Continuous Glucose Monitoring in Adults With Type 1 Diabetes With 35 Years Duration From the DCCT/EDIC Study

Diabetes Care 2022;45:659–665 | https://doi.org/10.2337/dc21-0629

*Rose A. Gubitosi-Klug,[1] Barbara H. Braffett,[2] Ionut Bebu,[2] Mary L. Johnson,[3] Kaleigh Farrell,[1] David Kenny,[2] Victoria R. Trapani,[2] Lynne Meadema-Mayer,[1] Elsayed Z. Soliman,[4] Rodica Pop-Busui,[5] John M. Lachin,[2] Richard M. Bergenstal,[3] and William V. Tamborlane,[6] for the DCCT/EDIC Research Group**

OBJECTIVE

We evaluated blinded continuous glucose monitoring (CGM) profiles in a subset of adults with type 1 diabetes from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study to characterize the frequency of glycemic excursions and contributing factors.

RESEARCH DESIGN AND METHODS

CGM-derived metrics were compared for daytime and nighttime periods using blinded CGM for a minimum of 6.5 days (average 11.9 days) and correlated with HbA_{1c} levels, routine use of diabetes devices, and other characteristics in 765 participants.

RESULTS

Participants were 58.9 ± 6.5 years of age with diabetes duration 36.8 ± 4.9 years and HbA_{1c} 7.8 ± 1.2%; 58% used insulin pumps, and 27% used personal, unblinded CGM. Compared with daytime, nighttime mean sensor glucose was lower, percent time in range 70–180 mg/dL (TIR) was similar, and hypoglycemia was more common. Over the entire recording period, only 9% of the 765 participants achieved >70% TIR and only 28% achieved <1% of observations of <54 mg/dL. Indeed, participants with the highest percentage of hypoglycemia had the lowest HbA_{1c} levels. However, use of insulin pumps and CGM decreased the percent time at <54 mg/dL.

CONCLUSIONS

In adults with long-standing type 1 diabetes, short-term blinded CGM profiles revealed frequent clinically significant hypoglycemia (<54 mg/dL) during the night and more time in hyperglycemia during the day. The small subset of participants using routine CGM and insulin pumps had fewer hypoglycemic and hyperglycemic excursions and lower HbA_{1c} levels. Thus, strategies to lower meal-stimulated hyperglycemia during the day and prevent hypoglycemia at night are relevant clinical goals in older patients with type 1 diabetes.

Hypoglycemia remains an ever-present concern for individuals living with diabetes, especially older adults with long-standing type 1 diabetes (1). It has been suggested that frequent, clinically significant hypoglycemia, particularly while asleep at night, may lead to devastating consequences, including loss of consciousness, seizures,

[1]Rainbow Babies and Children's Hospital, Case Western Reserve University, Cleveland, OH
[2]Biostatistics Center, George Washington University, Rockville, MD
[3]International Diabetes Center, Minneapolis, MN
[4]Wake Forest School of Medicine, Winston-Salem, NC
[5]University of Michigan, Ann Arbor, MI
[6]Yale University, New Haven, CT

Corresponding author: Barbara H. Braffett, braffett@bsc.gwu.edu

Received 22 March 2021 and accepted 17 December 2021

Clinical trial reg. nos. NCT00360815 and NCT00360893, clinicaltrials.gov.

This article contains supplementary material online at https://doi.org/10.2337/figshare.17282504.

**A listing of the DCCT/EDIC Research Group can be found in the supplementary material online.*

cardiac rhythm disturbances, dead-in-bed syndrome, and long-term effects on cognition (2–5). Avoidance of hypoglycemia often leads to chronic hyperglycemia, the primary risk factor for complications to the heart, kidney, retina, and nerves in type 1 diabetes (6). Personalization of diabetes management to reach treatment targets and avoid these glycemic excursions may change over the life span, matching the complexity of the regimen to considerations of age, physical and cognitive function, and other factors. Understanding the variation in glucose levels experienced by older adults with long-standing type 1 diabetes at home performing their usual daily activities and diabetes routine may inform approaches to improve glycemia. Yet, diurnal variations in sensor glucose excursions detected by and while blinded to continuous glucose monitoring (CGM) have not been measured in a large group of well-characterized patients with long-standing diabetes who are largely naive to CGM use.

The major aims of this observational study were to use blinded CGM to characterize the frequency of daytime and nocturnal hypo- and hyperglycemia in older adult patients with long-standing type 1 diabetes. To do so, individuals with type 1 diabetes for more than three decades were drawn from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study. We hypothesized that CGM assessments along with our historic phenotyping of this cohort would provide important insights regarding the frequency of hypoglycemia, as well as the failure to maintain glucose levels in the target range, and explored the impact of diabetes-related technology on achieving glycemic targets within a small cohort of this larger cohort of older adults with type 1 diabetes.

