A Randomized Trial of a Home System to Reduce Nocturnal Hypoglycemia in Type 1 Diabetes

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OBJECTIVE

Overnight hypoglycemia occurs frequently in individuals with type 1 diabetes and can result in loss of consciousness, seizure, or even death. We conducted an in-home randomized trial to determine whether nocturnal hypoglycemia could be safely reduced by temporarily suspending pump insulin delivery when hypoglycemia was predicted by an algorithm based on continuous glucose monitoring (CGM) glucose levels.

RESEARCH DESIGN AND METHODS

Following an initial run-in phase, a 42-night trial was conducted in 45 individuals aged 15–45 years with type 1 diabetes in which each night was assigned randomly to either having the predictive low-glucose suspend system active (intervention night) or inactive (control night). The primary outcome was the proportion of nights in which ≥1 CGM glucose values ≤60 mg/dL occurred.

RESULTS

Overnight hypoglycemia with at least one CGM value ≤60 mg/dL occurred on 196 of 942 (21%) intervention nights versus 322 of 970 (33%) control nights (odds ratio 0.52 [95% CI 0.43–0.64]; $P < 0.001$). Median hypoglycemia area under the curve was reduced by 81%, and hypoglycemia lasting >2 h was reduced by 74%. Overnight sensor glucose was >180 mg/dL during 57% of control nights and 59% of intervention nights ($P = 0.17$), while morning blood glucose was >180 mg/dL following 21% and 27% of nights, respectively ($P < 0.001$), and >250 mg/dL following 6% and 6%, respectively. Morning ketosis was present <1% of the time in each arm.

CONCLUSIONS

Use of a nocturnal low-glucose suspend system can substantially reduce overnight hypoglycemia without an increase in morning ketosis.

Overnight hypoglycemia occurs frequently in individuals with type 1 diabetes, and fear of hypoglycemia is a deterrent for some patients to achieve tight control. In a study utilizing continuous glucose monitoring (CGM), nocturnal hypoglycemia (≤60 mg/dL) occurred during 8.5% of nights, with 23% of events lasting at least 2 h (1). A major concern with prolonged nocturnal hypoglycemia is that it can lead to seizure or, in rare cases, death (2).

Since hypoglycemia results from insulin delivery, the ideal solution would be to suspend insulin delivery before hypoglycemia occurs, which is only possible in patients who use an insulin infusion pump. The Automation to Simulate Pancreatic Insulin REsponse (ASPIRE) Study (3) showed that suspension of pump insulin delivery

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**A complete list of the members of the In Home Closed Loop Study Group can be found in the Supplementary Data online.*

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when a near-hypoglycemia glucose threshold is reached can reduce the frequency and duration of hypoglycemia without increasing hyperglycemia. The next logical step is to suspend insulin delivery earlier, when the glucose trend predicts hypoglycemia.

We developed such a hypoglycemia prediction algorithm and have tested it in a system in which a CGM device communicates with an insulin pump via a laptop computer on which the algorithm resides (4). Following demonstration of efficacy by reducing nocturnal hypoglycemia in an inpatient study (5) and an outpatient pilot study (6), the current randomized trial was designed to assess the efficacy and safety of home use of the automated nocturnal predictive low-glucose suspend system in a larger number of individuals with type 1 diabetes over a longer time period.

RESEARCH DESIGN AND METHODS

The study was conducted at three clinical centers. The protocol was approved by each institutional review board, and written informed consent was obtained from each participant or parent, with assent obtained as required. An independent data and safety monitoring board provided oversight. The study is listed on ClinicalTrials.gov (NCT01591681). Key aspects of the study protocol are described below.

Major eligibility criteria included ages 15–45 years; type 1 diabetes with use of daily insulin therapy for ≥1 year and an insulin infusion pump for ≥6 months; and glycated hemoglobin level measured with a point-of-care device ≤8.0%. Exclusion criteria are listed in Supplementary Table 1.

