Overnight Closed-Loop Control Improves Glycemic Control in a Multicenter Study of Adults With Type 1 Diabetes

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Context: Closed-loop control (CLC) for the management of type 1 diabetes (T1D) is a novel method for optimizing glucose control, and strategies for individualized implementation are being developed.

Objective: To analyze glycemic control in an overnight CLC system designed to "reset" the patient to near-normal glycemic targets every morning.

Design: Randomized, crossover, multicenter clinical trial.

Participants: Forty-four subjects with T1D requiring insulin pump therapy.

Intervention: Sensor-augmented pump therapy (SAP) at home vs 5 nights of CLC (active from 23:00 to 07:00) in a supervised outpatient setting (research house or hotel), with a substudy of 5 nights of CLC subsequently at home.

Main Outcome Measure: The percentage of time spent in the target range (70 to 180 mg/dL measured using a continuous glucose monitor).

Results: Forty subjects (age, 45.5 ± 9.5 years; hemoglobin A1c, 7.4% ± 0.8%) completed the study. The time in the target range (70 to 180 mg/dL) significantly improved in CLC vs SAP over 24 hours (78.3% vs 71.4%; $P = 0.003$) and overnight (85.7% vs 67.6%; $P < 0.001$). The time spent in a hypoglycemic range (<70 mg/dL) decreased significantly in the CLC vs SAP group over 24 hours (2.5% vs 4.3%; $P = 0.002$) and overnight (0.9% vs 3.2%; $P < 0.001$). The mean glucose level at 07:00 was lower with CLC than with SAP (123.7 vs 145.3 mg/dL; $P < 0.001$). The substudy at home, involving 10 T1D subjects, showed similar trends with an increased time in target (70 to 180 mg/dL) overnight (75.2% vs 62.2%; $P = 0.07$) and decreased time spent in the hypoglycemic range (<70 mg/dL) overnight in CLC vs SAP (0.6% vs 3.7%; $P = 0.03$).

Conclusion: Overnight-only CLC increased the time in the target range over 24 hours and decreased the time in hypoglycemic range over 24 hours in a supervised outpatient setting. A pilot extension study at home showed a similar nonsignificant trend. **(*J Clin Endocrinol Metab* 102: 3674–3682, 2017)**

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received 2 March 2017. Accepted 22 June 2017.
First Published Online 28 June 2017

Abbreviations: AP, artificial pancreas; CGM, continuous glucose monitor; CLC, closed-loop control; DiAs, Diabetes Assistant; HbA1c, hemoglobin A1c; HFS-II, hypoglycemia fear survey, second revision; HFS-II-B, behavior subscale of HFS-II; HFS-II-W, worry subscale of HFS-II; SAP, sensor-augmented pump therapy; T1D, type 1 diabetes; USS, Unified Safety System.

Since the Diabetes Control and Complications Trial, the standard of care for type 1 diabetes (T1D) has been intensive insulin treatment (1). The current goals for glycemic control are hemoglobin A1c (HbA1c) of <7% in nonpregnant adults (2) and 7.5% in children (3). However, despite many advances in education, insulin delivery, and glucose monitoring technology, these goals are still not met (4). Closed-loop control (CLC) systems have shown promise for improving glucose control. These systems include a continuous glucose monitor (CGM) to provide data that modulate insulin delivery and have been demonstrated to be effective in glycemic control with reduced risk of hypoglycemia (4–8). These systems can be used in a variety of modes, including overnight only and 24/7 control.

In the present multicenter, multinational trial, the study subjects used the Diabetes Assistant (DiAs) portable artificial pancreas (AP) platform developed by University of Virginia and first used in outpatient trials in 2011 (9) with the Unified Safety System (USS) closed-loop algorithm overnight. They resumed their usual sensor-augmented pump (SAP) therapy during the day. The rationale for the present study was based on our prediction that CLC devices would be adopted by patients with T1D in a selective manner. CLC systems require a patient to trust an automated system, which can take time to achieve. Even of those who embrace it, some might find the systems most useful at night rather than during the day. Patients can choose to start using these systems for overnight control only to alleviate the well-documented fear of hypoglycemia occurring during sleep.

The goal of the present study was to test the safety and effectiveness of "bedside" overnight-only CLC in a transitional outpatient setting and to assess its effect on improved overall glycemic control during a 24-hour period. A subset of patients in the study continued the use of overnight-only CLC at home to assess the durability of the system and its effect on overall control. This protocol represents a culmination of previous clinical trials for the development of the USS Virginia system and benefits from the synthesis of those components.