RESEARCH DESIGN AND METHODS

Participants With Type 1 Diabetes

Detailed descriptions of the DCCT clinical trial and EDIC observational follow-up study have been published (6,7). Briefly, between 1983 and 1989, 1,441 participants with type 1 diabetes ages 13–39 years were randomly assigned into the DCCT, a multicenter controlled clinical trial designed to compare the effects of intensive and conventional diabetes therapy on the development and progression of diabetes-related complications. After an average of 6.5 years of follow-up (range 3–9 years), the DCCT was stopped 1 year early (1993) after demonstrating the benefit of intensive glycemic therapy on the development and progression of microvascular complications. In 1994, 1,375 (96%) of the 1,428 members of the surviving cohort agreed to participate in annual evaluations during the subsequent, ongoing EDIC observational study (7). After an additional 23 years of follow-up, 1,190 (93%) of the 1,282 surviving participants continued to be followed at the start of the current ancillary study that began data collection in January 2017. All surviving DCCT/EDIC participants were invited to participate in this ancillary study, and 934 (78.5%) were enrolled. This study was conducted across 27 EDIC clinical centers during EDIC years 24–26 (2017–2019).

EDIC Evaluations

Each annual EDIC visit included a detailed medical history, current medication use, medical outcomes, and physical examination with measurements of height, weight, sitting blood pressure, and pulse rate (7). Blood samples were assayed centrally for HbA_{1c} using high-performance ion-exchange liquid chromatography (8). Use of personal CGMs and insulin pumps was self-reported. Insulin doses were self-reported and expressed as the average total daily dose in units per kilogram of body weight.

CGM Study Protocol

Participants were recruited for this ancillary study during routine annual EDIC visits at all EDIC clinical centers. Exclusion criteria included the use of pacemakers, serious allergy to adhesive tapes, or doubtful adherence to a minimum of 7 days of CGM in the judgment of the investigators. Once consented, participants were asked to wear the CGM for 14 days (FreeStyle Libre Pro Flash Glucose Monitoring System; Abbott Diabetes Care, Alameda, CA) and to perform their typical daily routines. Sensor glucose levels were monitored every 15 min during the 14-day period in a masked fashion. Participants were provided a standard blood glucose meter (BGM) (FreeStyle Lite; Abbott Diabetes Care) and asked to check their blood glucose as they normally would and record meal and low glucose levels in the study log books. Following 14 days of recording, participants removed the CGM and used study-provided prepaid biohazard mailers to return the devices to the EDIC clinical centers for processing. Study coordinators at the EDIC clinical centers downloaded the raw sensor glucose data from the CGM devices using available software from the manufacturer and securely transferred the data to the EDIC data coordinating center (Biostatistics Center, George Washington University).

Of the 934 participants who enrolled in the study, 853 had a minimum of 6.5 days of continuous CGM data collection; 85 of these participants who were using an insulin-suspend pump during the ancillary study period were analyzed separately, and 3 participants who were missing information on whether they had used an insulin-suspend pump were excluded. Thus, the final sample size was 765 participants who did not use insulin-suspend pumps. Consistent with international consensus conference recommendations (9), a clinical hypoglycemia event was defined as below the two thresholds of 70 and 54 mg/dL. Other consensus recommendations regarding optimal metabolic control include >70% of target time in range 70–180 mg/dL (TIR), <1% time in hypoglycemia (<54 mg/dL), and <25% time in hyperglycemia (>180 mg/dL). Participants in this CGM study also obtained 14 days of simultaneously measured electrocardiograms (ECGs) using the small, wearable Ziopatch (iRhythm Technologies, Inc., San Francisco, CA) continuous single-lead ECG monitor. The combined measures were designed to evaluate the risk of hypoglycemia-induced arrhythmias among individuals with long-standing type 1 diabetes. Analyses of these simultaneous assessments of ECGs and CGM profiles are in progress and are not included in this report.

Statistical Considerations

CGM-derived metrics included mean glucose, SD of mean glucose values, coefficient of variation of sensor glucose levels, percent TIR, percentage of time in hypoglycemia defined as <54 or <70 mg/dL, and percentage of time in hyperglycemia defined as >180 or >250 mg/dL. Each metric was calculated separately for the

daytime (6:00 A.M.–11:59 P.M.) and nighttime (12:00 A.M.–5:59 A.M.) periods on the basis of prior literature. Mean ± SD and median (interquartile range) are reported (10,11).

