Predictive Hyperglycemia and Hypoglycemia Minimization: In-Home Evaluation of Safety, Feasibility, and Efficacy in Overnight Glucose Control in Type 1 Diabetes

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OBJECTIVE

The objective of this study was to determine the safety, feasibility, and efficacy of a predictive hyperglycemia and hypoglycemia minimization (PHHM) system compared with predictive low-glucose insulin suspension (PLGS) alone in overnight glucose control.

RESEARCH DESIGN AND METHODS

A 42-night trial was conducted in 30 individuals with type 1 diabetes in the age range 15–45 years. Participants were randomly assigned each night to either PHHM or PLGS and were blinded to the assignment. The system suspended the insulin pump on both the PHHM and PLGS nights for predicted hypoglycemia but delivered correction boluses for predicted hyperglycemia on PHHM nights only. The primary outcome was the percentage of time spent in a sensor glucose range of 70–180 mg/dL during the overnight period.

RESULTS

The addition of automated insulin delivery with PHHM increased the time spent in the target range (70–180 mg/dL) from 71 ± 10% during PLGS nights to 78 ± 10% during PHHM nights (_P_ < 0.001). The average morning blood glucose concentration improved from 163 ± 23 mg/dL after PLGS nights to 142 ± 18 mg/dL after PHHM nights (_P_ < 0.001). Various sensor-measured hypoglycemic outcomes were similar on PLGS and PHHM nights. All participants completed 42 nights with no episodes of severe hypoglycemia, diabetic ketoacidosis, or other study- or device-related adverse events.

CONCLUSIONS

The addition of a predictive hyperglycemia minimization component to our existing PLGS system was shown to be safe, feasible, and effective in overnight glucose control.

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There have been significant advances in the development of automated insulin delivery in recent years. In general, these systems use feedback from continuous glucose sensors to inform insulin delivery based upon current glucose values, rate of change, and various prediction models. Several approaches have demonstrated the feasibility of feedback-based insulin modulation, and advances in both sensor performance and algorithms have demonstrated a reduction in hypoglycemia, glucose variability, and decreased mean glucose levels in controlled inpatient settings (1–5) as well as outpatient studies (6–13) extending to 12 weeks of use in the home setting (14).

In patients with type 1 diabetes, the overnight period is a critical time for optimizing glucose control given the risk of prolonged nocturnal hypoglycemia, which can lead to seizures (15) and, rarely, death (16). Patients with type 1 diabetes have reduced counterregulatory hormone responses during sleep (17) as well as increased acoustic arousal threshold (18) and therefore do not always respond to hypoglycemia alarms (19). Much of the benefit conferred by the use of current closed-loop systems is largely gained through improved overnight control (20,21). In a multinational study (21) of 30 adults using the insulin-only closed-loop system initially overnight for 2 weeks followed by 24/7 closed-loop control for another 2 weeks, the overall percentage of time spent during the daytime and nighttime in range (70–180 mg/dL) was 73% for both overnight-only and 24/7 closed-loop control. Both were superior to sensor-augmented pump therapy alone.

A central objective in our approach has been to develop a simple system that was primarily operational at night, with minimal alarms and requiring minimal system maintenance, allowing patients to have undisturbed sleep. We have previously developed and tested a Kalman filter–based predictive low-glucose insulin suspension (PLGS) system in >2,600 nights in participants between 4 and 45 years of age (22,23). These initial randomized studies demonstrated a clear reduction in the duration of time spent at <60 mg/dL for >3 h, ranging from 68% to 81% across all age groups compared with sensor-augmented pump therapy. The reduction in hypoglycemia was accompanied by a modest increase in mean morning

glucose values ranging from 4 to 17 mg/dL, depending on the age group. To further improve glucose control, we added an insulin-dosing component to the existing PLGS to create a predictive hyperglycemia and hypoglycemia minimization (PHHM) system, allowing small amounts of insulin to be delivered beyond the existing predetermined basal insulin delivery. The objectives of this study were to determine the feasibility, efficacy, and safety of PHHM versus PLGS alone in a 6-week randomized controlled trial.

