Day and Night Home Closed-Loop Insulin Delivery in Adults With Type 1 Diabetes: Three-Center Randomized Crossover Study

Diabetes Care 2014;37:1931–1937 | DOI: 10.2337/dc13-2911

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OBJECTIVE

To evaluate the feasibility of day and night closed-loop insulin delivery in adults with type 1 diabetes under free-living conditions.

RESEARCH DESIGN AND METHODS

Seventeen adults with type 1 diabetes on insulin pump therapy (means ± SD age 34 ± 9 years, HbA_{1c} 7.6 ± 0.8%, and duration of diabetes 19 ± 9 years) participated in an open-label multinational three-center crossover study. In a random order, participants underwent two 8-day periods (first day at the clinical research facility followed by 7 days at home) of sensor-augmented insulin pump therapy (SAP) or automated closed-loop insulin delivery. The primary end point was the time when sensor glucose was in target range between 3.9 and 10.0 mmol/L during the 7-day home phase.

RESULTS

During the home phase, the percentage of time when glucose was in target range was significantly higher during closed-loop compared with SAP (median 75% [interquartile range 61–79] vs. 62% [53–70], *P* = 0.005). Mean glucose (8.1 vs. 8.8 mmol/L, *P* = 0.027) and time spent above target (*P* = 0.013) were lower during closed loop, while time spent below target was comparable (*P* = 0.339). Increased time in target was observed during both daytime (*P* = 0.017) and nighttime (*P* = 0.013).

CONCLUSIONS

Compared with SAP, 1 week of closed-loop insulin delivery at home reduces mean glucose and increases time in target without increasing the risk of hypoglycemia in adults with relatively well-controlled type 1 diabetes.

Despite significant improvements in the care of type 1 diabetes, achieving good glycemic control while avoiding hypoglycemia (1) remains a challenge for many patients (2,3). Insulin pump therapy and real-time continuous glucose monitoring (CGM) have been shown to improve HbA_{1c} (4,5) and reduce hypoglycemia (6,7), particularly when using low glucose suspend (8,9). Closed-loop insulin delivery is an emerging treatment option combining these technological advances (10) to modulate delivery of insulin in a glucose-responsive fashion. Closed loop differs from conventional pump therapy, characterized by preprogrammed basal delivery, through the use of a control algorithm that directs subcutaneous insulin delivery

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Received 12 December 2013 and accepted 21 February 2014.

Clinical trial reg. no. NCT01666028, clinicaltrials.gov.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc13-2911/-/DC1.

according to sensor glucose levels. Several studies have evaluated the safety and efficacy of closed loop under laboratory conditions and shown promising results. These include evaluations using a randomized design by our group in youths (11,12), adults (13), and pregnant women (14) and by others using the model predictive control algorithm (15,16), the proportional-integral-derivative approach (17,18), and the fuzzy logic controller (19,20). Insulin and glucagon coadministration have also been applied in studies (21–23).

In contrast to studies conducted in the clinical research facility with carefully controlled conditions, closed loop at home is exposed to considerably more varied meal and exercise patterns. Participants may over- or underestimate carbohydrate content and may undertake unplanned activity and/or exercise. Patients using insulin pump therapy are advised to use temporary reductions or increments of basal insulin delivery to meet these demands, but this requires a degree of planning and user intuition and interaction. Since closed-loop systems modulate delivery of insulin in a glucose-responsive fashion (10), they may be able to achieve better glucose control than preprogrammed basal rates of conventional pump therapy.

In February 2010, the European Union granted funding to the AP@home consortium of European academic medical centers, biotechnology companies, and industrial partners to carry out closed-loop glucose control research (24). The first major closed-loop study performed by the AP@home consortium evaluated the feasibility of day and night closed-loop insulin delivery using two different algorithms in 47 adults with type 1 diabetes (25). The current study was undertaken to evaluate the performance of day and night closed-loop insulin delivery with the Cambridge algorithm over 7 days at home preceded by 1 day control at the clinical research facility.

