ORIGINAL ARTICLE

Outpatient Safety Assessment of an In-Home Predictive Low-Glucose Suspend System with Type 1 Diabetes Subjects at Elevated Risk of Nocturnal Hypoglycemia

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Abstract

Objective: Nocturnal hypoglycemia is a common problem with type 1 diabetes. In the home setting, we conducted a pilot study to evaluate the safety of a system consisting of an insulin pump and continuous glucose monitor communicating wirelessly with a bedside computer running an algorithm that temporarily suspends insulin delivery when hypoglycemia is predicted.

Research Design and Methods: After the run-in phase, a 21-night randomized trial was conducted in which each night was randomly assigned 2:1 to have either the predictive low-glucose suspend (PLGS) system active (intervention night) or inactive (control night). Three predictive algorithm versions were studied sequentially during the study for a total of 252 intervention and 123 control nights. The trial included 19 participants 18–56 years old with type 1 diabetes (hemoglobin A1c level of 6.0–7.7%) who were current users of the MiniMed Paradigm[®] REAL-Time Revel[™] System and Sof-sensor[®] glucose sensor (Medtronic Diabetes, Northridge, CA).

Results: With the final algorithm, pump suspension occurred on 53% of 77 intervention nights. Mean morning glucose level was 144 ± 48 mg/dL on the 77 intervention nights versus 133 ± 57 mg/dL on the 37 control nights, with morning blood ketones >0.6 mmol/L following one intervention night. Overnight hypoglycemia was lower on intervention than control nights, with at least one value ≤ 70 mg/dL occurring on 16% versus 30% of nights, respectively, with the final algorithm.

Conclusions: This study demonstrated that the PLGS system in the home setting is safe and feasible. The preliminary efficacy data appear promising with the final algorithm reducing nocturnal hypoglycemia by almost 50%.

Introduction

NOCTURNAL HYPOGLYCEMIA REMAINS a significant concern to people with type 1 diabetes, even with the advent of real-time continuous glucose monitoring (CGM). In the Juvenile Diabetes Research Foundation CGM randomized trial, sensor hypoglycemia (≤ 60 mg/dL) occurred during 8.5% of nights with a mean duration of 81 min; 23% of events lasted at least 2 h, and 11% lasted at least 3 h despite the presence of alarms.¹ It has been demonstrated that seizures can occur after 2.25 h of nocturnal hypoglycemia (glucose levels of <60 mg/dL),² and in a case of the dead-in-bed syndrome over 3 h of sensor hypoglycemia was documented.³

Unfortunately, even when using CGM, a hypoglycemia alarm overnight is not protective, as most of the time a sleeping child will not be awakened by the alarm.⁴

The ideal system for preventing nocturnal hypoglycemia would work automatically without alarms and without a need for the patient to awaken by suspending or attenuating insulin delivery to prevent hypoglycemia and then returning to the usual basal insulin infusion rate when the risk of hypoglycemia abates. We previously tested such a system in an inpatient setting in which the basal insulin infusion rate overnight was increased to promote the occurrence of hypoglycemia. The hypoglycemia prediction algorithm and automatic pump suspension (predictive low-glucose suspend [PLGS]) reduced the

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incidence of nocturnal hypoglycemia by about 75% on nights when hypoglycemia otherwise would have occurred.⁵

The current study was designed to assess the safety of using PLGS and to provide preliminary efficacy data on reducing nocturnal hypoglycemia in an outpatient setting. An additional goal of these studies was to gain experience with changing some of the tunable parameters in the algorithm to determine the relative impact of these changes on measures of both hyperglycemia and hypoglycemia and to modify the hypoglycemia prediction horizon if necessary.

Research Design and Methods

The study was conducted at two clinical centers, at which the protocol was approved by each Institutional Review Board. Written informed consent was obtained from each subject. Key aspects of the study protocol are described below.

A sample size of 20 subjects was planned for this pilot study. Major eligibility criteria included age ≥ 18 years, type 1 diabetes for at least 1 year, current user of the MiniMed Paradigm[®] REAL-Time Revel[™] system and Sof-sensor[®] glucose sensor (Medtronic Diabetes, Northridge, CA) (referred to as the “Revel CGM” device), hemoglobin A1c level of $\leq 8.0\%$, access to the Internet, and at least one CGM glucose value ≤ 70 mg/dL during the most recent 15 nights of CGM glucose data. The study consisted of a run-in phase, a randomization phase, and a single follow-up visit at the completion of the study, each described below.

