuals' mean number of tests per day, was 5.0 (interquartile range [IQR], 4.0-6.0) in the CGM group and 4.0 (IQR, 3.0-5.5) in the standard BGM group during the baseline period of blinded CGM wear, and was 3.5 (IQR, 2.8-4.5) and 4.3 (IQR, 3.8-5.0), respectively, during follow-up.

Glycemic Control Outcomes

In the primary analysis, median percentage of time with glucose levels less than 70 mg/dL decreased from 5.1% (73 minutes per day) at baseline to 2.7% (39 minutes per day) during the 6 months of follow-up for the CGM group and remained relatively unchanged from 4.7% (68 minutes per day) at baseline to 4.9% (70 minutes per day) during follow-up for the standard BGM group, for an adjusted treatment group difference of −1.9% (95% CI, −2.8% to −1.1%; *P* <.001), corresponding to a significant reduction in hypoglycemia of 27 minutes per day (95% CI, −40 to −16 minutes per day; *P* <.001) (**Table 2** and eTable 10 and eFigure 2 in Supplement 2). Results were similar for other CGM hypoglycemia metrics (Table 2 and eTable 10). The significant treatment effect was evident in the first month and remained consistent over 6 months (**Figure 2**A and eTable 11 in Supplement 2). Results were similar in a sensitivity analyses that adjusted for characteristics with some imbalance at baseline (duration of diabetes, sex, education, severe hypoglycemia in the 12 months prior to the study, and functional activity [questionnaire score]) and in a per-protocol sensitivity analysis (eTable 12 in

Table 2. Glycemic Outcomes

Outcomes	Baseline		Follow-up (8, 16, and 26 wk pooled)[a]		Adjusted difference, CGM − standard BGM (95% CI)[b]	*P* value[b]
	CGM (n = 103)	Standard BGM (n = 100)	CGM (n = 102)	Standard BGM (n = 94)		
Primary outcome						
Time with glucose <70 mg/dL, %	5.1 (3.0-9.7)	4.7 (2.4-9.5)	2.7 (1.6-4.6)	4.9 (2.5-8.5)	−1.9 (−2.8 to −1.1)	<.001
Secondary continuous glucose monitoring outcomes						
Hours of CGM data, median (IQR)	324 (308-388)	327 (309-397)	473 (449-489)	465 (423-483)		
Hypoglycemia, median (IQR)						
Time with glucose <60 mg/dL, %	3.0 (1.5-5.5)	2.4 (1.1-5.9)	0.9 (0.5-1.9)	2.4 (0.8-5.1)	−1.4 (−2.0 to −0.8)	<.001
Time with glucose <54 mg/dL, %	1.9 (0.9-3.6)	1.5 (0.5-4.1)	0.5 (0.2-1.0)	1.6 (0.4-3.4)	−1.0 (−1.4 to −0.5)	<.001
Rate of hypoglycemia events per wk[c]	2.6 (1.5-3.9)	2.1 (0.9-4.1)	0.8 (0.3-2.2)	1.8 (0.7-4.0)	−0.9 (−1.3 to −0.5)	<.001
Time with glucose in range of 70-180 mg/dL, mean (SD), %	56 (13)	56 (14)	63 (13)	54 (14)	8.8 (6.0 to 11.5)	<.001
Glucose level, mean (SD), mg/dL	167 (29)	168 (31)	162 (23)	171 (30)	−7.7 (−13.1 to −2.4)	.005
Coefficient of variation, mean (SD), %[d]	41 (6)	42 (7)	37 (5)	42 (7)	−4.7 (−6.1 to −3.3)	<.001
Hyperglycemia						
Time with glucose >180 mg/dL, mean (SD), %	37 (16)	38 (17)	34 (14)	39 (16)	−5.8 (−8.8 to −2.8)	<.001
Time with glucose >250 mg/dL, mean (SD), %	10 (6-21)	13 (5-20)	9 (3-15)	13 (8-23)	−3.6 (−5.2 to −2.2)	<.001
Time with glucose >300 mg/dL, median (IQR), %	3.8 (1.5-8.5)	4.2 (1.3-9.4)	2.4 (0.6-5.2)	5.2 (2.2-9.4)	−1.7 (−2.5 to −0.9)	<.001
Secondary HbA_{1c} outcome						
HbA_{1c}, mean (SD), %[e]	7.6 (0.9) [n = 100]	7.5 (0.8) [n = 97]	7.2 (0.9) [n = 100]	7.4 (0.9) [n = 95]	−0.3 (−0.4 to −0.1)	<.001

Abbreviations: BGM, blood glucose monitoring; CGM, continuous glucose monitoring; HbA_{1c}, hemoglobin A_{1c}; IQR, interquartile range.