RESEARCH DESIGN AND METHODS

Participants and Study Design

The study adopted an open-label prospective multinational three-center randomized crossover design. The study protocol was approved by respective research ethics committees and regulatory authorities in the U.K., Germany, and Austria. Study participants were recruited between January 2013 and August 2013 through adult diabetes clinics and other established methods at each participating center (Addenbrooke's Hospital, Profil Institute for Clinical Research, and Medical University of Graz). Key inclusion criteria were age $\geq$18 years, diagnosis of type 1 diabetes, treatment with insulin pump therapy for at least 3 months, willingness to perform at least six fingerstick glucose measurements per day, and HbA_{1c} $\leq$10% (86 mmol/mol). Key exclusion criteria were concurrent illness or medications likely to interfere with interpretation of study results; recurrent severe hypoglycemia; significant hypoglycemia unawareness; total daily insulin dose $\geq$2.0 units/kg; clinically significant nephropathy, neuropathy, or retinopathy; severe visual or hearing impairment; pregnancy; and breastfeeding. All participants provided written informed consent prior to study-related activities.

Study Procedures

After enrollment, participants were trained on the use of the study insulin pump (DANA Diabecare R; SOOIL, Seoul, South Korea) and CGM device (FreeStyle Navigator; Abbott Diabetes Care, Alameda, CA) (26). The study insulin pump was programmed with the participant's usual basal settings as well as usual insulin-to-carbohydrate ratios and correction factors. Participants were advised to use the bolus calculator for all meals during the entire study period. Ability to use study devices was formally assessed using competency assessment, and additional training was provided as required. After a run-in period of 7 days–3 weeks, participants underwent two 8-day periods, in random order, when glucose was controlled either by sensor-augmented insulin pump therapy (SAP) or closed-loop insulin delivery. The first day of each study period was conducted at a clinical research facility. After the first day, participants continued study interventions for the next 7 days under free-living conditions in their home and work environment. The two intervention periods were separated by a 1- to 4-week washout. No changes were made to usual treatment parameters. Participants were advised to calibrate the CGM device according to the manufacturer's instructions (26) and use the built-in glucometer for all fingerstick measurements and to keep a diary for detailed documentation.

Inpatient Stay

At the start of each study intervention, participants were admitted to the clinical research facility at ~0730 h. On arrival, an intravenous cannula was inserted to allow for frequent venous sampling starting at 0830 h. Venous blood samples were collected at 30-min intervals for the measurement of plasma glucose between 0830 and 2300 h followed by every 60 min thereafter until 0700 h the following morning. Closed-loop and SAP treatment commenced at 0900 h with breakfast.

Participants consumed standardized meals: breakfast 50 g, lunch 60 g, and dinner 80 g carbohydrates at 0900, 1300, and 2000 h. Fifteen minutes before each meal, an insulin bolus was delivered, calculated according to usual settings and premeal fingerstick glucose levels. The insulin bolus was given with the meal if fingerstick glucose was $\leq$4.0 mmol/L. Meal content and bolus procedure of each study intervention were identical. Participants consumed optional snacks containing 20 g carbohydrate at 1600 h and 15 g carbohydrate at 2200 h. During the closed-loop visit, no insulin bolus was given for snacks, but during the SAP visit participants received presnack bolus as per usual practice. Rapid-acting insulin analog aspart (Novo Nordisk, Bagsvaerd, Denmark) was used throughout the study. During the closed-loop visit, participants received additional training on starting, stopping, and safe operation of the closed-loop system. Competency on the use of closed-loop system was assessed by the study team prior to discharge.

Home Phase

A 7-day home phase commenced at the end of the 1-day inpatient stay. Participants were provided with a custom-made pouch to carry the small portable computer running the algorithm and CGM device (Supplementary Fig. 1). As a precaution, participants were advised not to drive or undertake strenuous physical exercise while the closed-loop system was in operation but were encouraged to engage in usual daily activities including going to work and moderate activity such as walking and daily housework. Participants were provided

with a 24-h telephone help line and were advised to follow usual treatment guidelines during intercurrent illness, hyperglycemia, and hypoglycemia. They were free to consume meals of choice including eating out. During closed-loop intervention, participants were not required to give an insulin bolus for snacks <30 g carbohydrate, and during both study interventions participants were free to decide on alarm thresholds for the CGM device.