Materials and Methods

Subjects

The subjects were recruited at four clinical centers: University of Virginia (UVA), Mayo Clinic, Icahn School of Medicine at Mount Sinai, and University of Padua, Italy. The Clinical Trials Registration numbers were NCT 02131766 and NCT 02008188 (ClinicalTrials.gov). Eligible subjects (age, 21 to <65 years) were enrolled who had had T1D for ≥1 year, had been using an insulin pump for ≥1 year, and had HbA1c <10%. The exclusion criteria included diabetic ketoacidosis or a severe hypoglycemic event in the previous year, adrenal disorder, active gastroparesis, uncontrolled hypertension, oral steroids, uncontrolled active proliferative retinopathy, unstable coronary artery disease, acetaminophen use, the use of any other medications for glucose control other than insulin, and the use of β-blockers. The subjects were studied from January 2014 to March 2015. All subjects provided written informed consent, and the local ethics/institutional review boards approved the protocol. The studies in the United States were conducted under Food and Drug Administration Investigational Device Exemption number 140068 and at the University of Padua in compliance with the local regulations and ethical committee approval in Italy.

Study design

The study was a multicenter randomized crossover clinical trial. Subject eligibility was determined during a screening visit. The enrolled subjects were randomized to experimental (CLC) or control (SAP) sessions. Each session consisted of at least five consecutive 24-hour periods that concluded at 18:00 on the last day. The CLC session was conducted in a transitional setting (hotel or research house). The SAP session was completed at the subject's home or usual environment. A subset of 10 subjects then continued to use CLC at home for the same duration (5 at UVA and 5 at the University of Padua). These home study subjects were a convenience sample of subjects who were able to have a care partner present overnight at home, had not experienced any severe adverse events during the main trial, and were able to meet the target trial dates.

During all sessions, the subjects were asked to (1) check the capillary blood glucose level before meals and snacks, 2 hours after meals, and at 23:00, 03:00, and 07:00; (2) use the bolus calculator function of the study pump to record the carbohydrates consumed and deliver meal boluses; (3) make insulin dosing decisions per their usual care during the time that they were not in CLC (07:00 to 23:00); (4) continue their usual diet during both study sessions; and (5) exercise per their usual routine as long as the exercise did not exceed 1 hour of moderate intensity. During all study sessions, the subjects were asked to consume glucose tablets or liquid at any point the capillary blood glucose was <70 mg/dL, regardless of symptoms. During all study sessions, the insulin pump and the DiAs were preprogrammed with the subject's usual insulin parameters (*i.e.*, basal rates, carbohydrate ratios, correction factors).

Study equipment and technology

During the SAP portion, the subjects wore a study-provided insulin pump (Roche Accu-Chek Spirit Combo; Roche Diagnostics, Indianapolis, IN) and a CGM (DexCom G4 Platinum or AP Share; DexCom, San Diego, CA). During the CLC portion of the study, the DiAs, a modular portable AP platform developed at the UVA, was loaded onto an android smart phone (Xperia Arc S/LT18i; Sony Ericsson, Tokyo, Japan; or Nexus 5; Google, Mountain View, CA) and activated to control glycemia. The insulin pump and CGM wirelessly transmitted data to the DiAs phone using Bluetooth. In particular, communication between the DiAs and CGM was initially achieved using an additional Bluetooth relay device, followed by use of the DexCom AP Share. In addition, the DiAs allows for data transfer through either a wireless telephone network or WiFi to a secure central server for remote monitoring and automated alerts about the patient and state of the system. During the home study, the study staff received these automated alerts via text and E-mail messages.

The study used the USS Virginia CLC algorithm to adjust insulin administration during CLC in the transitional setting and during the substudy of CLC at home. The USS Virginia is based on a mathematical model of the human glucose–insulin dynamics and uses Kalman filtering to predict hypo- and hyperglycemia risks and adjust insulin administration according to these risks (10). These risks are displayed visually to the subject using "traffic light" signals, with green indicating no detected risk, yellow indicating basal rate modulation was occurring to decrease risk, and red indicating an acute risk that might require external intervention (11). This algorithm sets a target of 160 mg/dL after dinner and adjusts that target overnight down to 120 mg/dL by the morning (07:00).

The subjects received training on all study-related equipment and had a run-in period on the study pump at home for ≤7 days before beginning their first session (SAP or CLC). Those who were not previous CGM users (>5 days/wk during a 2-month period) wore a CGM for ≤3 weeks before starting their first study session (SAP or CLC). The CGM was calibrated in accordance with the manufacturer's guidelines.

Experimental session

The subjects stayed overnight in a transitional setting such as a hotel or research house, with the study staff in an adjacent room. The study staff could access the remote monitoring system during this time and were nearby in the event a subject required assistance. The subjects wore two CGMs during CLC at the hotel/research house: one primary CGM driving the control algorithm and a secondary one exclusively for added safety per study protocol to be used in the case of primary CGM malfunction. Each day, the DiAs was started in open-loop mode between 20:00 and 22:00, with basal rates delivered without modulation by the controller. At 23:00, the DiAs was switched to CLC mode if the capillary blood glucose was ≥80 but <250 mg/dL. CLC could be delayed for ≤2 hours if these conditions were not met. The subjects were able to snack and use a bolus as usual before the start of CLC but were asked not to consume snacks from 23:00 to 07:00. The CLC was stopped at 07:00 the next day, and the subject continued with the study pump and CGM from 07:00 until restarting the open-loop mode on the DiAs at 20:00. The subjects were allowed to leave the study site during the day, when the DiAs was disconnected from the subject.