The pump suspension system consisted of the Revel CGM device communicating with a laptop computer that contained the hypoglycemia prediction algorithm (referred to as “the system”) and that was used for data input by the participant. The algorithm used a Kalman filter-based model to predict whether the sensor glucose level would fall below 80 mg/dL within a given time period and suspended the insulin pump if this event was predicted.⁶ The laptop was placed at the bedside and turned on by the participant at bedtime and off on arising in the morning. The laptop contained a randomization schedule that indicated whether the hypoglycemia prediction algorithm would be in operation that night (intervention night) or would not be activated (control night), to which the participant was blinded. Audible glycemic alarms were set for 60 mg/dL and 250 mg/dL. There was no alarm or other indication of pump suspension during the night, but the following morning the laptop screen indicated if pump suspension had occurred. The system had a button on the laptop interface so that the participant could deactivate the system at any time and resume basal insulin delivery if it had been stopped. The system automatically deactivated itself, and usual basal insulin doses were resumed if there were persistent communication problems between any of the system components lasting more than 20 min or unexpected errors. During the day, the participant used the CGM device and pump in an open-loop manner similar to their pre-study use.

After turning on the laptop at bedtime, the participant entered a current blood glucose measurement, obtained within 15 min of bedtime with a study-provided OneTouch[®] Ultra[®]2 meter (LifeScan, Milpitas, CA), confirmed that CGM calibration had been performed within 90 min of bedtime, and indicated whether a bedtime snack was eaten and any physical exercise had occurred during the day. If calibration was not possible because of rapid fluctuation in the participant's

glucose level or the blood glucose level was ≤ 90 mg/dL or >270 mg/dL, the system was not activated that night. When the system was stopped in the morning, blood glucose, blood ketone (measured with a provided Precision Xtra[™] meter [Abbott Diabetes Care, Alameda, CA]), and urine ketone (measured with Ketostix[®] strips [Bayer, Leverkusen, Germany]) measurements were entered, as was the occurrence of any overnight carbohydrate intake. Data were automatically sent to the study coordinating center each morning.

Participants initially completed a 5-night run-in phase at home with the nocturnal hypoglycemia prediction algorithm active to verify functionality of the system and the participant's ability to use it properly. All enrolled individuals successfully completed this phase, but one did not proceed in the randomized phase. The study protocol consisted of 21 study nights, defined as a night with at least 4 h of sensor glucose data between the time the system was activated at bedtime and the time it was discontinued in the morning (referred to as a “study night”). The hypoglycemia prediction algorithm was active for 14 nights and inactive for 7 nights of the 21-night period. Pump suspension occurred for a maximum of 2 h for a single event and could not exceed more than 120 min in a 150-min window or a cumulative total of 3 h for the whole night. Participants were instructed to use the system on consecutive nights if possible but were instructed to avoid system use during periods of illness or if the blood glucose level was ≥ 270 mg/dL with a ketone level of >0.6 mmol/L during the 2 h prior to bedtime. The 21 study nights needed to be completed within 35 calendar days. Participants were instructed to contact the study physician for a morning blood glucose level of ≥ 300 mg/dL, blood ketone level of ≥ 1.0 mmol/L, or urine ketone level of ≥ 40 mg/dL. Participants were contacted on an ad hoc basis for data transmission inquiries and on a scheduled weekly basis to check for adverse events and system usage problems. No limitations were placed on the adjustment of insulin therapy by participants and their physicians during the course of the study.

An objective of this pilot study was to evaluate and refine the control algorithm. The data were reviewed periodically during the study with the prestated goal of determining whether any changes should be made in the control algorithm. We were particularly interested in modifying the hypoglycemia prediction horizon if necessary. After the first 105 nights of the study (algorithm 1), the frequency of pump suspension was higher than expected, and the mean morning fasting blood glucose level was higher following intervention nights compared with control nights. The algorithm was then modified (algorithm 2) to reduce the hypoglycemia prediction horizon from 70 min to 50 min, to suspend the pump only when the CGM glucose value was ≤ 230 mg/dL, to not suspend the pump if there was a drop of ≥ 40 mg/dL in consecutive CGM readings, and to resume insulin delivery at the first rise in sensor glucose level following a suspension. After a review of data from 156 nights using algorithm 2, the hypoglycemia prediction horizon was reduced further (algorithm 3) from 50 min to 30 min. The algorithm was modified while subjects were completing the 21 study nights, so that subjects could be studied on multiple algorithms.