Closed-Loop System

The Florence closed-loop system (University of Cambridge) (27) comprises a model predictive control algorithm residing on an ultraportable laptop (OQO Model 02 computer; OQO, San Francisco, CA), which is linked to the CGM receiver by a universal serial bus cable and controls the study pump over wireless communication. Every 12 min, the algorithm calculated a new insulin infusion rate, which was automatically sent to the study insulin pump. The calculations used a compartment model of glucose kinetics (28) describing the effect of rapid-acting insulin analogs and the carbohydrate content of meals on glucose levels. Participants were required to count the carbohydrates and use the pump bolus calculator for premeal boluses as per usual practice. Meal bolus also included a correction bolus as calculated by the bolus wizard if the glucose was outside target range.

Carbohydrate content of consumed meals and insulin delivery history, including manually instructed bolus, were downloaded automatically from the study pump. The algorithm was initialized using preprogrammed basal insulin delivery downloaded from the study pump. Additionally, the participant's weight and total daily insulin dose were entered at setup. During closed-loop operation, the algorithm adapted itself to a particular participant. The treat-to-target control algorithm aimed to achieve glucose levels between 5.8 and 7.3 mmol/L and adjusted the actual level depending on fasting versus postprandial status and the accuracy of model-based glucose predictions. A sample 24-h section of the closed-loop study arm is shown in Supplementary Fig. 2, and interface of the closed-loop system is shown in Supplementary Fig. 3. Algorithm version 0.3.24 with interface version 1.0.7 was used (University of Cambridge).

Safety Precautions During Closed Loop

Participants were trained to perform a calibration check before the breakfast and evening meal. If sensor glucose was above fingerstick glucose by >3 mmol/L, the CGM was recalibrated. There was no recalibration for sensor under reading. These instructions resulted from an in silico evaluation of hypoglycemia and hyperglycemia risk (29) using the validated Cambridge simulator (30).

If sensor glucose became unavailable, preprogrammed insulin delivery was automatically restarted within 30 min or within 1 h in case of other failures. This limited the risk of insulin under- and overdelivery (29). Safety rules limited maximum insulin infusion and suspended insulin delivery at sensor glucose ≤4.3 mmol/L or when sensor glucose was rapidly decreasing.

Assays

During the inpatient stay, a YSI 2300 STAT Plus Analyzer (YSI, Lynchford House, Farnborough, U.K.) (intra-assay coefficient of variation [CV] 1.5% and interassay CV 2.8%) was used for determination of plasma glucose.

Statistical Analysis

The analysis plan was agreed upon in advance. All analyses were undertaken on an intention-to-treat basis. The primary outcome was the time when glucose was in the target range 3.9–10.0 mmol/L during the home study phase. Secondary outcomes were mean glucose, time when glucose was <3.9 and <2.8 mmol/L (hypoglycemia), time when glucose was >10.0 and >16.7 mmol/L (hyperglycemia), low and high blood glucose index, and insulin delivery. We estimated glycemic variability by the SD of glucose and the CV. The low and high blood glucose index assessing the duration and extent of hypo- and hyperglycemia was calculated as an average of transformed glucose measurements progressively increasing at low and high glucose levels (31). We corrected for bias resulting from simultaneous use of sensor glucose to direct insulin delivery and to assess outcomes by using adjusted glucose—a stochastic transformation of glucose metrics when assessing time that glucose was in, below, and above target range (32). Other glucose metrics such as mean glucose and glucose variability were calculated using native (unadjusted) sensor glucose levels.