Home study

During the CLC sessions with the DiAs, the subjects were asked to check their capillary blood glucose if a red light alarm occurred for either hypo- or hyperglycemia. The subjects who went home with CLC followed the same protocol as described for the experimental session. The study staff contacted the study subjects daily and were available by telephone, if needed. The subjects also had a care partner who had received basic training on the study equipment and emergency procedures. The care partner was required to be present at all times when the DiAs was active at home. Remote monitoring was in place with alerts to study staff to help troubleshoot events such as clinically relevant hypoglycemia (glucose <50 mg/dL for ≥30 minutes) and hyperglycemia (glucose >300 mg/dL for >2 hours). The study staff were instructed to view the remote monitoring system after receiving an alert to observe whether evidence was present of the subject taking action (*e.g.*, fingerstick glucose test being performed, carbohydrates being ingested) but not to contact the subject unless evidence was seen of prolonged inaction by the subject and a concern for subject safety.

Psychosocial analysis

To assess the human factors further, we used the second revision of the hypoglycemia fear survey (HFS-II) and the high blood sugar survey (UVA) (12–15). The surveys were administered during the overnight 5-day CLC study in the transitional hotel and again for the subset participating in the 5-day home study. The surveys measure behavior and worry related to hypo- and hyperglycemia in patients with T1D. Both surveys include two subscales to reflect that those with T1D (1) engage in behavior to avoid hypoglycemia and hyperglycemia (hypoglycemia fear survey, second revision, behavior subscale (HFS-II-B) and avoidance]; and (2) constantly worry [hypoglycemia fear survey, second revision, worry subscale (HFS-II-W)] about their consequences. The surveys were scored in accordance with a preset standard protocol.

Statistical analysis

The primary outcome was the percentage of time within the target range of 70 to 180 mg/dL from the CGM over 24 hours for the 5-day duration of each arm. The hypothesis was that CLC during the overnight-only hours (23:00 to 07:00) would improve time within the target range overall compared with SAP. The secondary endpoints were the mean glucose level on awakening (approximately 07:00), time spent in different ranges overnight (<70, 70 to 180, and >180 mg/dL), and glucose variability measures, such as low- and high-blood glucose indexes (16).

An intention-to-treat analysis was performed that included all data, regardless of whether the subject was in CLC during the entire overnight period. No night data were rejected for this analysis. All metrics were computed from the CGM data using the primary CGM during CLC. If the primary sensor was unavailable, the secondary CGM data were used. The data were compared using paired Student's *t* test. The Wilcoxon sign rank test was used when the Gaussian distribution of the outcome could not be assumed (percentage of CGM time <50, <60, and <70 mg/dL and >250 and >300 mg/dL). For all tests, the significance level was set at $P = 0.05$. The analyses were performed using SPSS (IBM Corp., Armonk, NY), version 22.

Results

Study subject characteristics

A total of 44 subjects were enrolled, with 40 completing the trial (9 at UVA, 9 at Mayo Clinic, 10 at Mt. Sinai, and 12 at the University of Padua). The reasons for withdrawal were as follows: 3 withdrew because of time constraints and 1 because of an inability to comply with the study protocol. The baseline characteristics of the study participants are listed in Table 1. One subject was unable to complete the first night of home use as intended because of pump site occlusion and, therefore, started the 5 nights at home the next night.

Primary endpoint

The primary endpoint of time in the target range of 70 to 180 mg/dL improved in CLC compared with SAP

Table 1. Baseline Patient Characteristics (n = 40)

Characteristic	Value
Age, y	45.5 ± 9.5
Sex, n	
Female	22
Male	18
Weight, kg	77.3 ± 14.8
Height, cm	171.0 ± 8.8
Body mass index, kg/m^2	26.4 ± 4.8
HbA1c, %	7.4 ± 0.8
Diabetes duration, y	28.7 ± 9.6
Total daily insulin dose, U	36.5 ± 13.5
Total daily insulin per weight, U/kg	0.47 ± 0.11

Data presented as mean ± standard deviation, except for sex.

(mean, 78.3% vs 71.4%; $P = 0.003$) when measured for 24 hours during the study period (Table 2). The time in the target range was also improved in the overnight hours (23:00 to 07:00) in CLC compared with SAP (85.7% vs 67.6%; $P < 0.001$). The median and interquartile ranges for the study overall and the overnight-only hours are presented in Fig. 1.