SI conversion: To convert glucose values to millimoles per liter, multiply by 0.0555.

[a] One participant in the CGM group and 6 participants in the standard BGM group were missing CGM data at follow-up. Missing data were handled using direct likelihood. Baseline data for these participants were included in the model.

[b] Outcomes were analyzed in a linear mixed-effects model that adjusted for baseline value of the outcome being assessed and clinical center as a random effect. The hypoglycemia metrics, time spent with glucose concentrations greater than 250 mg/dL and greater than 300 mg/dL, had skewed distributions and were modeled using a rank-based transformation. For these skewed outcomes, point estimates and confidence intervals for the treatment group difference were calculated using the technique described by Hodges and Lehmann.[28] *P* values and 95% confidence intervals for all secondary outcomes were adjusted for multiple comparisons to control the false-discovery rate.

[c] A CGM-measured hypoglycemia event was defined as 15 consecutive minutes with a sensor glucose value less than 54 mg/dL. The end of the hypoglycemia event was defined as a minimum of 15 consecutive minutes with a sensor glucose concentration greater than 70 mg/dL.[4]

[d] Coefficient of variation is defined as standard deviation divided by mean.

[e] Three participants in both groups were missing central laboratory HbA_{1c} data at baseline. Three participants in the CGM group and 5 participants in the standard BGM group were missing central laboratory HbA_{1c} data at 26 weeks. All participants had a least 1 central laboratory value and were included in the model for those time points. Missing data were handled using direct likelihood.

Supplement 2). A significant benefit of CGM in reducing time with glucose levels less than 70 mg/dL was observed both during daytime and overnight (Figure 2B and eTable 13 in Supplement 2) and was present for both insulin pump and injection users (eTables 14 and 15 in Supplement 2). The treatment effect was significantly greater in participants with higher levels of baseline time with glucose levels less than 70 mg/dL, with a higher coefficient of variation, and with presence of a detectable C-peptide level (*P* <.001 for interaction for each). There was no significant interaction of the treatment effect on time with glucose levels less than 70 mg/dL with respect to other baseline characteristics, including age (<70 vs ≥70 years), socioeconomic status, presence of cognitive impairment, or HbA_{1c} value (eTable 16 in Supplement 2).

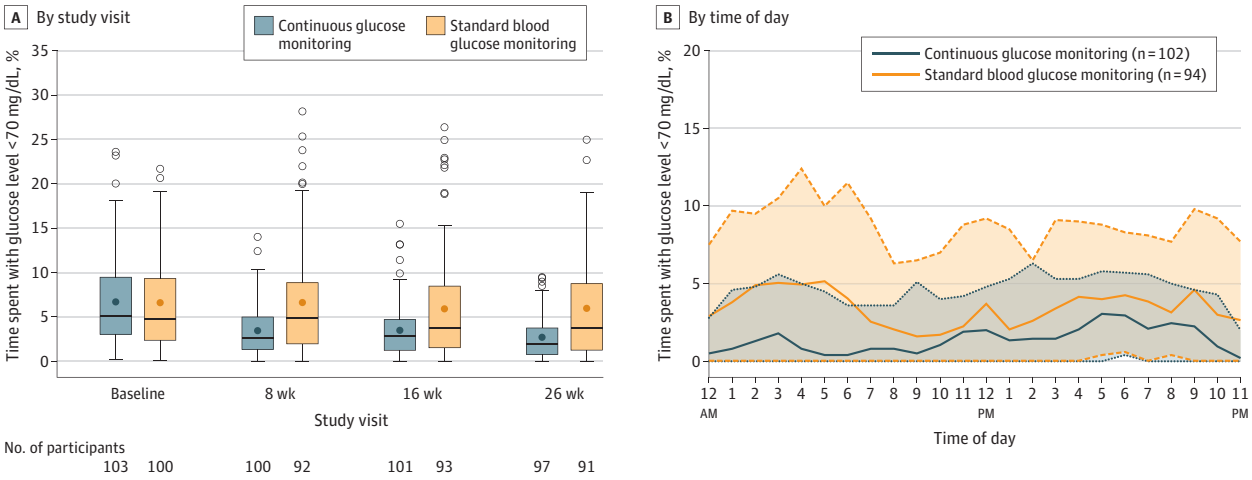
In addition to the reduction in hypoglycemia with CGM, significant treatment group differences were observed for hyperglycemia (glucose levels >180 mg/dL, >250 mg/dL, and >300 mg/dL), mean glucose concentration, and glycemic variability (Table 2 and eTable 10 in Supplement 2). Time spent in the target range of 70 to 180 mg/dL was 8.8% (2.1 hours per day) higher in the CGM group compared with the standard BGM group (95% CI, 6.0%-11.5% [1.4-2.8 hours per day]; *P* <.001) (Table 2 and eTable 10). Mean HbA_{1c} was 7.6% (SD, 0.9%) at baseline and 7.2% (SD, 0.9%) at 26 weeks in the CGM group and 7.5% (SD, 0.8%) and 7.4% (SD, 0.9%), respectively, in the standard BGM group (adjusted group difference, −0.3%; 95% CI, 0.4% to −0.1%; *P* <.001) (Table 2). Additional HbA_{1c} metrics are shown in eTable 17 in Supplement 2.