The pump suspension system consisted of a MiniMed Paradigm REAL-Time Veo System and Enlite glucose sensor (Medtronic Diabetes, Northridge, CA), in which the CGM and pump communicated with a bedside laptop computer that contained the hypoglycemia prediction algorithm (referred to as "the system"). The system used a Kalman filter to estimate the glucose level and rate of change and suspended basal insulin delivery if glucose was predicted to fall <80 mg/dL in the next 30 min (6). Additional suspension/restart rules included a threshold suspend override at 70 mg/dL, no suspension if CGM >230 mg/dL or if a pressure-induced sensor attenuation was suspected based on glucose rate of change, and restoration of basal insulin on the first CGM rise following a suspension. For safety reasons, pump suspension could not exceed 120 min in a 150-min window or a cumulative total of 180 min nightly. Audible alarms were set at 60 mg/dL on both intervention and control nights. Additional details about the system have been published (6).

A run-in phase preceded the randomized trial. During the initial part of the run-in phase, CGM was initiated and used for 10–15 days to verify that the participant could successfully use the CGM device and to document a minimum amount of nocturnal hypoglycemia (at least one night with a sensor glucose value ≤60 mg/dL or at least 3 different nights with a sensor glucose value ≤70 mg/dL). Successful participants then used the complete system at home for 5 nights to verify the ability to use it properly. Three participants did not successfully complete the first part of the run-in phase, and one additional participant did not successfully complete the second part (Supplementary Fig. 1).

During the randomized trial, the system was used until 42 nights with at least 4 h of sensor glucose data were completed. 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, with half of the nights being intervention nights and half control nights. A bedtime blood glucose level between 90 and 270 mg/dL was required to start the system. Participants were instructed to use the system on consecutive nights if possible but to avoid system use during periods of illness. The maximum allowable number of days to complete the 42 nights of the study was 70. Supplementary Fig. 2 shows a system schematic and example overnight data profile for an intervention night.

When the system was stopped in the morning, blood glucose (with OneTouch Ultra2 meter; LifeScan, Milpitas, CA), blood ketone (with Precision Xtra meter; Abbott Diabetes Care, Alameda, CA), and urine ketone (with Ketostix strips; Bayer, Pittsburgh, PA) levels were measured, and overnight carbohydrate intake was recorded. During the day, the participant used the CGM device and pump as it would be prescribed for usual diabetes management (without the algorithm being active). The threshold-based low-glucose suspend feature of the Veo pump was disabled while the pump was used in the study.

Adverse event reporting included severe hypoglycemia, diabetic ketoacidosis, and any study or device-related event.

Statistical Methods

Sample size was computed to be 45 participants using the system for 42 nights (21 nights with the system active and 21 control nights) for a total of 1,890 nights in order to have 90% power with a type 1 error rate of 5% to reject the null hypothesis of no difference in nocturnal hypoglycemia, assuming a true population rate of 30% of control nights and 15% of intervention nights with hypoglycemia after adjusting for the correlation from repeated nights and misclassification due to sensor inaccuracy (7).

The analysis followed the intent-to-treat principle with each night analyzed by the intervention arm assigned by randomization. The time period for outcome assessment each night was from the participant's initiation of the system at bedtime until deactivation the following morning. All randomized nights were included in safety analyses; however, only randomized nights with ≥4 h of CGM glucose data were included in the efficacy analysis based on an a priori rule.

The primary outcome was the proportion of nights in which one or more CGM glucose value ≤60 mg/dL occurred. Numerous other overnight CGM-measured outcomes were assessed. Primary safety outcomes included morning blood glucose and ketone levels. For continuous variables, repeated-measures regression models were used to test the differences between the two treatment arms, accounting for correlated data from the same participant and for the overnight measures, adjusting for the bedtime blood glucose value. Ranked normal score transformations were used for continuous outcomes variables with a skewed distribution. For binary variables, repeated-measures logistic regression was used to test the differences between the two treatment arms using mixed-effects and a within-subject

autocorrelation structure to account for multiple nights from the same subject. Four clinicians, blinded to control versus intervention, reviewed each night with a hypoglycemic outcome to opine whether the drop in glucose level appeared to be physiologic. In a secondary analysis, only outcomes in which at least two of four expert reviewers believed the outcome to be valid were included. All *P* values are two-tailed, and analyses were performed using SAS 9.3 (SAS Institute).