RESEARCH DESIGN AND METHODS

This 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. Major eligibility criteria included age range of 15–45 years, diagnosis of type 1 diabetes with use of daily insulin therapy for ≥12 months, and use of insulin pump therapy for ≥6 months. Participants were required to have an enrollment glycated hemoglobin (HbA$_{1c}$) concentration of ≤10.0% (86 mmol/mol), to live with a person available to provide assistance when the study system was in use at night, and to ensure uninterrupted internet access during system use. Participants were excluded if they had a history of diabetic ketoacidosis or severe hypoglycemia within the 6 months preceding study enrollment, were pregnant, or had a medical and/or psychiatric condition considered to interfere with the ability to complete the protocol. Additional eligibility criteria are listed in Supplementary Table 1.

PLGS

Details of the PLGS algorithm have been described previously (23–25) and are briefly summarized here. The algorithm suspended basal insulin delivery if the current sensor glucose concentration was ≤70 mg/dL at any time or <230 mg/dL and predicted to fall to <80 mg/dL in the next 50 min. Basal insulin was restored on the first sensor rise during insulin suspension, and suspension time could not exceed 120 min in a 150-min window or a cumulative total of 180 min/night. The PLGS component of the algorithm functioned during both intervention and control nights, enabling us to independently assess the effects of the hyperglycemia minimization component.

PHHM

Insulin was added via a series of automated fractional correction boluses for predicted hyperglycemia. Using a Kalman filter and a prediction horizon of 30 min, the system delivered an automated correction bolus when the estimated glucose concentration was predicted to exceed 140 mg/dL. The correction bolus used an insulin sensitivity factor calculated using individualized total daily dose (TDD) of insulin (1,800/TDD) with a target of 140 mg/dL, accounting for insulin-on-board (IOB) from any prior boluses. The IOB calculation used a 224-min linear insulin decay curve. The bolus amount was limited to 10% of the calculated amount for a correction to 140 mg/dL. This was a feedback process that occurred every 5 min. If there was no predicted hypoglycemia, the preprogrammed basal rate was continued. The system allowed the participant to modify the basal rates during the study and allowed manual boluses overnight if desired by the participant. Safety constraints included an IOB limit of 6× the basal rate (in units per hour), a maximum individual bolus of 7.5 units, and a maximum overnight cumulative bolus of 1.75× the mean basal insulin that would have been delivered over 8 h.

System

Both the PHHM and PLGS algorithms were implemented using a bedside computer with wireless communication to an insulin pump. The system included a MiniMed Paradigm REAL-Time Veo System and enhanced Enlite glucose sensor (Medtronic Diabetes, Northridge, CA), in which the sensor and pump communicated with a bedside laptop computer. Audible sensor glucose alerts were set at 60 and 300 mg/dL on the pump, but there were no additional alerts for automated pump suspensions or automated correction boluses. There were real-time automated notifications to clinical staff, triggered by glucose values <60 or >300 mg/dL or for the loss of sensor signal or loss of communication with the remote monitoring system after 90 min. Participants used the Bayer Contour Next Link Meter for capillary blood glucose monitoring (Bayer HealthCare LLC, Whippany, NJ).

Synopsis of Study Protocol

A run-in phase preceded the randomized trial. During the initial part of the

run-in phase, the sensor was initiated and used for 14–21 days to verify that the participant could successfully use the pump and sensor. Successful participants then used the complete system with the PHHM activated at home for 5 nights to verify the ability to use it successfully. Three participants did not successfully complete the first part of the run-in phase (Supplementary Fig. 2).

During the randomized trial, the system was used until 42 nights were completed with at least 4 h of sensor glucose data per night. Each night, following initiation procedures that included verification that the meter-measured blood glucose concentration was between 90 and 270 mg/dL, the system randomly activated either PHHM or PLGS according to a predefined schedule with the aim of completing 21 nights with PHHM and 21 nights with PLGS. Participants were blinded to the assignment. Participants were advised to use the system on consecutive nights if possible but to avoid system use during periods of illness. The maximum number of days to complete the 42 nights of the study was 90 days. Upon waking, the system was stopped, a meter blood glucose level was measured, and overnight carbohydrate intake was recorded. Participants were instructed to perform a blood ketone test if the blood glucose concentration was ≥300 mg/dL for >1 h or ≥400 mg/dL at any point during system use. During the day, participants used the Veo pump and enhanced Enlite glucose sensor in sensor-augmented pump mode only. The threshold-based low glucose suspend feature of the Veo pump was disabled during the study.