Secondary endpoints

The mean CGM glucose level was not different between the CLC and SAP study periods (Table 2). The mean glucose level overnight was significantly lower during CLC than during SAP (137.2 vs 154.9 mg/dL; $P < 0.001$). In addition, the mean glucose level on awakening was close to the algorithm target of 120 mg/dL and was improved compared with that in the SAP group (123.7 vs 145.3 mg/dL; $P < 0.001$). The distribution of the mean glucose level on awakening in the CLC sessions is presented in the Supplemental Appendix.

When comparing the time in the hypoglycemia range as defined by CGM levels <70 mg/dL, CLC showed substantial improvement during the entire study period and overnight (Table 2; Figs. 2 and 3). In addition, improvement was seen in the hyperglycemic range, defined by CGM levels >180 mg/dL, in the CLC period compared with SAP both overall and overnight (Table 2). When considering a tighter target glucose range of 80 to 140 mg/dL, the CLC period also showed improvement overall and overnight (Table 2) compared with SAP.

Table 2. Primary and Secondary Endpoints (n = 40)

Variable	CLC	SAP	*P* Value
Primary endpoint			
Time spent in target range (70–180 mg/dL) for 24 h, %	78.3 ± 10.2	71.4 ± 11.6	0.003
Secondary endpoint			
Mean glucose level, mg/dL			
Overall, 24 h	142.0 ± 15.5	147.0 ± 17.9	NS
23:00 to 07:00 (overnight*)	137.2 ± 19.7	154.9 ± 27.3	< 0.001
07:00 (waking up)	123.7 ± 17.8	145.3 ± 31.0	< 0.001
23:00 (bedtime)	142.6 ± 22.7	152.6 ± 33.9	NS
Time spent in range for 24 h, %			
<50 mg/dL	0.3 ± 0.4/0 (0–0.4)	0.6 ± 0.8/0.3 (0–0.7)	NS
<60 mg/dL	0.9 ± 0.8/0.6 (0.2–1.4)	1.9 ± 2.0/1.3 (0.4–2.7)	0.008
<70 mg/dL	2.5 ± 1.7/2.2 (1.2–3.2)	4.3 ± 3.6/3.8 (1.4–6.2)	0.002
>180 mg/dL	19.8 ± 10.7	24.7 ± 12.2	0.03
>250 mg/dL	3.0 ± 3.1/1.9 (0.6–5.0)	4.8 ± 5.1/3.5 (1.1–6.4)	NS
>300 mg/dL	0.7 ± 1.0/0 (0–1.2)	1.2 ± 2.3/0 (0–1.5)	NS
80–140 mg/dL	51.7 ± 12.8	42.9 ± 11.4	0.001
Time spent in range, overnight[a], %			
70–180 mg/dL	85.7 ± 12.9	67.6 ± 19.9	< 0.001
<50 mg/dL	0.05 ± 0.21/0 (0–0)	0.35 ± 0.61/0 (0–0.6)	0.005
<60 mg/dL	0.2 ± 0.5/0 (0–0)	1.4 ± 1.8/0.8 (0–2.2)	< 0.001
<70 mg/dL	0.9 ± 1.5/0 (0–1.3)	3.2 ± 3.4/2.5 (0.1–5.3)	< 0.001
>180 mg/dL	13.8 ± 13.2	29.4 ± 20.2	< 0.001
>250 mg/dL	1.7 ± 3.8/0 (0–2.1)	6.4 ± 8.8/2.6 (0–10.8)	0.004
>300 mg/dL	0.5 ± 1.6/0 (0–0)	1.8 ± 2.3/0 (0–0.3)	NS
80–140 mg/dL	61.1 ± 20.6	39.6 ± 18.3	< 0.001
Glucose variability			
Coefficient of variation for glucose overnight[a], %	25 ± 9	32 ± 8	< 0.001
LBGI overnight[a]	0.82 ± 0.81	1.62 ± 1.46	0.001
HBGI overnight[a]	3.94 ± 2.85	7.55 ± 4.68	< 0.001

Data presented as mean ± standard deviation for variables analyzed using parametric tests and mean ± standard deviation/median (interquartile range) for variables analyzed using nonparametric tests.

Abbreviations: HBGI, high-blood glucose index; LBGI, low-blood glucose index; NS, not significant ($P > 0.05$).

[a]Overnight was defined as 11 PM to 7 AM.