Severe Hypoglycemia and Other Adverse Events

One participant in the CGM group and 10 participants in the standard BGM group experienced a severe hypoglycemia event during the 6 months of follow-up (**Table 3**). Five of the 10 participants (50%) in the standard BGM group had an event that involved seizure or loss of consciousness, which did not occur in the 1 CGM participant.

One episode of diabetic ketoacidosis occurred during the study in a participant in the CGM group, unrelated to use of

Figure 2. Percentage of Time Spent With Less Than 70 mg/dL by Study Visit and Time of Day



To convert glucose values to millimoles per liter, multiply by 0.0555. A, By study visit: tops and bottoms of boxes indicate 25th and 75th percentiles; lines, medians; solid cirles, means; whiskers, minimums and maximums after removing outliers; and open circles, outliers. B, By time of day: thinner lines indicate 25th and 75th percentiles and thicker lines, medians. Participants with follow-up continuous glucose monitoring data had a minimum of 48 readings and maximum of 420 readings used to calculate percentage of time spent with glucose levels less than 70 mg/dL for each hour of the day.

Table 3. Safety Outcomes: Severe Hypoglycemia and Other Adverse Events

Outcomes	Participants with ≥1 event, No./total		Incidence rate					
			CGM		Standard BGM			
	CGM	Standard BGM	Total No. of person-years	Incidence rate per 100 person-years	Total No. of person-years	Incidence rate per 100 person-years	Difference, CGM − standard BGM (95% CI)[a]	*P* value[a]
Severe hypoglycemia events[b,c]								
Overall	1/103	10/100	51.5	1.9	49.1	22.4	−20.4 (−34.6 to −6.3)	.02
Insulin pump users[d]	1/56	4/49	28.2	3.5	24.1	16.6		
Insulin injection users[d]	0/45	5/48	22.3	0.0	23.5	25.5		
Other adverse events[c]								
Diabetic ketoacidosis	1/103	0/100	51.5	1.9	49.1	0.0		
Fractures	5/103	1/100	51.5	13.6	49.1	2.0	11.6 (−1.3 to 24.5)	.08
Falls	4/103	3/100	51.5	11.7	49.1	6.1	5.6 (−9.0 to 20.1)	.36
Hospitalizations	3/103	2/100	51.5	9.7	49.1	4.1	5.6 (−8.0 to 19.3)	.30
Emergency department visits	6/103	8/100	51.5	11.7	49.1	16.3	−4.6 (−18.8 to 9.5)	.53
Device-related events	0/103	0/100	51.5	0.0	49.1	0.0		

Abbreviations: BGM, blood glucose monitoring; CGM, continuous glucose monitoring.

[a] If there were enough events for analysis, safety outcomes for the overall cohort were compared between treatment groups using Poisson regression with the number of events as the outcome and the number of follow-up years as an offset. The model for severe hypoglycemia events was also adjusted for whether a participant had an event in the 12 months prior to the study. Confidence intervals for treatment group difference of incidence rate were calculated using bootstrapping.

[b] Five of the 10 participants with severe hypoglycemia events (50%) in the standard BGM group had an event that involved seizure or loss of consciousness, which did not occur in the 1 CGM participant with an event.