During the randomized trial, study visits occurred after completion of the run-in phase (baseline), after 21 days, and after completion of the study. HbA$_{1c}$ was measured using a point-of-care device (DCA 2000 or DCA Vantage; Siemens) at study enrollment and at each randomized trial visit. Adverse event reporting included severe hypoglycemia (participant required assistance of another person because of altered consciousness and required administration of carbohydrate or glucagon, or other resuscitative actions), diabetic ketoacidosis (as defined by the Diabetes Control and Complications Trial [26]), and any study- or device-related event.

Statistical Methods

The primary outcome was the percentage of time spent in the concentration range of 70–180 mg/dL pooled across nights. Assuming an SD of 8% (derived from prior studies) (23), a type I error rate of 5%, and a two-sided test with the null hypothesis stating that the difference is zero, a sample size of 29 participants using the system for 42 randomly assigned nights (21 PLGS and 21 PHHM nights) provided 90% statistical power to detect a difference as small as 5.0% in the primary outcome. The sample size was rounded up to 30 participants.

Analyses followed the intention-to-treat principle, with each night analyzed by the treatment arm assigned by randomization. Analysis included sensor readings from the time of system initiation at bedtime until deactivation the following morning. All participants and all randomized nights were included in the primary analysis.

Continuous glucose monitoring (CGM)–derived outcome measures were calculated by pooling sensor data over nights by treatment arm for each participant. Repeated-measures regression models with an unstructured covariance structure were used to test the differences between the two treatment arms while adjusting for the averaged bedtime blood glucose value across nights. Logarithmic or square root transformations were used for secondary outcome variables with a skewed distribution.

Additional analyses were performed for night-level binary secondary outcomes (e.g., the proportion of nights with at least one sensor glucose concentration of <70 mg/dL). These analyses were restricted to nights with at least 4 h of available sensor data. Generalized linear mixed models with a logistic or identity link function were used to test the differences between the two treatment arms using random participant effects and a within-participant autocorrelation structure to account for multiple nights from the same participant, while adjusting for the bedtime blood glucose levels.

For sensor accuracy analysis, all measurements made using the home blood glucose meter between the first and last day of randomized use were paired to the closest sensor reading within ±5 min. The difference, absolute relative difference (ARD), and International Organization for Standardization criteria (27)

(for reference values <100 mg/dL, CGM value within ±15 mg/dL, and reference values ≥100 mg/dL, the CGM value was within ±15%) were computed for each pair.

The percentage of time spent in the range from 70 to 180 mg/dL was the primary outcome, and the other efficacy metrics were considered secondary exploratory analyses. No adjustment was made for multiple comparisons. All P values are two tailed, and analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

The trial included 30 participants, 15–43 years of age, 50% male, 87% Caucasian, with a median duration of type 1 diabetes of 17 years, a median HbA$_{1c}$ level of 7.5% (58 mmol/mol) at study enrollment, and a median daily insulin dose of 0.58 units/kg/day (Supplementary Table 3). All 30 participants completed the protocol-specified 42 nights of the study (Supplementary Fig. 2). The median number of nights to complete the study was 66. Overall, there were 1,353 randomized nights included in the primary analysis with a median of 8.1 h of sensor data per night, for a total of 10,711 h of sensor data. Secondary night-level analyses were limited to the 1,289 nights (95%) with ≥4 h of sensor data.

Among randomized nights with ≥4 h of sensor data, one or more pump suspensions occurred on 433 (68%) of the 641 PLGS nights and on 459 (71%) of the 648 PHHM nights. The median total duration of suspension on nights with a pump suspension was 68 min (interquartile range [IQR] 29, 115) during PLGS nights and 63 min (IQR 30, 121) during PHHM nights. Median sensor glucose concentration at the first pump shutoff was 112 mg/dL for both PLGS and PHHM nights.