RESULTS

The randomized trial included 45 individuals with type 1 diabetes (age range 15–45 years; 47% male; 93% Caucasian; median type 1 diabetes duration 15 years; median glycated hemoglobin level 6.8%) (Supplementary Tables 2 and 3). Forty-one (91%) of the 45 participants completed the protocol-specified 42 nights of the study (30, 39, 41, and 41 nights completed in the other four participants). The median number of nights to complete the study was 60 (Supplementary Table 6). Overall, there were 1,912 nights in the analyses, with 942 being intervention nights and 970 control nights.

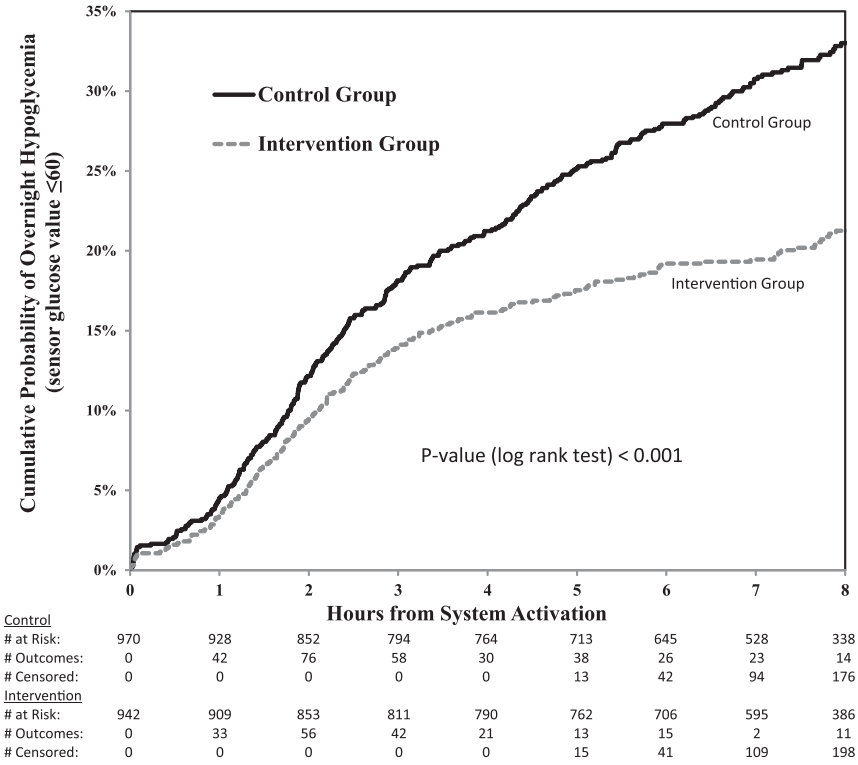
One or more pump suspensions occurred on 719 (76%) of the 942 intervention nights, with a median total duration of pump suspension of 71 (interquartile range [IQR] 29–115) minutes (Supplementary Table 4). On 10% of nights, there was a pump suspension lasting 120 min within a 150-min window, and on 3% of nights, cumulative suspension time was the maximum 3 h.

Overnight hypoglycemia with at least one CGM value ≤60 mg/dL occurred on 196 of 942 (21%) intervention nights versus 322 of 970 (33%) control nights (odds ratio 0.52 [95% CI 0.43–0.64]; $P < 0.001$) (Table 1). Results were consistent for other hypoglycemia outcomes overall (Table 1) and within age groups 21–45 and 15–20 years (Supplementary Table 5). As shown in Fig. 1, the treatment arm difference in first overnight occurrence