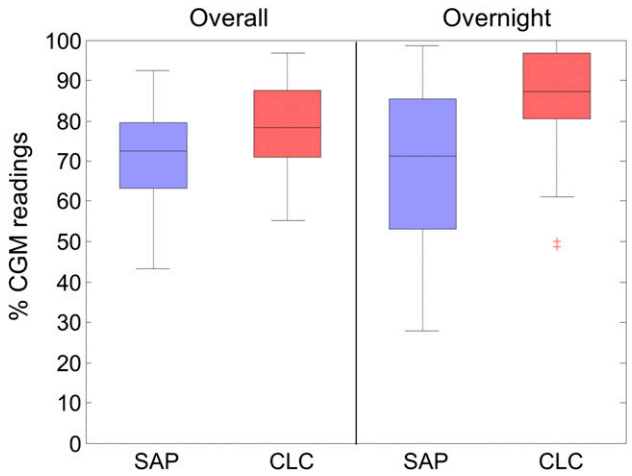

Figure 1. Time spent in target range of 70 to 180 mg/dL (median and interquartile range) measured by CGM for 24 hours and overnight only (11 PM to 7 AM). Double dagger indicates outlier.

The results of the subanalysis of the subjects who completed the trial at home (n = 10) are presented in Table 3. CLC at home demonstrated a decrease in the time spent in hypoglycemia overall compared with SAP (CLC home vs SAP, 2.2% vs 4.9%; $P < 0.05$). An improvement was also found when comparing the time spent in hypoglycemia in the overnight period, with almost no hypoglycemia occurring overnight at home (CLC home vs SAP, 0.6% vs 3.7%; $P = 0.03$). The percentage of time spent at 70 to 180 mg/dL was not substantially different when comparing CLC at home and SAP overall (CLC home vs SAP, 75.3% vs 71.1%; P = NS). However, a trend was seen for a longer period for CLC at home when considering the overnight period (CLC home vs SAP, 75.2% vs 62.2%; $P = 0.07$). The period spent at >180 mg/dL overall and overnight was also not substantially different between CLC at home and SAP.

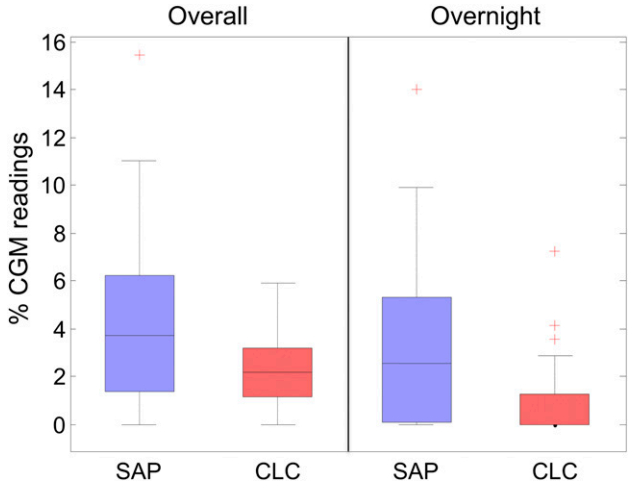

Figure 2. Time spent in hypoglycemia range (<70 mg/dL; median and interquartile range) measured by CGM for 24 hours and overnight only (11 PM to 7 AM). Plus signs indicate outliers.

The time spent in CLC during the overnight hours (23:00 to 07:00) was 98.1% for the main CLC group (n = 40) and 93.2% for the substudy of CLC at home (n = 10).

Safety and adverse events

No serious adverse events occurred. No subjects experienced severe hypoglycemia requiring outside intervention from a third party or administration of glucagon. No cases of diabetic ketoacidosis developed. The subjects were treated for a capillary blood glucose level of <70 mg/dL, regardless of symptoms. One subject reported otitis media that was believed to be unrelated to the study. For no patient was the system stopped by the study team because of safety concerns.

System acceptance

A total of 32 subjects finished the surveys during the randomized controlled trial. For the subjects who completed surveys both before and after CLC, the HFS-II showed statistically significant changes (1.0 ± 1.2 vs 1.1 ± 1.2; $P = 0.0072$). However, no such difference was found for the hyperglycemia surveys (1.8 ± 1.3 vs 1.9 ± 1.3; $P = 0.268$). When the subscales were compared, the scores for the HFS-II-B and hyperglycemia avoidance surveys were not significantly different after the outpatient period [1.0 ± 1.2 vs 1.0 ± 1.2 ($P = 0.1212$) and 1.98 ± 1.3 vs 2.1 ± 1.3 ($P = 0.1459$)]. Also, although the HFS-II-W subscale showed statistically significant changes after the outpatient period (1.1 ± 1.2 vs 1.24 ± 1.2; $P = 0.0247$), no statistically significant difference was observed in the hyperglycemia worry subscale (1.7 ± 1.3 vs 1.7 ± 1.2; $P = 0.9486$). In the subjects who completed the overnight CLC at home substudy, the HFS-II and HFS-II-B scores were not different [0.9 ± 0.9 vs 0.9 ± 0.9 ($P = 0.140$) and 0.9 ± 1.2 vs 0.9 ± 1.1 ($P = 0.5067$), respectively]. However, the HFS-II-W scores showed statistically significant changes (0.9 ± 0.8 vs 0.8 ± 0.8; $P = 0.0063$). Similarly, no statistically significant changes were observed for the hyperglycemia survey (1.8 ± 1.3 vs 1.7 ± 1.2; $P = 0.153$), including the avoidance subscale (2.2 ±1.3 vs 2.1 ± 1.3; $P = 0.2184$) and worry subscale (1.5 ± 1.2 vs 1.4 ± 1.1; $P = 0.4598$) after home CLC. Although the overall fear of hypoglycemia worsened despite the decrease in hypoglycemia during overnight CLC in the transitional environment for 5 days, the worry related to hypoglycemia improved after an additional 5 days of CLC at home. However, patients' perception of their fear of hyperglycemia did not change.