One or more automatic boluses occurred during 506 (78%) of the 648 PHHM nights; the median total insulin delivery given by automatic bolus was 1.2 (IQR 0.4, 2.5) units/night (Supplementary Table 4), with a median individual bolus of 0.05 units (range 0.025–1.225 units). The median sensor glucose concentration at the time of the first automatic bolus was 152 mg/dL. With respect to total insulin delivery overnight, there was a median of 7.5 (IQR 5.2, 10.8) units of total manual

boluses plus basal insulin delivered during PLGS nights and a median of 8.4 (IQR 6.0, 12.0) units of total automatic, manual boluses, and basal insulin delivered during PHHM nights ($P < 0.001$). There were 347 (54%) nights with both pump suspensions and automatic boluses during the 648 PHHM nights, with a representative example shown in Supplementary Fig. 5.

The mean ± SD time spent in the range of 70–180 mg/dL was 71 ± 10% during PLGS nights versus 78 ± 10% during PHHM nights ($P < 0.001$) (Fig. 1 and Table 1). Figure 2 shows that many, but not all, participants had a higher percentage of time spent in the range of 70–180 mg/dL on the PHHM nights compared with the PLGS nights. The mean ± SD overnight mean sensor glucose concentration was 152 ± 16 mg/dL during PLGS nights versus 143 ± 15 mg/dL during PHHM nights ($P < 0.001$) (Fig. 3). The median overnight sensor coefficient of variation was 34% (IQR 30%, 37%) during PLGS nights versus 31% (IQR 27%, 34%) during PHHM nights ($P < 0.001$) (Fig. 3). As shown in Figs. 1 and 3, the PHHM system required ~3 h from the time of activation before improvements in glycemic metrics compared with PLGS started to appear, and the curves were still diverging at 8 h.

The median time spent at a concentration <70 mg/dL was 1.0% (IQR 0.6%, 2.5%) during PLGS nights and 1.1% (IQR 0.7%, 2.3%) during PHHM nights ($P = 0.75$). Other sensor-measured hypoglycemic outcomes also were similar between PLGS and PHHM nights (Table 1 and Supplementary Table 6). The above-mentioned increase in time spent at a concentration of 70–180 mg/dL was achieved by a corresponding decrease in the median time spent at a concentration of >180 mg/dL: from 26% (IQR 21%, 35%) during PLGS nights to 20% (IQR 14%, 26%) during PHHM nights ($P < 0.001$). Similar improvements were observed for other sensor-measured hyperglycemic outcomes (Table 1 and Supplementary Table 6).

The mean ± SD morning blood glucose concentration was 163 ± 23 mg/dL after PLGS nights versus 142 ± 18 mg/dL after PHHM nights ($P < 0.001$, Table 1), with sensor glucose levels equalizing ~2 h after system deactivation (Supplementary Fig. 7). As seen in Supplementary Table 6, the frequency of elevated blood ketones was low in both treatment arms.
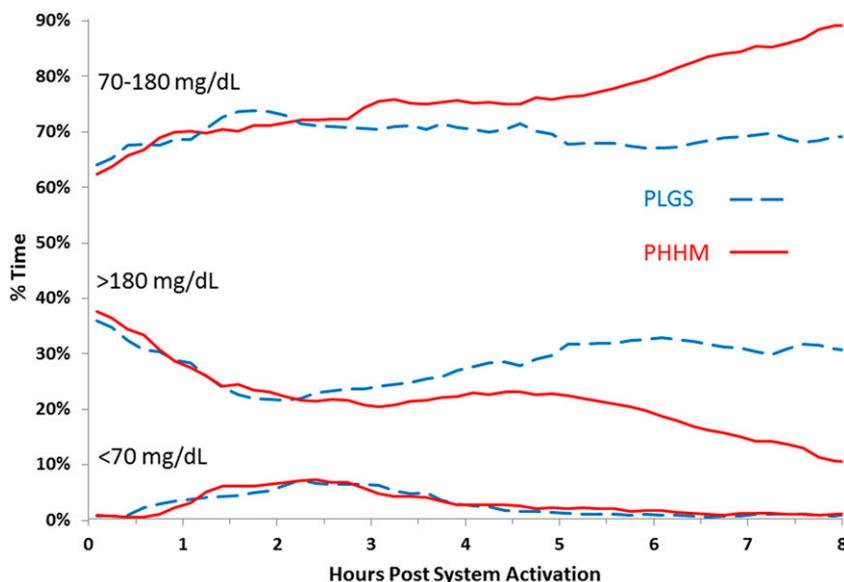
Figure 1—CGM metrics for percentage of time spent in range, above range, and below range from system activation by treatment arm.