Secondary outcomes were calculated for the 1-day inpatient stay, 7-day home phase as a whole, and daytime (0700–2300 h) and overnight (2300–0700 h) periods. During the inpatient stay, study outcomes were calculated using both YSI laboratory glucose measurements and sensor glucose. Calculations were made using Gstat software, version 2.0 (University of Cambridge). Statistical analyses were conducted with the use of SPSS, version 19 (IBM Software, Hampshire, U.K.). Normally distributed data were compared using a paired *t* test, while nonnormally distributed data were compared using Wilcoxon signed rank test. Values are reported as means ± SD or median (interquartile range [IQR] [quartile 1–quartile 3]) unless stated otherwise. All *P* values are two tailed, and values <0.05 were considered statistically significant.

RESULTS

From January 2013 to August 2013, 24 volunteers were screened and 21 enrolled. Four dropouts were recorded—2 during the first study period, 1 during the run-in phase, and another during the washout period—leaving 17 completed participants (age 34 ± 9 years, HbA_{1c} 7.6 ± 0.8%, duration of diabetes 19 ± 9 years, and duration of pump therapy 5.6 ± 6.9 years) (Supplementary Table 1).

Glucose Control and Insulin Delivery During the Home Phase

The primary study outcome, the adjusted percentage of time spent in target glucose range 3.9–10.0 mmol/L at home, was higher during closed-loop insulin delivery (median 74.5% [IQR 61.1–78.9] vs. 61.8% [53.3–70.1], *P* = 0.005) (Table 1). Closed loop reduced mean glucose (8.1 ± 1.0 vs. 8.8 ± 1.0 mmol/L, *P* = 0.027) and the adjusted time spent above target glucose level (median 21.9% [IQR 16.7–32.3] vs. 30.5% [24.3–41.4], *P* = 0.013) without increasing the time spent in hypoglycemia. Measured as the SD, variability of glucose was lower during closed loop (2.9 ± 0.6 vs.

Table 1—Glucose control during closed loop and SAP over the 7-day home phase and 1-day stay at the clinical research facility in 17 patients with type 1 diabetes

	Closed loop	SAP	*P**
Free-living conditions (7 days); based on CGM			
Mean glucose (mmol/L)**	8.1 ± 1.0	8.8 ± 1.0	0.027
SD of glucose (mmol/L)**	2.9 ± 0.6	3.3 ± 0.8	0.034
CV of glucose (%)**	35.7 ± 5.9	37.7 ± 7.6	0.149
Percent time spent at glucose level			
3.9–10.0 mmol/L†	74.5 (61.1–78.9)	61.8 (53.3–70.1)	0.005
3.9–10.0 mmol/L**	75.3 (62.1–82.0)	62.6 (54.8–72.4)	0.006
3.9–8.0 mmol/L†	54.9 (42.2–58.3)	43.3 (33.0–49.1)	0.017
>10.0 mmol/L†	21.9 (16.7–32.3)	30.5 (24.3–41.4)	0.013
>16.7 mmol/L†	1.5 (0.5–3.5)	3.3 (1.4–5.0)	0.049
<3.9 mmol/L†	3.7 (2.2–7.9)	5.0 (2.3–8.5)	0.339
<2.8 mmol/L†	0.3 (0.2–1.1)	0.6 (0.2–1.6)	0.124
AUC_{day} <3.5 mmol/L (mmol/L × min)**	2.9 (1.4–15.8)	7.9 (1.3–24.1)	0.149
LBGI**	0.6 (0.5–1.4)	0.9 (0.5–1.5)	0.309
HBGI**	4.5 (3.3–7.2)	7.2(4.8–9.1)	0.039
Clinical research facility (1 day), based on YSI glucose			
Mean glucose (mmol/L)	8.2 ± 1.0	8.6 ± 1.6	0.292
SD of glucose (mmol/L)	2.4 ± 0.7	2.8 ± 0.7	0.079
CV of glucose (%)	27.5 ± 8.3	33.0 ± 8.4	0.095
Percent time spent at glucose level			
3.9–10.0 mmol/L	73.7 (63.4–84.1)	60.7 (49.2–76.8)	0.044
<3.9 mmol/L	1.8 (0–5.8)	4.7 (0–7.8)	0.221
>10.0 mmol/L	21.4 (13.6–33.5)	24.5 (16.0–49.1)	0.124

Data are means ± SD or median (IQR). AUC calculated per day. HBGI, high blood glucose index; LBGI, low blood glucose index. *Paired samples *t* test or Wilcoxon signed rank test. **Based on native CGM. †Adjusted for CGM measurement error assuming a relative absolute deviation of 15%.