Discussion

The results of the present study have demonstrated that overnight CLC in a supervised outpatient setting improves glucose control with less hypoglycemia overnight

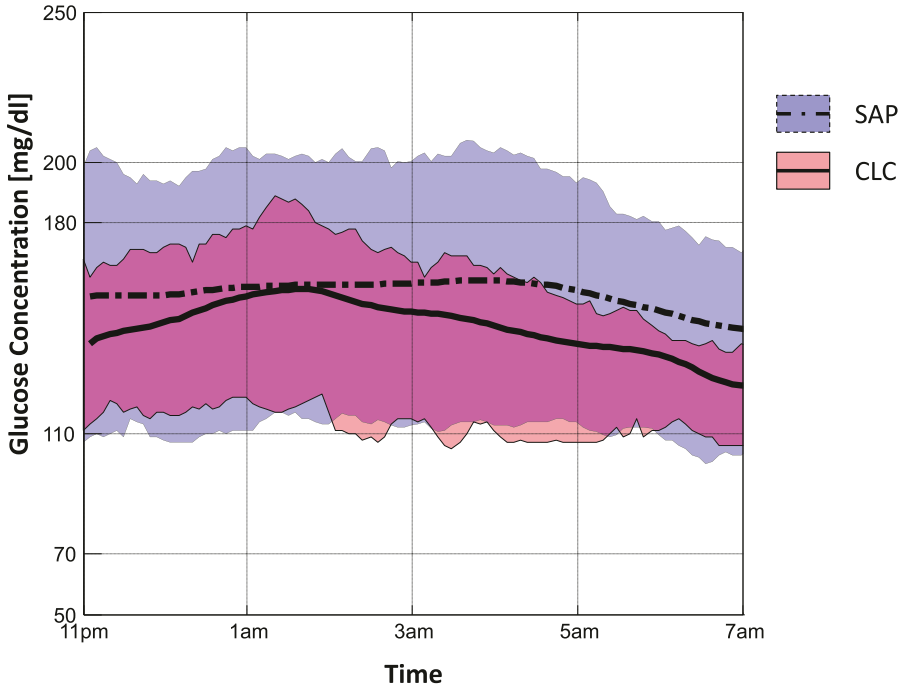

Figure 3. CGM glucose levels overnight (11 PM to 7 AM) in SAP therapy compared with CLC (mean and interquartile range).

and extended those benefits to glucose control during the day. One strength of the present study was the inclusion of four different clinical sites in the United States and Italy, which allowed for greater heterogeneity in patient selection and demonstrated that the DiAs closed-loop system running the USS Virginia CLC algorithm can work well in multiple settings. A subset of patients studied at home showed a further improvement in hypoglycemia, with a trend seen toward improving the time spent in the target range overall. During overnight CLC, the results showed improvement in the time in target range, with less hypoglycemia and less hyperglycemia experienced.

Other groups have also examined the efficacy of overnight CLC, with similar results in pediatric and adult patients in other countries. Nimri *et al.* (7) reported the results with the use of the MD-Logic AP system with 6 weeks of consecutive nights on closed-loop or SAP at home in 24 pediatric patients in Israel, Germany, and Slovenia. The time spent in the hypoglycemic range of <70 mg/dL was less (2.53% vs 5.16%; $P = 0.020$), with more time spent in the target range of 70 to 140 mg/dL

Table 3. Secondary Endpoints for Substudy of Subjects at Home (n = 10)

Variable	CLC at Home	CLC in Outpatient	SAP	*P* Value[a]
Time spent in range for 24 h, %:				
70–180 mg/dL	75.3 ± 11.7	78.1 ± 9.6	71.1 ± 15.9	NS
<70 mg/dL	2.2 ± 2.3/1.9 (0–2.9)	2.9 ± 1.4/2.7 (1.9–3.6)	4.9 ± 4.1/5.3 (0.8–8.4)	< 0.05
>180 mg/dL	23.3 ± 12.2	19.4 ± 10.1	24.2 ± 16.8	NS
Mean glucose level, mg/dL				
For 24-h period	147.2 ± 17.6	142.0 ± 17.3	145.7 ± 26.9	NS
Overnight[b]	150.8 ± 15.9	145.5 ± 26.0	161.1 ± 38.4	NS
At 07:00	113.8 ± 12.1	123.9 ± 16.5	141.3 ± 30.3	0.008
Time spent in range overnight[b], %				
70–180 mg/dL	75.2 ± 13.8	82.8 ± 15.2	62.2 ± 22.1	0.07
<70 mg/dL	0.6 ± 1.1/0 (0–0.4)	1.1 ± 1.0/0.9 (0–2.3)	3.7 ± 4.4/2.7 (0–5.9)	0.03
>180 mg/dL	25.0 ± 14.4	16.1 ± 16.0	34.1 ± 23.3	NS

Data presented as mean ± standard deviation for variables analyzed using parametric tests and mean ± standard deviation/median (interquartile range) for variables analyzed using nonparametric tests.