Table 1—Efficacy and safety outcome measures

	Control arm (*N* = 45)	Intervention arm (*N* = 45)	*P* value
Number of nights	970	942	
Bedtime measures			
Bedtime sensor glucose, mg/dL [median (IQR)]	144 (109–192)	143 (110–189)	
Bedtime blood glucose, mg/dL [median (IQR)]	152 (114–197)	144 (115–195)	
Overnight measures using CGM sensor			
Number of measurements/night [median (IQR)]	96 (84–110)	96 (85–107)	
Hypoglycemia outcomes			
Percentage of nights with ≥1 value, mg/dL			
≤50	19	10	<0.001
≤60*	**33**	**21**	**<0.001**
≤70	45	32	<0.001
Percentage of nights with ≥2 consecutive values ≤60 mg/dL	31	19	<0.001
Percentage of nights with ≥5 consecutive values ≤60 mg/dL	25	14	<0.001
Participant time <60 mg/dL per 8 h, min [median (IQR)]†	23 (11–45)	7 (3–12)	<0.001
Participant time <50 mg/dL per 8 h, min [median (IQR)]†	10 (4–25)	2 (0–4)	<0.001
Participant overnight AUC 60 mg/dL per 8 h [median (IQR)]†	215 (88–482)	40 (18–96)	<0.001
Participant LBGI [median (IQR)]	2.28 (1.45–3.52)	0.92 (0.69–1.63)	<0.001
Hyperglycemia outcomes			
Percentage of nights with ≥1 value, mg/dL			
>180	57	59	0.17
>250	20	20	0.93
>300	5	6	0.37
>400	0	0	—
Participant time >250 mg/dL per 8 h, min [median (IQR)]†	12 (5–19)	10 (4–19)	0.78
Participant overnight AUC 250 mg/dL per 8 h [median (IQR)]†	236 (83–772)	219 (72–666)	0.98
Participant HBGI [median (IQR)]	4.17 (2.99–5.30)	3.99 (2.50–5.73)	0.95
Overall control outcomes			
Overnight mean glucose, mg/dL [median (IQR)]	125 (98–163)	132 (110–163)	<0.001
Percentage of glucose values 71–180 mg/dL [median (IQR)]	75 (46–93)	82 (54–99)	<0.001
Morning measures			
Morning blood glucose, mg/dL [median (IQR)]‡	129 (96–173)	144 (114–186)	<0.001
Percentage of mornings with blood glucose, mg/dL			
≤60	4	<1	<0.001
≤70	9	2	<0.001
71–180	70	70	0.87
>180	21	27	<0.001
>250	6	6	0.71
Percentage of mornings with blood ketone >1.0 mmol/L§	0.3	0.1	0.62‖
Percentage of mornings with urine ketones ≥15 mg/dL¶	2	3	0.10

*Boldface indicates prespecified primary outcome. †For each patient, time below and above a threshold and AUC was divided by total time and multiplied by 8 h. ‡One morning blood glucose measurement in the control arm was missing. §Nine blood ketone measurements in the control arm and 10 blood ketone measurements in the intervention arm were missing. ‖*P* value computed using permutation test because parametric analysis had convergence issue. ¶Twelve urine ketone measurements in the control arm and 12 urine ketone measurements in the intervention arm were missing.



Control									
# at Risk:	970	928	852	794	764	713	645	528	338
# Outcomes:	0	42	76	58	30	38	26	23	14
# Censored:	0	0	0	0	0	13	42	94	176
Intervention									
# at Risk:	942	909	853	811	790	762	706	595	386
# Outcomes:	0	33	56	42	21	13	15	2	11
# Censored:	0	0	0	0	0	15	41	109	198

Figure 1—Cumulative probability of first overnight hypoglycemia event. During the first 3 overnight hours, the cumulative probability of hypoglycemia (sensor glucose value ≤60 mg/dL) was 14% on intervention nights compared with 18% on control nights, while after the first 3 hours, the conditional probabilities of a first overnight hypoglycemia event were 8 and 18%, respectively.

of hypoglycemia was most prominent after the first 3 h. Results were similar when hypoglycemic outcomes were confirmed by the clinician-blinded review in which hypoglycemic glucose values were considered to be invalid (nonphysiologic) on 27 intervention nights and 30 control nights. Reclassifying these nights as "no hypoglycemia," overnight hypoglycemia with at least one CGM value ≤60 mg/dL occurred on 169 of 942 (18%) intervention nights versus 292 of 970 (30%) control nights (odds ratio 0.50 [95% CI 0.41–0.62]; $P < 0.001$).