[c] Each event can be counted in more than 1 category; ie, a fracture may also be included as a hospitalization.

[d] Participants who switched insulin delivery modes were not included in the stratified analyses.

CGM (Table 3). There were no statistically significant treatment group differences in fractures, falls, hospitalizations, or emergency department visits.

There were 22 CGM device issues reported over the 26-week follow-up (eTable 18 in Supplement 2), none of which were related to an adverse event.

Patient-Reported Outcomes and Cognitive Assessments

No significant treatment group differences were observed at 26 weeks for any of the participant-reported questionnaires or cognitive assessments, including measures of hypoglycemia awareness, diabetes-specific quality of life (hypoglycemia fear, diabetes distress, and glucose monitoring

satisfaction), general quality of life, and cognition (eTable 19 in Supplement 2).

Discussion

Among adults aged 60 years or older with type 1 diabetes, use of CGM resulted in a small but statistically significant reduction in time spent with hypoglycemia (glucose level less than 70 mg/dL) compared with periodic finger-stick monitoring using standard BGM. A similar degree of hypoglycemia reduction was seen in those using insulin pump therapy and those using multidose insulin injection therapy. Results were consistent across the age range of 60 to 86 years, across the baseline HbA_{1c} range of 5.6% to 10.8%, among those with and without cognitive impairment, and at all education levels. The higher the amount of baseline hypoglycemia and glycemic variability, risk factors for severe hypoglycemia in older adults with type 1 diabetes,[22] the greater the treatment effect. In this study, the risk of a severe hypoglycemia event was significantly reduced with use of CGM, but the majority of participants using CGM did not achieve the less-than-1% target for time with a glucose level less than 70 mg/dL recommended for older adults.[23]

Reducing time with a glucose level less than 70 mg/dL is important, as it has been associated with risk of a subsequent severe hypoglycemia event, demonstrating the potential for clinical importance.[4,8] However, further research of longer duration and with clinical outcomes is needed before reaching any conclusions about the clinical value of these findings.

Despite improvements in various measures of hypoglycemia and glycemic control and the high degree of CGM use after 6 months, there were no significant treatment group differences in patient-reported outcomes, including fear of hypoglycemia and diabetes distress. One possible explanation is that the baseline scores on these measures were quite low, indicating already good adjustment to managing diabetes.

The findings in this trial are consistent with a subgroup analysis of the participants in the DIAMOND study, who were aged 60 years or older, with respect to the high degree of CGM use after 6 months and the benefit of CGM on reducing hyperglycemia and HbA_{1c}; however, the DIAMOND cohort had too little baseline hypoglycemia for a meaningful assessment of the effect of CGM on hypoglycemia.[9,14]

The strengths of this study include random treatment assignment, high participant retention rate, high degree of CGM use by the CGM group, and only 2 treatment crossovers by the standard BGM group. Although treatment group assignment could not be masked, the amount of contact with participants was similar between groups.

Limitations

This study has several limitations. First, the study cohort had relatively high socioeconomic status and consisted of individuals receiving specialized diabetes care. On average, baseline glycemic control was good and the amount of biochemical hypoglycemia was modest. Median age at diagnosis was 30 years, but the treatment effect appeared similar irrespective of age at diagnosis. Second, there was a relatively short intervention period of 6 months. This study included an extension phase during which the CGM group continued using CGM through 12 months and the standard BGM group initiated CGM. Results of the extension phase may provide insight into longer-term use of CGM. Third, the study intervention used an older version of the CGM sensor than what is now commercially available. It is unknown whether the additional features of the newer CGM sensor (such as no calibration requirement, easier insertion process, and a predictive low glucose alert) would have further increased CGM use in this population. Fourth, the study intervention also did not include a system that suspends insulin delivery from a pump when hypoglycemia is predicted based on the CGM glucose readings. Such a system for pump users might have an even greater effect on reducing hypoglycemia than was seen in this study.[24,25] Fifth, by chance, the CGM group had a higher frequency of severe hypoglycemia events in the year prior to the study than the standard BGM group; adjusting for this factor did not alter the result.

Conclusions

Among adults aged 60 years or older with type 1 diabetes, CGM compared with standard BGM resulted in a small but statistically significant improvement in hypoglycemia over 6 months. Further research is needed to understand the long-term clinical benefit.

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