3.3 ± 0.8, *P* = 0.034), but no difference was observed using the CV (35.7 ± 5.9 vs. 37.7 ± 7.6, *P* = 0.149). Sensor glucose profiles during the two treatments periods are shown in Fig. 1 with particularly pronounced difference during the overnight period. Fourteen participants (82%) showed increased time in target during closed loop compared with SAP (Fig. 2). Native sensor glucose levels (Supplementary Table 2) concurred with the assessment by adjusted values (Table 1).

As expected, variability of basal insulin delivery was significantly higher during closed loop (Table 2). Bolus and basal insulin infused during the day was significantly different between the two interventions; during the closed-loop period, lower bolus amount and higher basal dose were observed. Overall, there was a tendency toward lower total daily dose during closed loop, but this did not reach statistical significance (*P* = 0.109).

Day and Night Glucose Control During the Home Phase

Closed loop increased time in target during both daytime (target 3.9–10.0 mmol/L, 72.5 vs. 65.4% time in target, *P* = 0.017) and nighttime (target 3.9–8.0 mmol/L, 48.4 vs. 35.1%, *P* = 0.013) (Table 2). In addition, mean sensor glucose was lower during the nighttime period (8.3 ± 1.3 vs. 9.3 ± 1.1 mmol/L, *P* = 0.015). There was no difference in the area under the curve (AUC) for hypoglycemia during either period (Table 2).

Glucose Control and Insulin Delivery During the 1-Day Inpatient Stay

Time spent in target glucose range 3.9–10.0 mmol/L was higher with closed loop during the inpatient stay. (YSI-based results can be found in Table 1

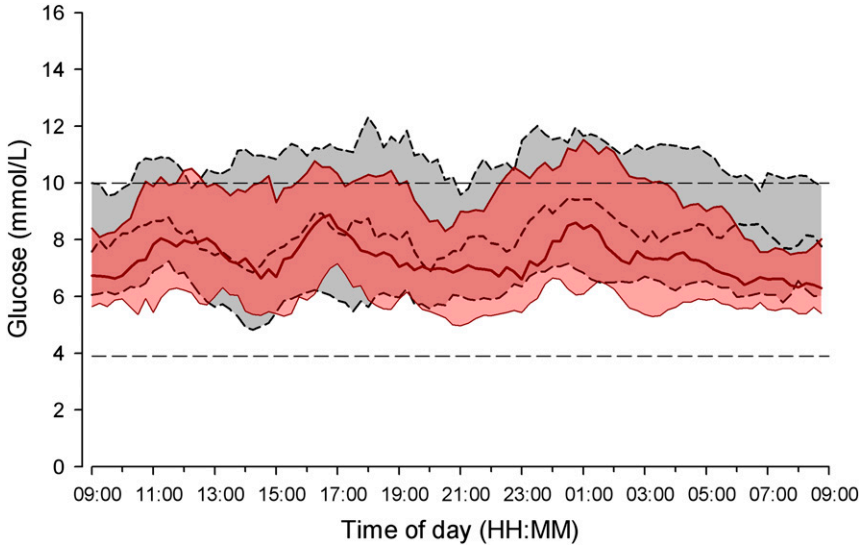

Figure 1—Twenty-four-hour glucose profiles during home use of closed loop and SAP. The target glucose range 3.9–10.0 mmol/L is denoted by the dashed lines. Data shown are median (IQR). Closed loop denoted by pink solid line and pink-shaded area. SAP denoted by gray dashed line and gray-shaded area.