The Cochran-Armitage trend test was used for categorical variables and the Kruskal-Wallis test for quantitative variables. Additional comparisons were made between participants who did and did not use personal insulin-suspend pumps during the data collection period, as well as between participants who reported use of CGM sensors and insulin pumps (nonhybrid systems) for their diabetes management. Use of these devices was confirmed by self-report to the study team at the initiation of the study and after completion of the 2-week study period. Pearson correlation coefficients were calculated, and linear regression models were used to assess the relationship of HbA_{1c} as a function of TIR and mean glucose. Given the exploratory nature of our analyses, the results were not adjusted for multiple testing, and associations with $P < 0.05$ were considered nominally significant.

RESULTS

At the start of the study, the 765 participants included in these analyses had a mean age of 58.9 ± 6.5 years, diabetes duration of 36.8 ± 4.9 years, and HbA_{1c} of 7.8 ± 1.2%; 47% were female (Table 1). With an average 11.9 days of CGM data (range 6.5–13 days, median 13 days, 75% with ≥12 days of continuous recording), correlations between TIR and mean sensor glucose with HbA_{1c} were −0.61 and 0.66, respectively (Fig. 1). Diabetes management regimens included personal CGM use in 27% of participants, pump use without insulin-suspend features in 58%, and combined CGM and pump use without insulin-suspend features in 21% (Table 1). Within these categories, 6% of participants reported only using CGM, 37% of participants reported only using pumps without insulin-suspend features, and 36% did not use these technologies. Participants with the highest frequency of hypoglycemia had lower mean HbA_{1c} levels ($P < 0.0001$), were more likely to be smokers ($P = 0.0291$), and were less likely to be routinely using a personal CGM and/or an insulin pump (Table 1 for percent time <70 mg/dL and Supplementary Table 1 for percent time <54 mg/dL).

Diurnal variations in CGM metrics are shown in Table 2. Compared with the daytime CGM values, nighttime CGM values revealed a pattern of lower mean glucose with more nocturnal hypoglycemia; both percent time <54 mg/dL (mean 7.2% nighttime vs. 3.9% daytime) and percent time <70 mg/dL (mean 13.1% nighttime vs. 8.2% daytime) were higher. Conversely, during the daytime, time spent in hyperglycemia was increased (Table 2). Of note, only 9% of all 765 participants achieved the target recommendation of >70% of observations in TIR (Table 3). The percentage of participants achieving <1% of time <54 mg/dL was 26% among those who did not use advanced technologies, 36% among those who used CGM and insulin pumps without insulin-suspend features, and 47% among those who used insulin-suspend pumps (Table 3). A similar pattern is apparent for hyperglycemia: For the clinical goal of <25% of time >180 mg/dL, the percentage of participants reaching this clinical target was 21% for

Table 1—Characteristics of participants overall and by percentage of time in hypoglycemia (<70 mg/dL)

Characteristic	Overall	Percentage of time <70 mg/dL				*P**
		<4% (target)	4–8% (2× target)	8–12% (2–3× target)	≥12% (>3× target)	
Participants, *n*	765	228	169	142	226	
Age (years)	58.9 ± 6.5	59.0 ± 6.4	59.6 ± 6.5	57.7 ± 6.3	59.0 ± 6.7	0.0669
Sex (% female)	47	49	47	46	47	0.7716
Race (% non-Hispanic White)	97	98	95	99	96	0.4993
DCCT treatment (% intensive)	52	54	50	46	53	0.7361
DCCT cohort (% primary prevention)	49	46	51	50	49	0.6751
Diabetes duration (years)	36.8 ± 4.9	36.8 ± 4.9	36.7 ± 4.8	37.0 ± 5.1	37.0 ± 4.9	0.9348
BMI (kg/m^2)	29.0 ± 5.6	29.2 ± 5.3	29.4 ± 6.0	28.3 ± 5.5	28.8 ± 5.6	0.2881
Current smoker	8	7	4	8	12	0.0291
CGM sensor use	27	34	32	23	17	<0.0001
Insulin pump use	58	66	60	51	54	0.0023
Use CGM/pump without insulin-suspend	21	26	25	19	14	0.0005
Insulin dose (units/kg/day)	0.62 ± 0.26	0.62 ± 0.28	0.62 ± 0.22	0.62 ± 0.28	0.60 ± 0.24	0.6580
Blood pressure (mmHg)						
Systolic	122.8 ± 14.5	123.3 ± 15.0	122.9 ± 14.9	122.2 ± 14.3	122.4 ± 13.9	0.7829
Diastolic	68.9 ± 9.4	69.5 ± 9.7	68.3 ± 8.9	68.1 ± 9.8	69.3 ± 9.4	0.2322
HbA_{1c}‡	7.8 ± 1.2	8.3 ± 1.2	8.0 ± 1.1	7.7 ± 1.1	7.4 ± 1.2	<0.0001

Data are mean ± SD or %. Based on recommendations from the International Consensus on Time in Range (2019) (9) and American Diabetes Association Standards of Medical Care (2019) (24). **P* value from the Cochran-Armitage trend test for categorical variables or the Kruskal-Wallis test for quantitative variables. ‡To convert HbA_{1c} to the SI units of mmol/mol, multiply the HbA_{1c} percent value by 10.93 and subtract 23.5 from the product.