Median HbA$_{1c}$ levels were 7.5% (IQR 6.9%, 7.7%) (58 mmol/mol; IQR 52 mmol/mol, 61 mmol/mol) at study enrollment, 7.1% (IQR 6.7%, 7.4%) (54 mmol/mol; IQR 50 mmol/mol, 57 mmol/mol) at randomization, and 7.1% (IQR 6.6%, 7.4%) (54 mmol/mol; IQR 49 mmol/mol, 57 mmol/mol) at the end of the trial.

Sensor data were available to the controller for an average across participants of 91% of the time the system was running on randomized nights (Supplementary Table 8). Among PHHM nights, the system delivered 95% of the automatic boluses requested by the controller within 5 min.

Table 1—Efficacy and safety participant-level outcomes (N = 30 participants)

	PLGS nights	PHHM nights	*P* value
Randomized nights (*n*)	22 (22, 23)	22 (21, 23)	NA
Sensor readings (total h)	174 (167, 186)	180 (169, 195)	NA
Bedtime blood glucose (mg/dL)	163 ± 21	166 ± 17	NA
Overall outcomes			
Time spent in range 70–180 mg/dL			
(primary outcome) (%)	71 ± 10	78 ± 10	<0.001
Overnight mean glucose (mg/dL)	152 ± 16	143 ± 15	<0.001
SD (mg/dL)	51 (46, 56)	43 (38, 48)	<0.001
Coefficient of variation (SD/mean) (%)	34 (30, 37)	31 (27, 34)	<0.001
Time spent in range 70–140 mg/dL (%)	48 ± 13	52 ± 12	0.03
Hypoglycemia outcomes			
Time spent at <70 mg/dL (%)	1.0 (0.6, 2.5)	1.1 (0.7, 2.3)	0.75
Time spent at <60 mg/dL (%)	0.3 (0.0, 1.0)	0.4 (0.1, 0.8)	0.99
Time spent at <50 mg/dL (%)	0.0 (0.0, 0.2)	0.1 (0.0, 0.2)	>0.99
Area over curve 70 mg/dL	0.10 (0.03, 0.26)	0.11 (0.04, 0.22)	0.60
Low blood glucose index	0.50 (0.32, 0.85)	0.52 (0.38, 0.75)	0.17
Hyperglycemia outcomes			
Time spent at >180 mg/dL (%)	26 (21, 35)	20 (14, 26)	<0.001
Time spent at >250 mg/dL (%)	5 (2, 9)	2 (1, 3)	<0.001
Time spent at >300 mg/dL (%)	0.2 (0, 1.3)	<0.1 (0, 0.2)	0.006
Area over curve 180 mg/dL	9.64 (7.97, 15.33)	5.64 (3.65, 7.93)	<0.001
High blood glucose index	5.23 (4.29, 7.42)	3.87 (3.03, 5.08)	<0.001
Morning glucose outcomes			
Mean morning blood glucose (mg/dL)	163 ± 23	142 ± 18	<0.001