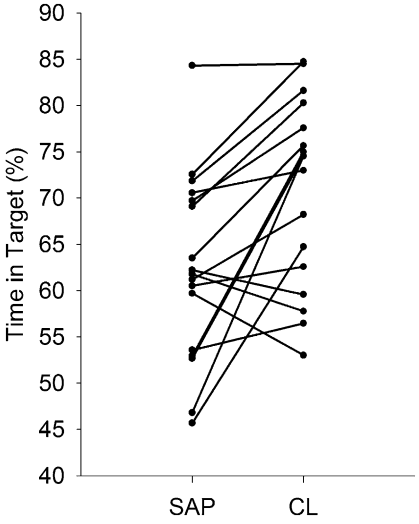

Figure 2—Time spent in target glucose range 3.9–10.0 mmol/L by participants (N = 17) at home. Fourteen (82%) participants showed increased time in target range during closed loop (CL) compared with SAP.

and CGM-based results in Supplementary Table 3.) The number of rescue carbohydrate treatments required was lower during closed loop (closed loop 7 vs. SAP 16) but did not reach statistical significance (P = 0.215). Closed loop administered a significantly lower total insulin daily dose during the inpatient stay (36.8 vs. 41.8 units, P = 0.028).

Sensor Accuracy During Inpatient Stay

Sensor performance was good with median absolute deviation of 0.8 mmol/L (IQR 0.4–1.3) and median absolute relative deviation of 10.0% (4.7–16.3). Detailed clinical and numerical sensor accuracy is shown in Supplementary Table 4. Eighty-three percent of YSI-sensor pairs were in Clarke Error Grid Zone A.

Adverse Events

Two severe hypoglycemia events occurred during the study; one event in the closed-loop arm and one event during the washout period. The severe hypoglycemia event during the closed-loop period occurred at a time when the closed loop was nonoperational owing to sensor unavailability and insulin was being delivered according to the participant's usual pump settings. The second severe hypoglycemia episode leading to hospital admission occurred during washout while the participant was using usual pump treatment in the context of intercurrent illness. Both participants fully recovered with no clinical sequela. Both episodes most likely resulted from overaggressive manual insulin bolus corrections. Four episodes of high glucose occurred owing to infusion set failure (no significant ketosis). One participant suffered from a transient vasovagal episode during the 1-day inpatient stay and fully recovered with intravenous fluid treatment.

Utility Analysis

During the 1-day inpatient stay, closed loop was operational a median of 98.4% (IQR 95.8–100) of the time. During the home phase, closed-loop operational time was 83.0% (71.1–92.3). Availability of CGM during the home phase was 95.0% (85.2–97.8) during closed loop and 95.1% (92.6–97.4) during SAP. Closed-loop operational time when CGM data were available was 90.9% (83.7–96.2).

Reasons for not using closed loop during the home phase included unavailability of CGM data, periods of driving and strenuous exercise, a nonoperational laptop, and unreliable Bluetooth communication between pump and the computer. Detailed analysis of failure events is shown in Supplementary Table 5. The most common reason for undesired cessation of closed loop was failure of Bluetooth pump communication. In total, there were 91 instances of pump communication failures, giving a mean interval between failures of 25.6 h. Of the 91 instances, 47 were recorded in three participants. With these three participants excluded, the mean interval between pump communication failures was 53 h.

Table 2—Insulin delivery and daytime and nighttime glucose control during the home phase

	Closed loop	SAP	P*
Insulin delivery			
Total basal (units/day)	20.1 (17.2–24.7)	18.9 (15.4–20.4)	0.017
Total bolus (units/day)	18.9 (15.5–25.5)	26.5 (20.6–30.1)	0.002
Total daily dose (units)	39.1 (34.7–45.7)	44.7 (36.3–51.0)	0.109
SD of basal insulin	0.7 (0.6–0.9)	0.2 (0.1–0.2)	<0.001
Daytime and nighttime glucose control			
Daytime (0700–2259 h)			
Mean glucose	8.1 ± 1.0	8.5 ± 1.2	0.147
Percent time in target (3.9–10.0 mmol/L)†	72.5 (63.4–78.6)	65.4 (54.6–71.0)	0.017
AUC_{day} <3.5 mmol/L (mmol/L × min)	2.3 (0.9–19.3)	6.3 (0.4–30.1)	0.225
Nighttime (2300–0659 h)			
Mean glucose	8.3 ± 1.3	9.3 ± 1.1	0.015
Percent time in target (3.9–8.0 mmol/L)†	48.4 (32.5–64.5)	35.1 (28.4–47.5)	0.013
AUC_{day} <3.5 mmol/L (mmol/L × min)	3.1 (0–17.5)	3.2 (0.1–33.5)	0.163