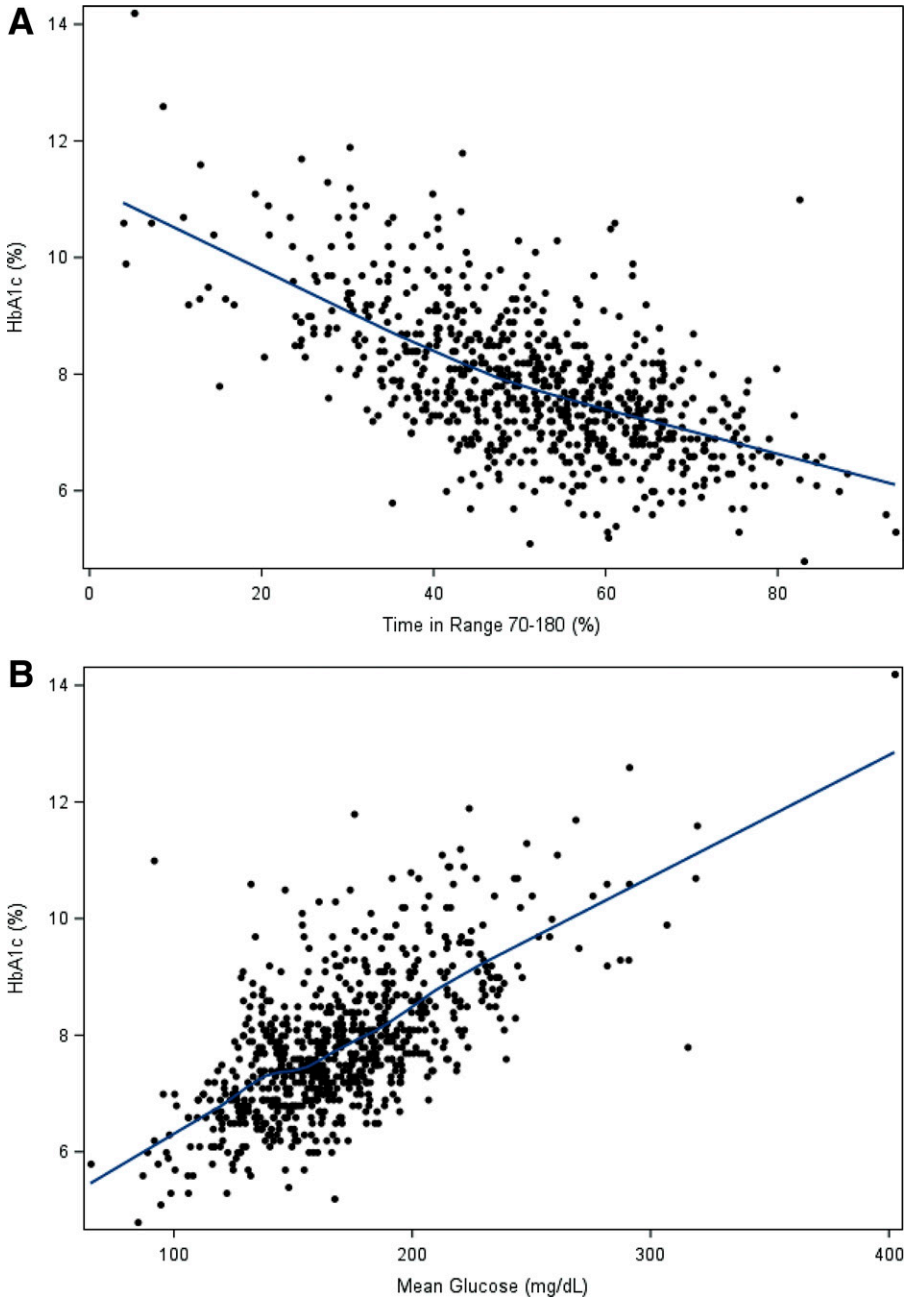

Figure 1—Scatterplot with locally weighted smoothing (LOESS) curve of the association of HbA_{1c} with TIR (*A*) and mean glucose (*B*) (*n* = 765).

no technology, 29% with CGM and pumps without insulin-suspend features, and 35% with insulin-suspend pumps (Table 3).