Abbreviation: NS, not significant ($P > 0.05$).

[a]Comparing CLC at home vs SAP.

[b]Overnight was defined as 11 PM to 7 AM.

both overnight (47.41% vs 36.36%; $P = 0.003$) and during the day. Overnight CLC led to more time spent in the target range of 70 to 180 mg/dL during the day compared with SAP use overnight (66.1% vs 62.3%; $P = 0.006$) (7). Thabit *et al.* (8) reported a three-center United Kingdom study of adults receiving 4 weeks of overnight CLC with the Florence automated closed loop system compared with SAP. They reported a mean difference of 13.5% for the time spent overnight with the blood glucose in the target range ($P = 0.0002$) (8). The daytime glycemic control was not reported in their study (8). Hovorka *et al.* (6) reported that overnight CLC in adolescents during a 3-week period compared with SAP also increased the time spent in the target range overnight (64% vs 47%; $P < 0.001$). Also, the 24-hour glucose level was reduced by a mean of 9 mg/dL ($P = 0.006$) during CLC (6). Moreover, Kropff *et al.* (17) reported a European multicenter crossover trial, in which CLC implementing the modular model predictive controller was compared against SAP for 32 T1D adults at dinner and overnight for 2 months. They showed a simultaneous reduction in the time spent in hypoglycemia (1.7% vs 3.0%; $P < 0.0001$) and hyperglycemia (31.6% vs 38.5%; $P < 0.0001$) and clinically relevant improvement in the time in the target range (66.7% vs 58.1%; $P < 0.0001$), leading to a better, albeit modest, reduction in the HbA1c compared with that achieved after 2 months of SAP (−0.3% vs −0.2%; $P = 0.047$) (17). When comparing SAP with low glucose suspend function, Sharifi *et al.* (18) reported on the use of an overnight hybrid closed-loop system in adults and adolescents for 4 nights compared with SAP with low-glucose suspend function. They did not find statistically significant differences in the time spent in the target range overnight (target 72 to 144 mg/dL from 12:00 to 08:00) (18).

Overnight CLC could also result in better sleep owing to the reduced nocturnal hypoglycemia, less subject stress, and increased time in the glucose target range. This might reduce counterregulatory hormone release and thus result in less physiologic stress during a 24-hour period and an increase in daytime blood glucose levels in the target range. Although studies evaluating counterregulatory hormone levels during a 24-hour period involving uninterrupted vs interrupted sleep have been performed, these hormones have not been evaluated to the best of our knowledge in the field of CLC (19, 20).

Our survey results regarding the perceptions of hyperglycemia and hypoglycemia are difficult to interpret. It is possible that the fear of hypoglycemia might have increased owing to concerns regarding the loss of the use of CLC overnight. Barnard *et al.* (21) reported mixed results in adolescents and their parents regarding hypoglycemia fear with overnight closed loop systems. The short duration of our study and small number of participants also made the data more challenging to interpret. The explanation for these findings and psychological factors should be explored further.

Thus, our findings add to the growing body of evidence of the general efficacy and safety of overnight CLC. The unique features of the present report include (1) the use of a portable closed-loop system running on a smart phone; (2) that it was a multicenter international study enrolling a diverse patient population in both transitional and home environment settings; and (3) the performance of CLC in outpatient settings and home under an Food and Drug Administration Investigational Device Exemption, facilitating larger and longer CLC trials in the U.S. population.

The system performed as expected by bringing patients to a narrow morning blood glucose range consistently. It was designed to bring the blood glucose level to 120 mg/dL on awakening and achieved a mean glucose level of 124 mg/dL. This mean glucose level was 21 mg/dL lower than that during the SAP session. In addition, despite this tighter control, the hypoglycemic risk was lower.