Data are means ± SD or median (IQR). AUC calculated per day. *Paired samples t tests or Wilcoxon signed rank test. †Adjusted for CGM measurement error assuming a relative absolute deviation of 15%.

CONCLUSIONS

The current study demonstrates the feasibility of unsupervised day and night closed-loop insulin delivery under free-living conditions in adults with type 1 diabetes. When applied in a relatively well-controlled cohort, compared with current best therapy, closed loop increased the time when glucose was in the target range while reducing the mean glucose. Importantly, these improvements were achieved without increasing the risk of hypoglycemia while administering a similar total daily insulin dose. Benefits of closed loop were more pronounced during the overnight period, although glucose control was superior during both day- and nighttime. Other benefits include reduced glucose variability as measured by SD and reduced high glucose excursions. In agreement with results obtained during the 7-day home phase, participants also showed improved plasma glucose control with closed loop during the 1-day stay at the clinical research facility while infusing a significantly lower amount of insulin.

In the current study, there was no statistically significant decrease in the time spent in hypoglycemia. This can be explained by the study not being powered to detect such a difference, although a trend toward a lower hypoglycemia

exposure was observed (AUC <3.5 mmol/L 71% lower during closed loop; 2.9 vs. 7.9% closed loop vs. SAP; P = 0.14). Low levels of hypoglycemia were observed compared with, for example, the JDF CGM trial (5), which recorded time spent in hypoglycemia (<3.9 mmol) of 89 and 60 min per day prior and after the use of real-time CGM. Participants in the current study spent 40 and 49 min per day during closed loop and control periods; excluding subjects with significant comorbidities and hypoglycemia unawareness may have led to selection of participants with a lower hypoglycemia risk.

A smartphone–based closed-loop control platform was previously evaluated in 20 adults in four clinical centers in a nonrandomized single-arm study design in a home-like environment (hotel/guest house or mixed hospital-hotel admissions) (33). The study duration was 42 h with the first 14 h of operation under open-loop control followed by 28 h of closed loop. In contrast, outpatient closed-loop duration in the current study was longer at 168 h per participant. Two further randomized crossover studies have evaluated the use of overnight closed loop outside the clinical research facility. The first study showed reduced rates of hypoglycemia during a single night at three youth diabetes camps (34). An interim analysis from the second study using closed loop at home for 4 nights has also shown reduced hypoglycemia burden (35). Feasibility of dual-hormone closed loop under free-living conditions at home for 48 h has been evaluated, but despite the use of glucagon this study reported more hypoglycemia in the closed-loop arm (36).

During the present proof-of-concept study, a prototype closed-loop system was used with the objective being to assess the feasibility of day and night hybrid closed loop. Participants were required to carry the ultraportable computer in a removable pouch. When CGM was available, closed loop was operational for >90% of the time during the home phase. Based on encouraging results from the current study, a closed-loop system based on smartphone technology suitable for longer studies is under development. During the current study, there was no dedicated treatment optimization period and participants were only informed about insulin requirements in each study period after completion of the study minimizing any influence arising from the crossover study design.

Training on the closed-loop system took ~60 min. Closed-loop technology appears simple to initiate once insulin pump therapy and CGM are established. A more comprehensive training was administered at the study start to familiarize participants with the study pump and CGM. The two severe hypoglycemic events seen during the current study were unrelated to closed-loop insulin delivery.

The strengths of our study are the integration of closed loop into normal life including use at work, weekends, holidays, varied diet and sleeping patterns, and a randomized crossover study design in multinational multicenter settings. Participants started and stopped closed loop without supervision. Weaknesses include a small sample size, an early-generation closed-loop system (which is not a commercially available product), and a relatively short study duration.