Statistical methods

Because the study was a feasibility and preliminary safety study, sample size was not statistically derived, and no formal

statistical testing was performed. The time period for outcome assessment each night was from system activation at night to deactivation in the morning. The closest blood glucose to the system activation and deactivation was taken as the bedtime and morning blood glucose, respectively. All participants entering the randomized trial were included in the analyses; 43 nights with <4 h of CGM data were not included. All outcomes were reported separately for each of the three algorithms.

The primary safety outcomes were fasting blood glucose, blood ketone, and urine ketone measurements. Secondary safety outcomes included the overnight CGM-measured mean glucose level and percentage of hyperglycemic values. Efficacy outcomes (reduction of hypoglycemia) included percentage of nights with CGM ≤ 70 mg/dL, CGM area under the curve ≤ 70 mg/dL, and percentage of morning blood glucoses ≤ 70 mg/dL. Similar analyses were conducted for a threshold of ≤ 60 mg/dL. For hypoglycemic events, duration of time with glucose values ≤ 60 mg/dL was computed.

To assess for the occurrence of false hypoglycemic values due to sensor anomalies, four clinicians, blinded to whether a night was intervention or control, reviewed all nights with a CGM nadir ≤ 60 mg/dL and judged whether or not the glucose tracing appeared physiologic. Hypoglycemia was considered to be real when at least two of the four graders classified it as such. Analyses were replicated using this outcome definition. Analyses were performed using SAS version 9.3 software (SAS Institute, Cary, NC).

Results

The analysis included 19 individuals with type 1 diabetes (age range, 18–56 years; 58% female; 100% white; hemoglobin A1c range, 6.0–7.7%) who completed 375 study nights in the

randomized phase (from 5 to 21 nights per participant; median, 21 nights). Five participants were studied using algorithm 1 (67 intervention and 38 control nights), 12 with algorithm 2 (108 intervention and 48 control nights), and nine with algorithm 3 (77 intervention and 37 control nights). Supplementary Tables S1–S3 (Supplementary Data are available online at www.liebertpub.com/dia) provide a data listing for each participant.

As a result of decreasing the projection horizon and modifying the algorithm for a more rapid restoration of basal insulin following a suspension, the mean glucose level at pump shut off decreased from 139 mg/dL (algorithm 1, 70-min horizon) to 113 mg/dL (algorithm 3, 30-min horizon), the peak glucose level following pump suspension decreased from 185 mg/dL to 135 mg/dL, the median duration of pump shut off decreased from 85 to 55 min, and the percentage of nights with a pump suspension decreased from 78% to 53% of nights (Table 1). With the first algorithm the mean morning blood glucose level was substantially higher on the intervention versus the control nights (158 ± 52 vs. 125 ± 53 mg/dL), but the percentage of nights with CGM glucose levels above 250 mg/dL was not higher (24% vs. 29%, respectively) (Table 2). With algorithm 2 the mean morning blood glucose level was 151 ± 57 mg/dL on intervention nights versus 138 ± 63 mg/dL on control nights; 15% versus 6% of nights, respectively, had peak CGM glucose levels above 250 mg/dL. With algorithm 3 the mean morning blood glucose level on intervention versus control nights was 144 ± 48 versus 133 ± 57 mg/dL; 21% versus 8% of nights, respectively, had peak CGM glucose levels above 250 mg/dL. A blood ketone level of >0.6 mmol/L was present on none, three, and one mornings following an intervention night for algorithms 1, 2, and 3, respectively, and on one morning following a control night for algorithm 2 (Table 2).