The cumulative amount of hypoglycemia exposure was substantially less on intervention nights compared with control nights (Table 1). Median hypoglycemia area under the curve (AUC) was 81% lower on intervention nights compared with control nights, median time <60 mg/dL was 70% lower, and median time <50 mg/dL was 80% lower (Table 1). Results were unchanged when these analyses included the 95 nights with <4 h of sensor glucose data. Sensor values were ≤60 mg/dL for >2 h on 3% of intervention nights versus 11% of control nights ($P < 0.001$; Fig. 2, Supplementary Fig. 3, and Supplementary Table 8). Participants reported overnight carbohydrate intake on 75 (8%) intervention nights and 142 (15%) control nights.

Although overnight mean glucose was slightly higher on intervention than control nights (median 132 [IQR 110–163] vs. 125 [98–163] mg/dL, respectively; $P < 0.001$) (Fig. 3), the percentages of nights with a glucose value >180 or >250 mg/dL were not (59 vs. 57% >180 mg/dL, $P = 0.17$; and 20 vs. 20% ≥250 mg/dL, $P = 0.93$), and the median percentage of glucose values 71–180 mg/dL was higher on intervention nights compared with control nights (82 [IQR 54–99] vs. 75% [46–93%], respectively; $P < 0.001$) (Table 1).

Median morning blood glucose was 144 mg/dL (IQR 114–186 mg/dL) following intervention nights versus 129 mg/dL (IQR 96–173 mg/dL) following control nights ($P < 0.001$). In each arm, 6% of nights had values >250 mg/dL. As seen in Table 1, the frequency of elevated morning urine or blood ketones was low and similar in the two treatment arms. Median glycated hemoglobin level of 6.8% at study completion was unchanged from baseline (Supplementary Table 7).

CONCLUSIONS

Several inpatient and closely monitored short-term outpatient studies in camps or other settings have shown reduction

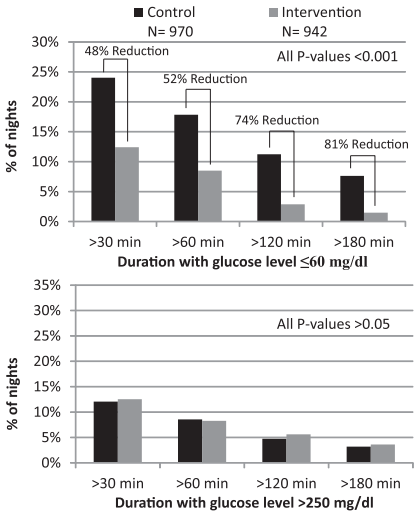


Figure 2—Duration of overnight hypoglycemia (*top*) and hyperglycemia (*bottom*).