Participants who used insulin-suspend pumps (*n* = 85) had significantly less daytime and nighttime hypoglycemia than the 765 participants who did not (Supplementary Table 2). However, the frequency of nocturnal hyperglycemia did not differ between these two groups. Moreover, CGM metrics favored participants who used CGM with an insulin pump without insulin-suspend features (*n* = 160) than the 605 participants who did not (Supplementary Table 3). Participants who used insulin--suspend pumps or CGM with an insulin pump without insulin-suspend features had lower HbA_{1c} and insulin doses than those who did not use these advanced devices (Supplementary Table 4).

CONCLUSIONS

The aim of the current study was to use masked CGM to explore day and night variations in sensor glucose levels in a large group of older patients with long-standing type 1 diabetes who had been followed prospectively in the DCCT and subsequently in the EDIC, which began in 1993. As previously reported, there has been little difference in HbA_{1c} levels between former DCCT intensive and conventional treatment groups during annual follow-up in EDIC, with an average HbA_{1c} of 7.8 ± 1.2%, which is above current guidelines (12). While the rates of hypoglycemia during EDIC were also similar in the former intensive and conventional treatment groups, these findings indicate that hypoglycemia in both

Table 2—CGM-derived metrics (n = 765)

	Entire follow-up (24 h)		All days (6:00 A.M.–11:59 P.M.)		All nights (12:00 A.M.–5:59 A.M.)	
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)
Mean glucose (mg/dL)	169.6 ± 37.3	166.5 (144.3, 189.4)	173. 1 ± 38.6	169.5 (148.1, 192.9)	159.3 ± 43.1	154.7 (128.6, 185.3)
SD (mg/dL)	73.2 ± 17.6	71.4 (62.0, 83.2)	73.2 ± 17.7	71.4 (61.8, 83.2)	66.7 ± 19.6	64.6 (52.8, 78.0)
Glucose CV (%)	43.6 ± 7.8	42.9 (38.2, 48.5)	42.6 ± 7.5	42.2 (37.8, 47.3)	43.0 ± 11.3	42.1 (34.2, 49.7)
Target range						
Percentage TIR	51.5 ± 14.3	51.9 (42.4, 61.4)	51.4 ± 14.8	52.2 (42.0, 61.2)	51.7 ± 17.5	51.5 (40.4, 63.8)
Hypoglycemia						
Percentage of time <54 mg/dL	4.4 ± 5.2	2.7 (0.8, 6.2)	3.5 ± 4.6	1.9 (0.4, 4.5)	7.2 ± 9.3	3.9 (0.3, 9.9)
Percentage of time <70 mg/dL	9.4 ± 7.9	7.5 (3.3, 13.4)	8.2 ± 7.3	6.2 (2.9, 11.4)	13.1 ± 12.9	9.5 (3.0, 19.0)
Hyperglycemia						
Percentage of time >180 mg/dL	39.1 ± 17.7	38.7 (26.0, 50.5)	40.4 ± 18.1	39.9 (27.5, 52.0)	35.2 ± 21.5	32.6 (17.9, 50.3)
Percentage of time >250 mg/dL	16.3 ± 13.3	13.1 (6.7, 22.2)	17.2 ± 14.0	14.2 (7.2, 23.2)	13.7 ± 14.5	9.6 (2.4, 19.6)

Data are for a minimum period of 6.5 days (average 11.9 days). CV, coefficient of variation; IQR, interquartile range.

groups remained at a concerningly high rate (1). In this cohort, mean sensor glucose levels were elevated (i.e., ∼169 mg/dL), with only ∼50% of time spent in the target range. Indeed, only 9% of participants maintained >70% of observations within TIR, a metric commonly used to indicate success in studies of hybrid closed-loop insulin delivery systems.

Regarding hypoglycemia, the percent time <70 mg/dL (mean 9.4%) was two- to threefold greater than the percent time <54 mg/dL (mean 4.4%) in this cohort, and several consensus conferences have suggested that <54 mg/dL is more clinically important (13). However, only 28% of participants were able to maintain the recommended goal of <1% of observations <54 mg/dL. The time in hypoglycemia was greater during the night than during the day, and the time in hyperglycemia was greater during the day than during the night.