TABLE 1. DISTRIBUTION OF PUMP SUSPENSION AND DURATION PER NIGHT

	Intervention		
	Algorithm 1 (n = 5 participants)	Algorithm 2 (n = 12 participants) ^a	Algorithm 3 (n = 9 participants) ^a
Intervention nights (n)	67	108	77
Nights with pump suspension (n)	52 (78%)	84 (78%)	41 (53%)
Pump suspensions per night (n)			
[median (IQR)]	2 (1, 3)	1 (1, 3)	1 (0, 2)
Range	[0, 7]	[0, 8]	[0, 8]
0 shutoffs	22%	22%	47%
1–2 shutoffs	43%	47%	31%
3–4 shutoffs	31%	19%	12%
5–8 shutoffs	3%	11%	10%
Mean glucose at first shutoff (mg/dL) ^b	139 (37)	121 (29)	113 (33)
Peak glucose following first shutoff (mg/dL) ^b	185 (159, 234)	147 (122, 186)	135 (107, 189)
Shutoff duration per night (min) ^b			
[median (IQR)]	85 (45, 128)	70 (35, 108)	55 (25, 105)
Range	[5, 180]	[5, 175]	[5, 185]
5–30 min	21%	24%	32%
31–60 min	12%	20%	24%
61–120 min	37%	39%	22%
121–185 min	31%	17%	22%

^aHypoglycemia prediction horizon shortened from 70 min to 50 min to 30 min; new rule restarts insulin pump with first positive change in sensor glucose level following a suspension.

^bRestricted to nights with pump suspension.

IQR, interquartile range.

TABLE 2. SAFETY AND EFFICACY MEASURES ACROSS ALGORITHMS

	Algorithm 1		Algorithm 2		Algorithm 3	
	Control (n=5 participants)	Intervention (n=5 participants)	Control (n=10 participants)	Intervention (n=12 participants)	Control (n=8 participants)	Intervention (n=9 participants)
Nights (n)	38	67	48	108	37	77
CGM measurements per night (n) [median (IQR)]	103 (82, 110)	103 (88, 111)	86 (75, 96)	86 (74, 96)	91 (82, 103)	89 (77, 102)
Mean bedtime BG (mg/dL)	166 (51)	155 (46)	139 (45)	148 (47)	152 (41)	157 (44)
Mean overnight sensor glucose (mg/dL)	145 (42)	158 (34)	123 (40)	137 (36)	133 (37)	148 (42)
% of nights with CGM values ≤ 60 mg/dL						
Without clinicians' review ^a	9 (24%)	8 (12%)	12 (25%)	12 (11%)	8 (22%)	6 (8%)
With clinicians' review ^a	8 (21%)	8 (12%)	12 (25%)	10 (9%)	7 (19%)	5 (6%)
≤ 3 h from start	4 (11%)	5 (7%)	9 (19%)	10 (9%)	3 (8%)	6 (8%)
> 3 h from start	7 (18%)	3 (4%)	8 (17%)	8 (7%)	6 (16%)	2 (3%)
% of CGM values ≤ 60 mg/dL [median (IQR)]	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 1%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)
% of nights with CGM values $\leq 70 / \leq 60$ mg/dL						
> 0 min	26%/24%	19%/12%	33%/25%	19%/11%	30%/22%	16%/8%
> 30 min	24%/16%	13%/6%	31%/17%	15%/8%	22%/14%	10%/4%
> 60 min	21%/11%	10%/3%	25%/15%	11%/5%	14%/3%	8%/3%
> 120 min	11%/3%	0%/0%	15%/4%	5%/3%	8%/0%	3%/0%
% of nights with AUC 70/60 mg/dL						
> 0.00	26%/24%	18%/9%	33%/21%	18%/10%	27%/19%	14%/5%
> 2.00	11%/0%	4%/0%	15%/6%	6%/2%	14%/0%	4%/0%
> 5.00	3%/0%	0%/0%	4%/0%	3%/1%	0%/0%	0%/0%
% of CGM values 71–180 mg/dL [median (IQR)]	76% (46%, 100%)	71% (51%, 91%)	91% (68%, 100%)	90% (65%, 100%)	94% (69%, 100%)	89% (50%, 100%)
% of nights with CGM values $> 180 / > 250$ mg/dL						
> 0 min	63%/29%	78%/24%	29%/6%	56%/15%	49%/8%	60%/21%
> 30 min	55%/18%	72%/18%	23%/6%	46%/8%	35%/5%	52%/14%
> 60 min	47%/16%	64%/9%	21%/4%	38%/6%	32%/3%	40%/12%
> 120 min	34%/8%	54%/3%	17%/2%	27%/2%	22%/3%	32%/4%
> 240 min	24%/3%	19%/3%	10%/0%	16%/1%	14%/0%	23%/0%
% of nights with AUC 180/250 mg/dL						
> 0.00	63%/29%	78%/24%	29%/6%	56%/15%	49%/8%	60%/21%
> 2.00	47%/13%	63%/10%	19%/6%	36%/4%	30%/5%	40%/9%
> 10.00	34%/8%	37%/3%	10%/2%	19%/1%	16%/0%	29%/4%
> 20.00	11%/3%	6%/1%	6%/0%	5%/0%	5%/0%	14%/1%
Nights where patient was awoken (n) ^b	16 (42%)	21 (31%)	17 (35%)	22 (20%)	6 (16%)	17 (22%)
Nights with food intake for low treatment (n)	7 (18%)	5 (7%)	9 (19%)	6 (6%)	2 (5%)	4 (5%)
Mean morning BG (mg/dL)	125 (53)	158 (52)	138 (63)	151 (57)	133 (57)	144 (48)
% of mornings with BG						
$\leq 70 / \leq 60$ mg/dL	11%/8%	4%/1%	4%/0%	4%/1%	11%/5%	3%/1%
71–180 mg/dL	71%	63%	77%	70%	68%	71%
$> 180 / > 250$ mg/dL	18%/3%	33%/3%	19%/8%	26%/6%	22%/3%	26%/1%
Mornings (n) with						
Blood ketone > 0.6 mmol/L ^c	0	0	1 (2%)	3 (3%)	0	1 (1%)
Urine ketones ≥ 15 mg/dL ^d	1 (3%)	0	0	7 (7%)	0	0