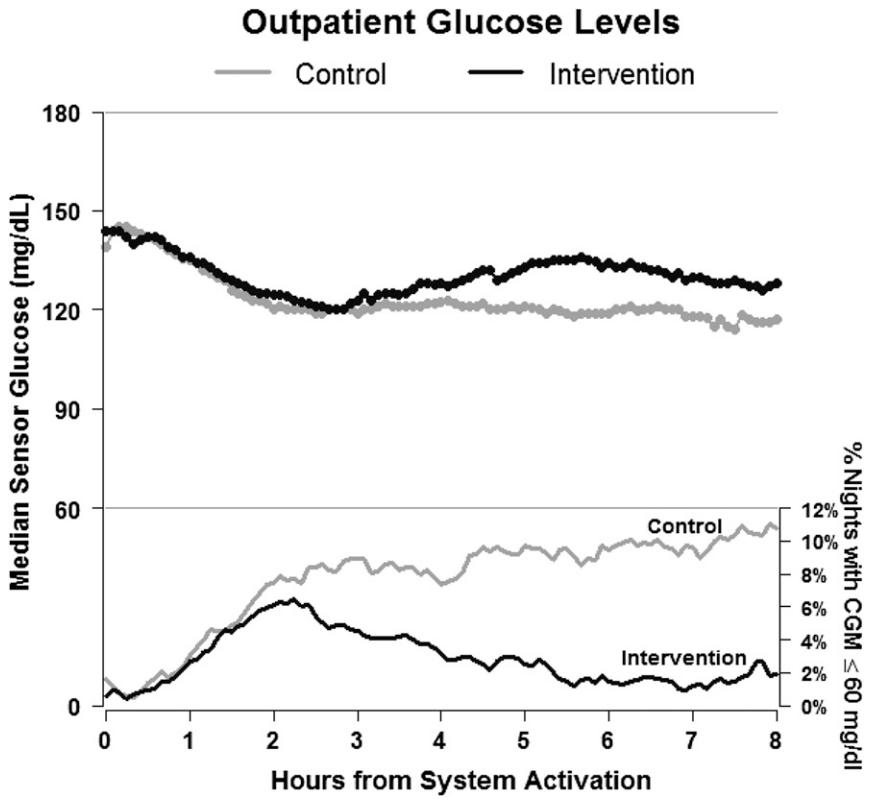


Figure 3—Sensor glucose levels overnight. The *top portion* of the figure shows the median glucose level across all nights in each treatment arm. The *bottom portion* of the figure shows the frequency of glucose level ≤60 mg/dL across all nights in each treatment arm.

in overnight hypoglycemia using a predictive algorithm (8–12). In this randomized, controlled trial conducted during 1,912 nights, home use of a predictive low-glucose suspend system substantially reduced the frequency and duration of nocturnal hypoglycemia. Importantly, cumulative exposure to hypoglycemia as measured with the AUC was reduced by 81%, and episodes of prolonged overnight hypoglycemia (≤60 mg/dL for >2 h) were reduced more than threefold. This was accomplished without an increase in overnight hyperglycemia despite the fact that pump suspension occurred on 76% of intervention nights. Although morning blood glucose levels were higher following intervention nights, the frequency of levels >250 mg/dL (6 vs. 6%) and frequency of morning ketosis (0.1 vs. 0.3%) were similar. There were no serious adverse events in either arm.

The system was most effective as the night progressed. This likely reflects the inability of the system to effectively compensate during the initial part of the night for insulin given prior to the system being activated for the night. Given current insulin analog actions, the effect of insulin delivered prior to activation of the system will be a limitation of any artificial pancreas system used intermittently and is an important finding in these data. The potential tradeoff for reducing hypoglycemia with insulin suspension is an increase in hyperglycemia and theoretically an increased risk of ketoacidosis. Importantly, ketosis was no more likely after an intervention versus control night, alleviating potential concern that suspension of insulin delivery could increase the risk of ketoacidosis. Thus, as demonstrated in this study and others (3,6,13–22), insulin delivery from a pump can be safely stopped for several hours without developing substantial ketosis. Although the study was not long enough to see the full effect of hyperglycemia on glycated hemoglobin levels, it was reassuring to find that levels did not increase during the study.

The study used a novel design in which random assignment to intervention or control was made each night when the system was activated, and the participant was blinded to that night's assignment. This design minimized bias due to awareness of treatment assignment, which could occur with either a parallel group or a two-period crossover design. The primary outcome of a single glucose value ≤60 mg/dL was chosen for simplicity and because prior studies had shown a high correlation between this outcome and numerous other hypoglycemia outcomes (14). However, the secondary outcomes related to prolonged hypoglycemia are more clinically relevant. The profound reduction seen in duration of hypoglycemia is important since prolonged very low glucose levels can produce loss of consciousness, seizure, or even death (23–26). To account for sensor inaccuracy, the sample size (number of nights) was increased by a factor of 6 to account for anticipated false-positive and false-negative hypoglycemia outcomes, estimated from prior study data (14). The observed 33% frequency of nocturnal hypoglycemia ≤60 mg/dL on the control nights was similar to the 30% projection used in the sample size estimation based on data from the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Trial for participants with glycated hemoglobin levels ≤8.0% (27,28). Use of the system's sensor for outcome assessment would not affect the probability of a type 1 error

but could produce a slight overestimate of the true treatment effect (7).