In this study, personal use of advanced devices was the leading factor affecting a participant's ability to achieve CGM treatment goals. Specifically, participants using CGM and pumps were more likely to have lower HbA_{1c} levels, with a reduced frequency of clinically significant hypoglycemia. The reduction in HbA_{1c} was ∼0.5% with advanced device use, which is similar to the reduction in hypoglycemia reported by the Wireless Innovation for Seniors With Diabetes Mellitus (WISDM) study, an interventional study of CGM in older patients with type 1 diabetes (14). Looking at the impact of CGM technology alone in our study, a similar proportion (∼40%) of participants who used CGM in conjunction with multiple daily insulin injections (n = 43) achieved target recommendations to minimize hypoglycemia compared with participants who used CGM and pumps (n = 160) (Supplementary Table 5). This beneficial effect of CGM use for both insulin pump and injection users is consistent with the results from the WISDM and Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes (DIAMOND) studies (14,15). Of note, in our small subset of participants who used insulin pumps with insulin-suspend capability (n = 85), we observed higher proportions of participants reaching

Table 3—Participants meeting consensus clinical targets by use of diabetes devices in diabetes management

	Did not use insulin-suspend pumps	Used insulin-suspend pumps	P†	Did not use CGM sensors and insulin pumps	Used CGM sensors and insulin pumps	P‡
Participants, n	765	85		605	160	
Clinical targets						
Target range						
Percentage TIR >70%	69 (9)	16 (19)	0.0043	37 (6)	32 (20)	<0.0001
Hypoglycemia						
Percentage of time <54 mg/dL <1%	214 (28)	40 (47)	0.0003	156 (26)	58 (36)	0.0087
Percentage of time <70 mg/dL <4%	228 (30)	34 (40)	0.0534	168 (28)	60 (38)	0.0167
Hyperglycemia						
Percentage of time >180 mg/dL <25%	172 (22)	30 (35)	0.0085	125 (21)	47 (29)	0.0189
Percentage of time >250 mg/dL <5%	132 (17)	27 (32)	0.0011	87 (14)	45 (28)	<0.0001

Data are n (%). TIR based on recommendations from the International Consensus on Time in Range (2019) (9) and American Diabetes Association Standards of Medical Care (2020) (25). †P value comparing participants who did not (n = 765) and did (n = 85) use insulin-suspend pumps during the study. ‡P value comparing participants who did not (n = 605) and did (n = 160) use CGM sensors and insulin pumps without insulin-suspend features.

clinical targets and limiting hypoglycemia and hyperglycemia.

Yet, the proportion of participants reaching clinical targets in EDIC remained lower than expected. For instance, the lower frequency of hypoglycemia in WISDM participants compared with EDIC participants may reflect several factors. First, WISDM is an interventional trial evaluating CGM use in motivated participants recruited from academic specialized care centers, while the EDIC study is a long-term observational study where the majority of participants (approximately three out of four) seek care from community providers and not the EDIC clinical centers, including 27% of participants receiving care from nondiabetes specialists. In addition, 40–50% of WISDM participants reported personal use of CGM, while less than one-third of EDIC participants reported personal CGM use. Finally, physiologic factors, such as older age of diagnosis of type 1 diabetes in WISDM, may afford additional residual β-cell function and protection from hypoglycemia. As well, in prior studies and per U.S. Food and Drug Administration regulatory documents, the Abbott FreeStyle Libre Pro sensor has been reported to overestimate hypoglycemia (16,17). Thus, our rates of hypoglycemia may also be affected, which may have an impact on the comparison with WISDM and other studies.

In our study, ∼79% of participants (n = 605) did not use both CGM and insulin pumps (i.e., 6% using CGM only, 37% using pumps without insulin-suspend features, and 36% using neither CGM or pump). In this subset of participants not using both devices, lower HbA_{1c} levels were associated with an increased frequency of hypoglycemia ($P < 0.0001$) (data not shown). Smokers were also more likely to experience hypoglycemia (P = 0.0404) (data not shown), which is consistent with the results of other studies in type 1 diabetes (18–20).

Notably, the reported proportion of CGM users in the EDIC population during this study period (2017–2019) is similar to prior reports, such as 34% of T1D Exchange participants age ≥50 years during 2016–2018 (21). Mirroring national trends with improved access, efficacy, and clinical utilization of CGM, we have observed a steady rise in CGM use among the EDIC participants over time; as of 2021, >65% of participants from the EDIC CGM study reported personal CGM use. Hopefully, future evaluations of hypoglycemia rates in the EDIC cohort will be affected by this accelerated adoption of CGM.