The study limitations included the short duration of the present trial. An additional limitation was the small sample size of the at-home study. These subjects had an average HbA1c of 7.4%, which is reasonable control but does not indicate tight control. These results might not be generalizable to a large population of patients with T1D with uncontrolled HbA1c. Additional considerations included that these subjects were in a transitional setting that required a stay in a hotel or research house with study staff nearby during the CLC session in contrast to being in their home environment during the SAP sessions. Although the study staff attempted to minimize any interventions, this limitation and the availability of remote monitoring could have favored the CLC sessions by allowing for more intervention by the study staff during them. To increase the comparability of the study settings regarding meals, the subjects were allowed to purchase food at a grocery store to prepare their own meals, although the subjects also were allowed to eat at restaurants during the CLC session. Care was taken to allow dinner to be comparable to that in their home setting. During the day, the subjects engaged in activities of their choice: working, shopping, errands, exercise, leisure activities, and/or returning home if living locally.

In conclusion, the results of the present study indicates that viability exists in consideration of a strategy involving overnight-only CLC, which might be a treatment paradigm chosen by a substantial proportion of patients when these systems are available commercially.

Acknowledgments

The authors thank the study participants without whom this work was not possible. In addition, the authors thank the multiple team members who contributed to the successful execution of our study, including Molly McElwee-Malloy, Christian Wakeman, Elaine Schertz, Jill Greiner, Benton Mize, Antoine Robert, and Mary Oliveri.

Financial Support: This study was supported by National Institutes of Health Grants DK 085623, DK 101055 to the University of Virginia and Grant DK85516 the Mayo Clinic; the Urdang Family Fund (to Y.C.K.); and JDRF to Mt. Sinai/University of Virginia (Grant 1-SRA-2014-239-M-R). Material support was provided by Roche Diagnostics (Indianapolis, IN).

Author Contributions: S.A.B. was the principal investigator; S.M.A. and L.K. provided medical support and the study design; M.D.B. and B.P.K. provided engineering support, trial design, and study funding; P.K.-H. led the engineering support and designed the DiAs; all the authors edited the manuscript; Y.C.K. and A.B. were the study physicians at Mayo Clinic; S.M.-S., V.D., and L.H. were study assistants (all edited the manuscript); study funding was secured by Y.C.K. and A.B; D.B. was the main study physician in Padua; R.V. was the senior engineer responsible for the trial in Padua; S.G. was the senior clinician coordinating the medical team in Padua; S.d.F. and Y.L. were the engineers providing technical support during the trial in Padua; F.B. was the clinician providing medical support to the patients during the trial in Padua; A.A. was the coordinating physician for the performance of the trial in Padua; C.C. was the principal investigator in Padua (all edited the manuscript); C.J.L. and D.W.L. were the study physicians at Mount Sinai; C.L. was the study assistant; N.B. was the engineer at Mount Sinai (all edited the manuscript).

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Disclosure Summary: S.A.B. reports materials support from Roche Diagnostics, Inc. and materials support from DexCom during the course of the study, grants and materials support from Animas Corp., and grants from Medtronic outside the submitted work. B.P.K. reports grants from BD Medical Technology, grants from Sanofi-Aventis, personal fees from Sanofi-Aventis, nonfinancial support from Roche Diagnostics, Inc., and nonfinancial support from Tandem Diabetes Care, outside the submitted work. B.P.K. has patent no. 8,562,587, October 22, 2013, with royalties paid by Animas Corp., patent no. PCT/US12/43883, July 2012, licensed to TypeZero Technologies, and patent no. PCT/US12/43910, June 2012, licensed to TypeZero Technologies, and is a shareholder in TypeZero Technologies. M.D.B. holds patents or patent applications related to the study technology; is a consultant for Animas Corp., DexCom, Roche Diagnostics, Inc., Bayer, and Sanofi and has received research grants or study materials support from Animas Corp., BD Biosciences, DexCom, Insulet Corp., LifeScan, Inc., Sanofi, and Tandem Diabetes Care, Inc.; is a founder and equity holder of TypeZero Technologies LLC, and holds equity in Inspark LLC. S.M.A. reports support from DexCom and Roche Diagnostics, Inc., during the conduct of the study, grants from Medtronic, personal fees from Senseonics, and grants from InSpark outside the submitted work. P.K.-H. is an employee and shareholder of TypeZero Technologies. C.J.L. reports materials support from Roche Diagnostics, Inc., and DexCom during the course of the study and research support from Senseonics and Lexicon, managed by the Icahn School of Medicine at Mount Sinai outside submitted work, and has provided advisory services to Novo Nordisk. Y.C.K. reports materials support from Roche Diagnostics, Inc., and DexCom during the course of the study and clinical study support from Medtronic outside the submitted work. C.C. reports 10 patents and patent applications related to glucose sensors and artificial pancreas, nonfinancial support from Roche Diagnostics, Inc., and DexCom, research support managed by the University of Padua from DexCom, Sanofi Aventis, and Adocia, and participation on an advisory panel for Novo Nordisk. F.B. has received personal fees from Roche Diagnostics, Inc., outside the submitted work. D.B. has received lecture fees from Eli Lilly, LifeScan, Roche Diagnostics, Inc., and Sanofi and has provided advisory services to Abbott. The remaining authors have nothing to disclose.

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