Values are reported as the median (IQR) or mean ± SD, unless otherwise indicated. Glucose results from CGM unless specified as blood glucose. To convert glucose to mmol/L, divide by 18. NA, not applicable.
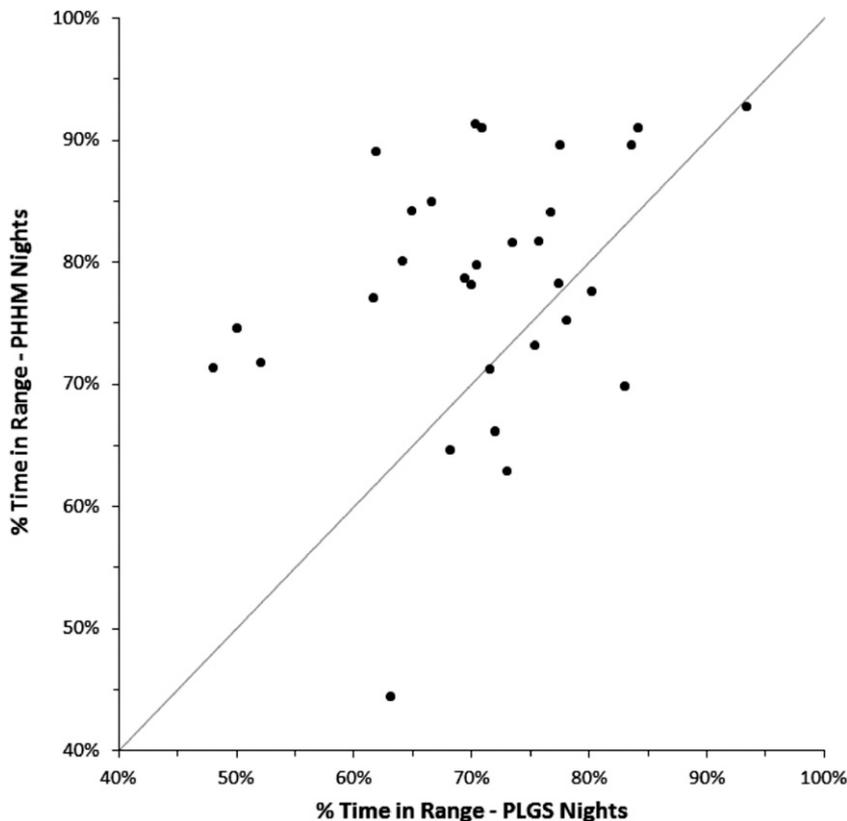
Figure 2—Percentage of time spent in the glucose concentration range of 70–180 mg/dL by treatment arm (*N* = 30 participants). The diagonal represents the line of identity.

Among *N* = 7,443 sensor-meter glucose pairs obtained during day and night CGM use, the overall median difference for the enhanced Enlite glucose sensor was −1 mg/dL (IQR −19, 13), the median ARD was 11% (IQR 5%, 20%), the mean ARD was 16%, and 65% of pairs met the International Organization for Standardization criteria (27).

There were no cases of severe hypoglycemia, diabetic ketoacidosis, or other serious, study-related, or device-related adverse events during the trial.

CONCLUSIONS

The PHHM algorithm doses insulin in a conservative, gradual fashion and is safe and effective in overnight glucose control. In this double-blind, 6-week at-home study with night-level randomization, PHHM demonstrated increased time in range, lower mean glucose level, and reduced hyperglycemia without increased hypoglycemia compared with PLGS alone. In addition, there was a reduction in glucose variability as well as a 21 mg/dL reduction in average morning blood glucose level. There were no serious adverse

events such as diabetic ketoacidosis, severe hypoglycemia, or hospitalizations.

The addition of insulin delivery resulted in improved glucose control after 3 h of system activation and was increasingly effective as the night progressed. As is common with overnight systems (28), there is an extended effect from evening meals and insulin, which may take several hours of system use to equilibrate. Greater time spent in range and a reduction in hyperglycemia were achieved through increased insulin delivery (median 1.2 units) during the night. Overall, there was ~10% more insulin dosed during PHHM nights compared with PLGS nights. This result is similar to that in the study by Hovorka et al. (29), where lower glucose levels during use of a closed-loop system at night were achieved by delivering an increased amount of insulin during the overnight period (8.1 vs. 7.2 units). On PHHM nights, there was no increased activity of the PLGS component of the system despite the additional insulin dosing. After PHHM nights, improved glycemic control persisted for ~2 h in the morning after system deactivation, after

which time glycemic control was similar after PLGS and PHHM nights.