Data are mean (SD) values, median (interquartile range [IQR]), or n (%) as indicated.

^aFour clinicians manually reviewed all nights with a continuous glucose monitoring (CGM) value of ≤ 60 mg/dL using an interface that blinded them to the treatment group. Each clinician judged whether the night was misclassified (false-positive) due to nonphysiologic explanations. A night was reclassified as not having a true glucose level ≤ 60 mg/dL if at least three clinicians separately agreed on a misclassified night.

^bPatient considered awoken if a metered measurement occurred or carbohydrate intake was reported 1 h after session started to 1 h before session ended.

^cFour blood ketone measurements were missing from the algorithm 1 group.

^dTen urine ketone measurements were missing (two from the algorithm 1 group, eight from the algorithm 2 group).

AUC, area under the curve; BG, blood glucose.

Overnight hypoglycemia with at least one CGM value ≤ 70 mg/dL occurred on 13 of 67 (19%) intervention nights versus 10 of 38 (26%) control nights with algorithm 1, 20 of 108 (19%) versus 16 of 48 (33%), respectively, with algorithm 2, and 12 of 77 (16%) versus 11 of 37 (30%), respectively, with algorithm 3. Hypoglycemia (≤ 60 mg/dL) occurred on 12% of intervention nights versus 21% of control nights with algorithm 1, 9% versus 25%, respectively, with algorithm 2, and 6% versus 19%, respectively with algorithm 3. Hypoglycemia (≤ 60 mg/dL) occurred for more than 1 h on 3% of intervention nights versus 11% of control nights with algorithm 1, 5% versus 15%, respectively, with algorithm 2, and 3% versus 3%, respectively, with algorithm 3. Overnight mean glucose and morning blood glucose levels generally were lower on nights with a suspension compared with nights without a suspension, demonstrating the system successfully suspended insulin delivery on nights with low glucose and did not suspend glucose on nights with high glucose (see Supplementary Table 4).

There were no instances of severe hypoglycemia, diabetic ketoacidosis, or other significant adverse events.

Discussion

Overnight hypoglycemia occurs frequently in individuals with type 1 diabetes, and fear of hypoglycemia is a deterrent for some patients to try to achieve tight control. Although it will still be several years before a fully functional automated closed-loop system will be available, suspension of insulin delivery from a sensor-augmented pump when a hypoglycemic threshold is reached is already available. The next logical step in the closed-loop development process is to suspend insulin delivery before hypoglycemia occurs. In this regard, we conducted a preliminary outpatient study to test an algorithm that suspends pump insulin delivery when hypoglycemia is predicted. During the course of the study, we modified the algorithm twice, largely to shorten the hypoglycemia prediction horizon, after finding that pump suspension was occurring on a high proportion of nights. Shortening the horizon caused fewer pump shut offs, and there was a trend to have less of an increase in overnight sensor glycemia and fasting capillary glucose levels.