The study cohort was limited to individuals with type 1 diabetes and a glycated hemoglobin level ≤8.0% who demonstrated at least a minimum amount of nocturnal hypoglycemia during a run-in phase. These restrictions were placed since a prior study showed that the frequency of nocturnal hypoglycemia with higher glycated hemoglobin levels was low, which would impair the ability to compare intervention and control nights (29). Thus, although the predictive low-glucose suspend system would work irrespective of glycated hemoglobin level, the benefit-to-risk ratio might differ in those with very infrequent nocturnal hypoglycemia. The study included individuals 15–45 years old, and the results may not be generalizable to younger and older ages. We will be conducting a trial using this predictive low-glucose suspend system in 3–14 year olds. Although our study was of short duration, we expect the benefit and low risk would be similar with longer duration of use outside of a clinical trial.

The development of a closed-loop system to control glucose levels will be an incremental process, with safety being the foremost criterion for progression from one stage to the next (30). The first step in the progression toward a fully closed-loop system is suspending insulin when the sensor glucose level is in the hypoglycemic range and the patient does not respond to an alarm or suspending insulin when hypoglycemia is predicted. Threshold suspension, available on the Veo pump outside the U.S. since 2009, was shown in a study by Ly et al. (18) to reduce the frequency of moderate or severe hypoglycemic events compared with pump use alone. In the ASPIRE study (3), the Veo system was shown to be effective in reducing biochemical hypoglycemia without increasing hyperglycemia. Although our results using a predictive hypoglycemia algorithm to suspend insulin delivery showed an 81% relative reduction in the hypoglycemia AUC compared with the 37.5% relative reduction found in the ASPIRE study, substantial differences in study design preclude a conclusion that predictive suspension is better than threshold suspension. Full nocturnal closed loop has the potential to mitigate both hypoglycemia and hyperglycemia, and early inpatient and outpatient studies are promising (8,11,31,32).

In conclusion, we have demonstrated that in 15–45 year olds with type 1 diabetes and frequent nocturnal hypoglycemia, use of our nocturnal low-glucose suspend system can substantially reduce overnight hypoglycemia without a meaningful increase in hyperglycemia and no increase in ketoacidosis. Use of a nocturnal low-glucose suspend system has the potential to not only reduce nocturnal hypoglycemia but also to reduce fear of hypoglycemia, which can be a significant deterrent to achieving blood glucose targets.

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Duality of Interest. D.M.M. received grants from American Diabetes Association–Medtronic. B.A.B. received grants from Medtronic, Inc. and has a patent on Kalman filter–based hypoglycemia prevention algorithm pending. H.P.C., F.C., and B.W.B. have a patent on Kalman filter–based hypoglycemia prevention algorithm pending. I.H. serves as a board member for Medtronic. R.S. received grants from and has an advisory board membership for Medtronic. D.M.W. has a patent on Kalman filter–based hypoglycemia prevention algorithm pending. C.K. has received consultant fees from Medtronic. R.W.B. received grants to his institution from the National Institutes of Health and the Juvenile Diabetes Research Foundation for conducting the study and payments to his institution from Animas for statistical consulting outside the submitted work. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. D.M.M., B.A.B., and R.W.B. wrote the manuscript, contributed to discussion, and reviewed and edited the manuscript. P.C., J.L., and C.K. contributed to discussion and reviewed and edited the manuscript. H.P.C., I.H., F.C., B.W.B., T.A., T.P., R.S., R.P.W., and D.M.W. researched data, contributed to discussion, and reviewed and edited the manuscript. All of the authors designed and conducted the study. D.M.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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