This was a multicenter study with a unique design of night-level randomization. Unlike the more commonly used crossover study design, bias was minimized as both participants and investigators were blinded to treatment assignment each night. This study was conducted at home in free-living conditions. There were no restrictions on exercise, food intake, or insulin delivery before or during system use.

The system administered fractional boluses, and therefore participants were still able to use the bolus calculator function to deliver manual corrections if desired during the night and in the morning after the system was deactivated. Our system was designed as a simple, safe, minimal-maintenance, add-on approach to current pump therapy. Unlike some other systems, it did not take full control of insulin delivery, and it allowed participants to intervene at any stage. To our knowledge, there is only one clinical study (30) to date directly comparing different (model predictive control and proportional-integral-derivative) algorithms. At present, conclusions based on performance comparisons of systems between different studies must be taken cautiously and in the context of limited evidence.

A continuum exists between basal-only closed-loop control and combination basal/bolus control. The distinction between the two types of controller becomes less meaningful as the maximum delivery rate of the basal-only controller increases or the typical correction bolus size of the basal/bolus controller decreases. With our basal/bolus controller, individual correction boluses were typically very small (Supplementary Fig. 5 and Supplementary Table 4), but the controller occasionally delivered larger boluses (>1.0 units) when participants' TDD was large and predicted CGM values were very high. This approach reduced the risk of over-delivery while retaining the ability to correct significant hyperglycemia more rapidly than a typical basal-only system.

There are several closed-loop approaches designed to provide 24/7 closed-loop control (14,20,21,31); however, the improvement in glycemic outcomes has been largely realized by improved overnight glucose control. In other insulin-only overnight closed-loop systems, the mean overnight glucose
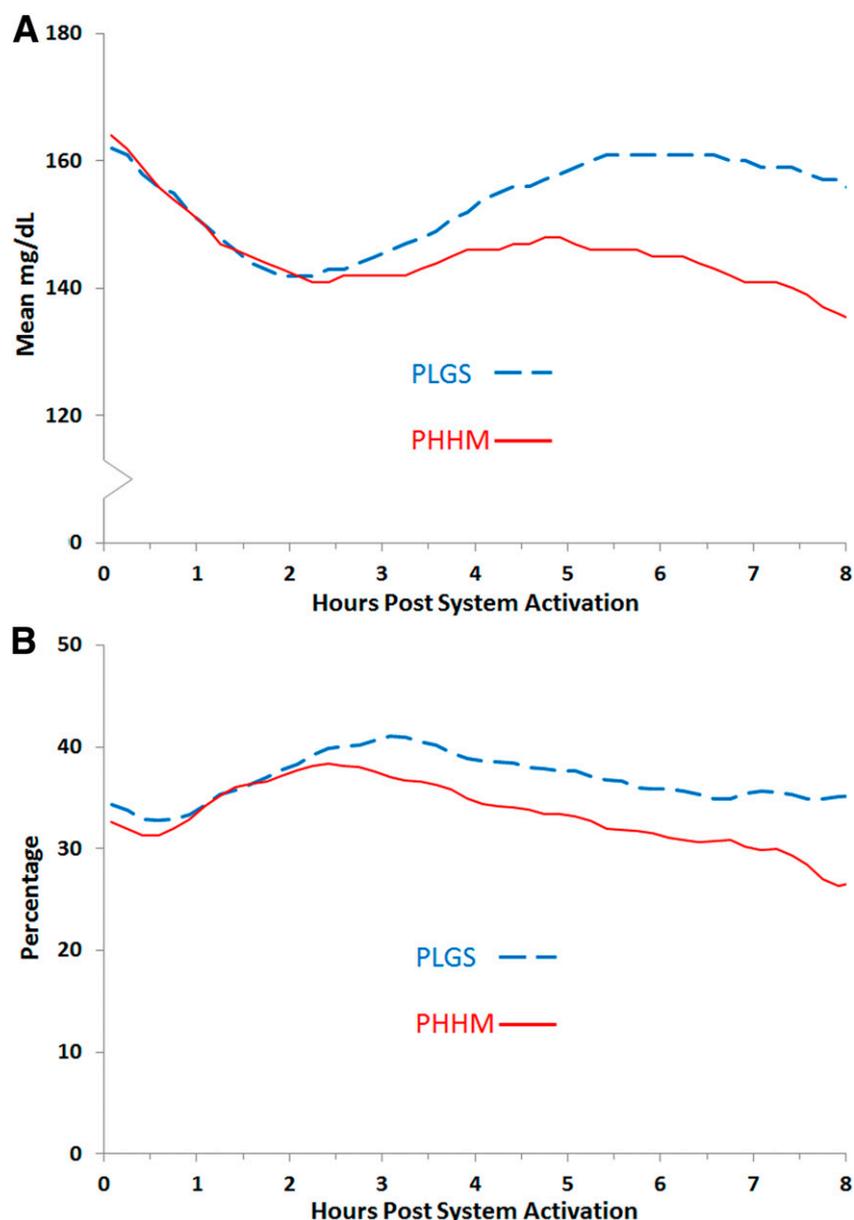
Figure 3—Mean glucose (A) and glucose coefficient of variation (B) from system activation by treatment arm.