Limitations of this study are the review of a mean recording period of 11.9 days (range 6–13 days), yet other studies have suggested that 7–14 days may provide a useful evaluation of glycemic excursions for an individual (22,23). Reassuringly, the similarity of our association of TIR and mean sensor glucose with HbA_{1c} to that determined by other studies supports a representative assessment (13) (Fig. 1). We used a minimum cutoff of 6.5 days of continuous CGM recordings to represent sufficient data for our analyses. Exclusion of 81 participants because of insufficient data may be a source of potential bias. However, the clinical characteristics between those with insufficient data and sufficient data are clinically similar, and thus, any bias is minimized (Supplementary Table 6). As well, overall, those who participated in this ancillary study compared with all nonparticipants were similar in all baseline characteristics except baseline DCCT HbA_{1c} (Supplementary Table 7). Thus, this subsample of the DCCT/EDIC cohort is representative of all surviving participants. As other studies have discussed, this association between TIR and HbA_{1c} could be affected by many factors, including CGM device tendency in the lower glucose ranges to have a negative bias and interindividual differences in red blood cell kinetics (16). With a limited BGM dataset collected during the study (i.e., ∼46,000 BGM values corresponding to ∼5% of the CGM values), there was high concordance of BGM values with CGM values occurring within 15 min before or after testing, suggesting that our results are not likely to be affected by the FreeStyle Libre Pro sensor performance (Supplementary Table 8 and Supplementary Fig. 1). Although participants were masked to CGM glucose levels and instructed to follow their usual home insulin and eating regimens, we cannot exclude that they may have altered their routines as a result of participation in the study.

Like we have done in the current study, several others have illustrated that older individuals with long-standing diabetes are at increased risk of severe hypoglycemia. However, the recent introduction of hybrid closed-loop systems has been shown to decrease the frequency of nocturnal, as well as daytime, hypoglycemia in the late postmeal period. In addition, newer and more flexible full closed-loop systems (with or without dual hormone features) offer the potential to reduce the frequency of daytime and nighttime hyperglycemia. Such advances in diabetes devices and integrated diabetes technologies and data management systems, if economically and logistically feasible, offer the potential to improve the management of type 1 diabetes in older adult patients.

Funding. DCCT/EDIC has been supported by cooperative agreements (1982–1993, 2012–2017, 2017–2022) and contracts (1982–2012) with the Division of Diabetes Endocrinology and Metabolic Diseases of the National Institute of Diabetes and Digestive and Kidney Disease (current grants U01-DK-094176 and U01-DK-094157) and through the National Eye Institute, National Institute of Neurologic Disorders and Stroke, General Clinical Research Centers Program (1993–2007), and Clinical Translational Science Center Program (2006–present). Additional support for this study was provided by grant DP3-DK-106890.

Duality of Interest. R.M.B. has received research support, has acted as a consultant, or has been on the scientific advisory board for Abbott Diabetes Care, Ascensia, Dexcom, Eli Lilly, Johnson & Johnson, Medtronic, Novo Nordisk, Roche, and Sanofi. R.M.B.'s employer, the nonprofit HealthPartners Institute, contracts for his services, and no personal income goes to him. The following industry contributors have provided free or discounted supplies or equipment to support participants' adherence to the study protocol: Abbott Diabetes Care; Animas; Bayer Diabetes Care; Becton, Dickinson and Company; Eli Lilly; Extend Nutrition; Insulet Corporation; LifeScan; Medtronic Diabetes; Nipro Home Diagnostics; Nova Diabetes Care; Omron; Perrigo Diabetes Care; Roche Diabetes Care; and Sanofi. No other potential conflicts of interest relevant to this article were reported.

Industry contributors have had no role in the DCCT/EDIC study.

Author Contributions. R.A.G.-K. had final responsibility for the decision to submit the manuscript for publication. R.A.G.-K., B.H.B., J.M.L., R.M.B., and W.V.T. designed the analyses and wrote the manuscript. B.H.B. conducted the statistical analyses and prepared the tables and figures. I.B., M.L.J., K.F., D.K., V.R.T., L.M.-M., E.Z.S., and R.P.-B. wrote portions of the manuscript and reviewed and edited the manuscript. R.A.G.-K. and B.H.B. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in oral form at the 55th Annual Meeting of the European Association for the Study of Diabetes, Barcelona, Spain, 16–20

September 2019, and at the 13th International Conference on Advanced Technologies & Treatments, Madrid, Spain, 19–22 February 2020.

Data Sharing. Data collected for the DCCT/EDIC study through 30 June 2017 are available to the public through the National Institute of Diabetes and Digestive and Kidney Diseases Central Repository (https://repository.niddk.nih.gov/studies/edic). Data collected in the current cycle (July 2017–June 2022) will be available within 2 years after the end of the funding cycle.