In conclusion, day and night closed loop can be used safely at home, and its benefits include increased time with glucose in the target range and reduced mean glucose. Larger and longer studies are warranted.

Acknowledgments. The authors are grateful to the study volunteers for their participation. Jasdip Mangat supported development and validation of the closed-loop system. Josephine Hayes (Institute of Metabolic Science, University of Cambridge) provided administrative support. Arti Gulati and Samyyia Ashraf (University of Cambridge) provided data-management support. Karen Whitehead (University of Cambridge) provided laboratory support.

Funding. This study was funded by the Seventh Framework Programme of the European Union (grant agreement no. 247138). Further support was received from the JDRF (22-2006-1113, 22-2007-1801, 22-2009-801, and 22-2009-802) and the National Institute for Health Research Cambridge Biomedical Research Centre. Abbott Diabetes Care supplied continuous glucose delivery devices and sensors and modified devices to facilitate real-time connectivity and read the manuscript before submission.

Duality of Interest. J.K.M. reports having received speaker honoraria from Novo Nordisk A/S. M.E. is employed by B. Braun Melsungen AG. L.H. is a partner and consultant of Profil Institut für Stoffwechselforschung, Neuss, Germany, and the Profil Institute for Clinical Research, San Diego, CA, and is a consultant for a number of companies that are developing novel diagnostic and therapeutic options. M.E.W. has received license fees from Becton Dickinson and has served as a consultant to Beckton Dickinson. M.E.W. and R.H. report patent applications. T.R.P. reports having received speaker honoraria from Novo Nordisk and Roche Diagnostics and serving on an advisory panel for Novo Nordisk, Bristol-Myers Squibb/AstraZeneca, and Roche Diagnostics. M.L.E. reports having received speaker honoraria from Abbott Diabetes Care and Animas and serving on an advisory board for Medtronic, Roche, and Cellnovo. R.H. reports having received speaker honoraria from MiniMed Medtronic, LifeScan, Eli Lilly, B. Braun, and Novo Nordisk; serving on advisory panel for Animas, MiniMed Medtronic, and Eli Lilly; receiving license fees from B. Braun and Beckton Dickinson; and having served as a consultant to Beckton Dickinson, B. Braun, Sanofi, and Profil. No other potential conflicts of interest relevant to this article were reported.

No sponsor had any role in the study design, data collection, data analysis, data interpretation, or writing of the manuscript.

Author Contributions. L.L. codesigned and coordinated the study, was responsible for screening and enrollment of participants, arranged informed consent from participants, provided patient care and/or took samples, carried out randomization and the data analysis including statistical analysis, contributed to the interpretation of the results, wrote the manuscript, and critically reviewed the manuscript. S.D. and J.K.M. codesigned the study, were responsible for screening and enrollment of participants, arranged informed consent from participants, provided patient care and/or took samples, and critically reviewed the manuscript. J.M.A. provided patient care and/or took samples and critically reviewed the manuscript. C.B. coordinated the study and critically reviewed the manuscript. W.D. provided patient care and/or took samples, carried out randomization, and critically reviewed the manuscript. M.E., L.H., T.R.P., S.A., and M.L.E. codesigned the study, contributed to the interpretation of the results, and critically reviewed the manuscript. S.H. and H.K. provided patient care and/or took samples and critically reviewed the manuscript. L.M. was responsible for screening and enrollment of participants, arranged informed consent for participants, provided patient care and/or took samples, carried out randomization, and critically reviewed the manuscript. M.N. carried out the data analysis including the statistical analysis and critically reviewed the manuscript. H.T. was responsible for screening and enrollment of participants, arranged informed consent from the participants, provided patient care and/or took samples, and critically reviewed the manuscript. M.E.W. codesigned the study, carried out randomization, and critically reviewed the manuscript. R.H. coordinated the study, designed and implemented the glucose controller, codesigned the study, contributed to the interpretation of the results, wrote the manuscript, and critically reviewed the report. R.H. 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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