in the range of 70–180 mg/dL with no increased hypoglycemia compared with the PLGS system alone. This was achieved with overnight closed-loop control with a system requiring minimal system maintenance.

concentration ranged from 137 to 148 mg/dL (9,14,32–34), and 1–2.6% of readings were <70 mg/dL. The present PHHM study was comparable with a mean sensor glucose concentration of 143 mg/dL and 1.1% of values <70 mg/dL.

Increasingly, there is a greater demand for customizability of closed-loop devices and perhaps a system that operates only at night and allows patients to continue with sensor-augmented pump therapy during the day may be a desired option prior to fully automated approaches being available.

Our goal was to develop an easy-to-use, safe system that would alleviate the burden of diabetes for patients. Patients report sensor alarms as annoying, intrusive, and disruptive to their sleep (35). Ease of use will impact the uptake of these technologies as they become commercially available.

There is no adaptive component to our PHHM algorithm at this stage, and this may be the focus of our future research. In addition, it will be important to determine the efficacy of this system in a younger cohort of participants with physiological differences in insulin sensitivity to see whether our approach is as successful in this group.

In conclusion, the PHHM system performed well, achieving 78% time spent

Appendix
THE IN-HOME CLOSED-LOOP (IHCL) STUDY GROUP

Clinical Centers. Clinical Centers are listed with clinical center name, city, and state. Personnel are listed as "PI" for Principal Investigator, "I" for co-Investigator, "C" for Coordinators, and "O" for Other Personnel. Division of Pediatric Endocrinology and Diabetes, Stanford University, Stanford, CA: Bruce Buckingham, MD (PI); Trang Ly, MBBS, FRACP, PhD (I); Darrell M. Wilson, MD (I); Tandy Aye, MD (I); and Paula Clinton, RD, CDE (C). Barbara Davis Center for Childhood Diabetes, University of Colorado, Denver, CO: H. Peter Chase, MD (PI); David M. Maahs, MD, PhD (I); Gregory Forlenza, MD (I); Emily Jost, MPH, RD, CDE, CSSD (C); Laurel Messer, RN, CDE (C); Emily Westfall, BA (O); Cari Berget (O); and Michelle Clay (O). St. Joseph's Health Care, London, ON, Canada: Irene Hramiak, MD, FRCP (PI); Terri Paul, MD, FRCPC; Tamara Spaic, MD, MSc, FRCPC; Marsha Driscoll, BScN, RN, CDE (C); and Sue Tereschyn, RN, CDE, CCRA (O). Rensselaer Polytechnic Institute, Troy, NY: B. Wayne Bequette, PhD (PI); and Faye Cameron, PhD (I).

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Data and Safety Monitoring Board. John C. Pickup, BM, DPhil (Chair); Irl Hirsch, MD; and Howard Wolpert, MD.

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