References

1. Gubitosi-Klug RA, Braffett BH, White NH, et al.; Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group. Risk of severe hypoglycemia in type 1 diabetes over 30 years of follow-up in the DCCT/EDIC study. Diabetes Care 2017;40:1010–1016
2. Buckingham B, Wilson DM, Lecher T, Hanas R, Kaiserman K, Cameron F. Duration of nocturnal hypoglycemia before seizures. Diabetes Care 2008;31:2110–2112
3. Tanenberg RJ, Newton CA, Drake AJ. Confirmation of hypoglycemia in the "dead-in-bed" syndrome, as captured by a retrospective continuous glucose monitoring system. Endocr Pract 2010;16:244–248
4. Novodvorsky P, Bernjak A, Chow E, et al. Diurnal differences in risk of cardiac arrhythmias during spontaneous hypoglycemia in young people with type 1 diabetes. Diabetes Care 2017;40:655–662
5. Martín-Timón I, Del Cañizo-Gómez FJ. Mechanisms of hypoglycemia unawareness and implications in diabetic patients. World J Diabetes 2015;6:912–926
6. Nathan DM, Genuth S, Lachin J, et al.; Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986
7. The DCCT/EDIC Research Group. Epidemiology of Diabetes Interventions and Complications (EDIC). Design, implementation, and preliminary results of a long-term follow-up of the Diabetes Control and Complications Trial cohort. Diabetes Care 1999;22:99–111
8. Steffes M, Cleary P, Goldstein D, et al. Hemoglobin A1c measurements over nearly two decades: sustaining comparable values throughout the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications study. Clin Chem 2005;51:753–758
9. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. Diabetes Care 2019;42:1593–1603
10. Shah VN, DuBose SN, Li Z, et al. Continuous glucose monitoring profiles in healthy nondiabetic participants: a multicenter prospective study. J Clin Endocrinol Metab 2019;104:4356–4364
11. Maahs DM, Chase HP, Westfall E, et al. The effects of lowering nighttime and breakfast glucose levels with sensor-augmented pump therapy on hemoglobin A1c levels in type 1 diabetes. Diabetes Technol Ther 2014;16:284–291
12. Nathan DM, Bayless M, Cleary P, et al.; DCCT/EDIC Research Group. Diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: advances and contributions. Diabetes 2013;62:3976–3986
13. Beck RW, Bergenstal RM, Cheng P, et al. The relationships between time in range, hyperglycemia metrics, and HbA1c. J Diabetes Sci Technol 2019;13:614–626
14. Pratley RE, Kanapka LG, Rickels MR, et al.; Wireless Innovation for Seniors With Diabetes Mellitus (WISDM) Study Group. Effect of continuous glucose monitoring on hypoglycemia in older adults with type 1 diabetes: a randomized clinical trial. JAMA 2020;323:2397–2406
15. Beck RW, Riddlesworth T, Ruedy K, et al.; DIAMOND Study Group. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: the DIAMOND randomized clinical trial. JAMA 2017;317:371–378
16. Jafri RZ, Balliro CA, El-Khatib F, et al. A three-way accuracy comparison of the Dexcom G5, Abbott Freestyle Libre Pro, and Senseonics Eversense continuous glucose monitoring devices in a home-use study of subjects with type 1 diabetes. Diabetes Technol Ther 2020;22:846–852
17. U.S. Food and Drug Administration. Summary of Safety and Effectiveness Data (SSED): Freestyle Libre Pro Flash Glucose Monitoring System. Accessed 12 December 21. Available from https://www.accessdata.fda.gov/cdrh_docs/pdf15/p150021b.pdf
18. Pedersen-Bjergaard U, Pramming S, Heller SR, et al. Severe hypoglycaemia in 1076 adult patients with type 1 diabetes: influence of risk markers and selection. Diabetes Metab Res Rev 2004;20:479–486
19. Braffett BH, Rice MM, Young HA, Lachin JM. Mediation of the association of smoking and microvascular complications by glycemic control in type 1 diabetes. PLoS One 2019;14:e0210367
20. Hirai FE, Moss SE, Klein BE, Klein R. Severe hypoglycemia and smoking in a long-term type 1 diabetic population: Wisconsin Epidemiologic Study of Diabetic Retinopathy. Diabetes Care 2007;30:1437–1441
21. Foster NC, Beck RW, Miller KM, et al. State of type 1 diabetes management and outcomes from the T1D Exchange in 2016-2018. Diabetes Technol Ther 2019;21:66–72
22. Riddlesworth TD, Beck RW, Gal RL, et al. Optimal sampling duration for continuous glucose monitoring to determine long-term glycemic control. Diabetes Technol Ther 2018;20:314–316
23. Xing D, Kollman C, Beck RW, et al.; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Optimal sampling intervals to assess long-term glycemic control using continuous glucose monitoring. Diabetes Technol Ther 2011;13:351–358
24. American Diabetes Association. 7. Diabetes technology: *Standards of Medical Care in Diabetes—2019*. Diabetes Care 2018;42(Suppl. 1):S71–80
25. American Diabetes Association. 7. Diabetes technology: *Standards of Medical Care in Diabetes—2020*. Diabetes Care 2020;42(Suppl. 1):S77–88