The study demonstrated that a PLGS system could be safely implemented overnight. There were few instances of morning ketonemia and no cases of ketoacidosis or the need to change therapy as a result of mild ketosis. Our finding of infrequent ketonemia following pump suspension is consistent with prior studies that have shown that pump insulin delivery can be suspended for up to 5 h without producing significant ketonemia.⁷⁻⁹ In studies of sensor-augmented pumps with a low glucose suspend feature (Paradigm Veo™; Medtronic Diabetes), no significant ketosis or ketoacidosis has been reported in thousands of 2-h nocturnal pump suspensions.¹⁰⁻¹³

On intervention nights (algorithm operational), glucose levels tended to be lower on nights with pump suspension compared with nights without pump suspension, reflecting that there were lower glucose levels on nights triggering a suspension. However, not unexpectedly, when comparing all intervention nights (with and without pump suspension) with control nights, mean overnight glucose and morning fasting glucose levels tended to be higher on the intervention nights.

Although the study was not designed to statistically evaluate the success of the algorithm in reducing hypoglycemia,

the algorithm appeared to be successful in reducing nocturnal hypoglycemia (≤ 70 mg/dL) by 40%, and the number of nights with prolonged hypoglycemia ≤ 60 mg/dL for more than 1 h was reduced by 60% with active intervention. We had hypothesized that some of the hypoglycemia was due to previous (inappropriately large) insulin boluses given before going to bed; however, when we looked at the data there was an equal distribution of hypoglycemic events occurring within the first 3 h of going to bed (37 events) and the rest of the night (34 events).

Study participation was limited to individuals already using the MiniMed CGM system (in order to avoid the learning effect that occurs when CGM is first implemented) who had at least one CGM glucose value ≤ 70 mg/dL during the most recent 15 nights of CGM glucose data. This requirement, based on an analysis of the Juvenile Diabetes Research Foundation CGM randomized trial data,¹⁴ was instituted to increase the number of nights during which hypoglycemia would be expected to occur during the course of the study. The study used an innovative design in having a randomization schedule on the bedside computer and randomly assigned each night to be an intervention or control night unbeknownst to the participant until the next morning. This has the benefit over a crossover design (in which participants would have one intervention period and one control period, with the order of periods determined through randomization) in limiting the potential bias that can occur because of participant behavior being different on intervention versus control nights. The large amount of data that were collected in a relatively short period of time highlights the value of being able to conduct outpatient studies over many nights compared with a small number of nights in inpatient studies as well as the value in not having to artificially induce hypoglycemia. The inpatient studies allowed us to assess efficacy (preventing hypoglycemia), and the outpatient studies allowed us to also assess safety (increasing overnight and fasting hyperglycemia and assessing the risk of ketosis).

In summary, we have demonstrated that use of a nocturnal hypoglycemia prediction algorithm in the home setting is safe and is feasible with use of a bedside computer communicating with an insulin pump and CGM device. Preliminary efficacy data appear promising for reducing nocturnal hypoglycemia. Without full closed-loop control to deliver insulin to minimize hyperglycemia, an increase in mean glucose level overnight is inevitable. Because it will be several years before full closed-loop control will be available, we believe that an increase in mean glucose level of the magnitude that was observed in this study will be an acceptable trade-off for many individuals with type 1 diabetes if it reduces the frequency and duration of nocturnal hypoglycemia. In view of the success of this preliminary study, we are proceeding to conduct a larger randomized study to evaluate the efficacy and safety of this PLGS system to reduce the risk of prolonged nocturnal hypoglycemia overnight.

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Author Disclosure Statement

The relationships of the investigators with companies that make products relevant to the manuscript are listed below. Research funds where listed were provided to the legal entity that employs the individual and not directly to the individual. B.A.B. reports having received grant support and serving on the Medical Advisory Board for Medtronic MiniMed, Inc. and grant support and a speaker honorarium from Abbott Diabetes Care, Inc. C.K. reports having received consulting fees from Medtronic MiniMed, Inc. D.M.M. has research funding from Eli Lilly and Abbott Diabetes Care. F.C., P.C., D.M.W., H.P.C., B.W.B., J.L., J.S., and R.B. declare no competing financial interests exist. The study was designed and conducted by the investigators. The Writing Group (see Supplementary Data) collectively wrote the manuscript and vouch for the data. The investigators had complete autonomy to analyze and report the trial results. There were no agreements concerning confidentiality of the data between the National Institute of Diabetes and Digestive and Kidney Diseases, the authors, or their institutions. The Jaeb Center for Health Research had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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