Safety of Outpatient Closed-Loop Control: First Randomized Crossover Trials of a Wearable Artificial Pancreas

Diabetes Care 2014;37:1789–1796 | DOI: 10.2337/dc13-2076

Boris P. Kovatchev,[1] Eric Renard,[2] Claudio Cobelli,[3] Howard C. Zisser,[4] Patrick Keith-Hynes,[1] Stacey M. Anderson,[1] Sue A. Brown,[1] Daniel R. Chernavvsky,[1] Marc D. Breton,[1] Lloyd B. Mize,[1] Anne Farret,[2] Jérôme Place,[2] Daniela Bruttomesso,[3] Simone Del Favero,[3] Federico Boscari,[3] Silvia Galasso,[3] Angelo Avogaro,[3] Lalo Magni,[5] Federico Di Palma,[5] Chiara Toffanin,[5] Mirko Messori,[5] Eyal Dassau,[6] and Francis J. Doyle III[6]

OBJECTIVE

We estimate the effect size of hypoglycemia risk reduction on closed-loop control (CLC) versus open-loop (OL) sensor-augmented insulin pump therapy in supervised outpatient setting.

RESEARCH DESIGN AND METHODS

Twenty patients with type 1 diabetes initiated the study at the Universities of Virginia, Padova, and Montpellier and Sansum Diabetes Research Institute; 18 completed the entire protocol. Each patient participated in two 40-h outpatient sessions, CLC versus OL, in randomized order. Sensor (Dexcom G4) and insulin pump (Tandem t:slim) were connected to Diabetes Assistant (DiAs)—a smartphone artificial pancreas platform. The patient operated the system through the DiAs user interface during both CLC and OL; study personnel supervised on site and monitored DiAs remotely. There were no dietary restrictions; 45-min walks in town and restaurant dinners were included in both CLC and OL; alcohol was permitted.

RESULTS

The primary outcome—reduction in risk for hypoglycemia as measured by the low blood glucose (BG) index (LGBI)—resulted in an effect size of 0.64, $P = 0.003$, with a twofold reduction of hypoglycemia requiring carbohydrate treatment: 1.2 vs. 2.4 episodes/session on CLC versus OL ($P = 0.02$). This was accompanied by a slight decrease in percentage of time in the target range of 3.9–10 mmol/L (66.1 vs. 70.7%) and increase in mean BG (8.9 vs. 8.4 mmol/L; $P = 0.04$) on CLC versus OL.

CONCLUSIONS

CLC running on a smartphone (DiAs) in outpatient conditions reduced hypoglycemia and hypoglycemia treatments when compared with sensor-augmented pump therapy. This was accompanied by marginal increase in average glycemia resulting from a possible overemphasis on hypoglycemia safety.

Despite its brief history, closed-loop control (CLC) of blood glucose (BG) using continuous glucose monitoring (CGM) and subcutaneous insulin delivery via insulin pump (continuous subcutaneous insulin infusion [CSII]), known as the artificial pancreas, is already having an impact on the treatment perspectives for type 1 diabetes (1). Between 2008 and 2011, promising results from inpatient CLC studies were reported by several groups (2–11). Most of these studies pointed out the

[1]Center for Diabetes Technology and Department of Medicine, Division of Endocrinology, University of Virginia, Charlottesville, VA
[2]Department of Endocrinology, Diabetes, and Nutrition, Montpellier University Hospital, INSERM Clinical Investigation Center 1001, Institute of Functional Genomics, CNRS UMR 5203, INSERM U661, University of Montpellier 1, Montpellier, France
[3]Department of Information Engineering and Department of Internal Medicine, Unit of Metabolic Disease, University of Padova, Padova, Italy
[4]Sansum Diabetes Research Institute, Santa Barbara, CA
[5]Department of Systems Engineering, University of Pavia, Pavia, Italy
[6]Department of Chemical Engineering, University of California, Santa Barbara, Santa Barbara, CA

Corresponding author: Boris P. Kovatchev, boris@virginia.edu.

Received 3 September 2013 and accepted 20 April 2014.

Clinical trial reg. nos. NCT01714505, NCT01727817, NCT01742741, clinicaltrials.gov.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc13-2076/-/DC1.

A slide set summarizing this article is available online.

B.P.K., E.R., C.C., and H.C.Z. contributed equally to this report.

superiority of CLC over standard CSII therapy in terms of *1*) increased time within target glucose range (typically 3.9–10 mmol/L), *2*) reduced incidence of hypoglycemia, and *3*) better overnight control. Two of these studies (5,10) had randomized crossover design but lacked automated data transfer—all CGM readings were transferred to the controller manually by the study personnel, and all insulin pump commands were entered manually as well (12). To distinguish the various degrees of automation, we introduced the notion of integrated CLC, defined as having all of the following components: *1*) automated data transfer from the CGM to the controller, *2*) real-time control action, and *3*) automated command of the insulin pump (13). Integrated CLC does not imply full automation of meal control—premeal boluses are typically requested by the patient, i.e., the system has a "meal announcement." Integrated CLC was tested in a randomized crossover study that enrolled 38 patients at three centers and used two different control algorithms, one of which—enhanced control-to-range—was used in this study as well (13). Most recently, an outpatient study of nocturnal CLC was reported where a laptop-based CLC system was taken into the ambulatory setting of a diabetes camp (14) and then to patients' homes (15), demonstrating the safety and feasibility of CLC outside the hospital. However, none of these previous trials had an artificial pancreas system suitable for outpatient use. The critical missing features were portability and user interface designed to be operated by the patient (16).

The transition of the artificial pancreas to portability began in 2011 with the introduction of the Diabetes Assistant (DiAs) developed at the University of Virginia (UVA) using an Android smartphone as a computational platform. The design specifications of DiAs were detailed in a now-published patent application (17). Parallel developments toward system portability were made by an inpatient study of overnight CLC running the algorithm on a Blackberry Storm smartphone (18). In October 2011, DiAs was used in two pilot trials done simultaneously at the Universities of Padova (Italy) and Montpellier (France) (19), followed by a feasibility study of ambulatory CLC conducted at UVA, the Universities of Padova and Montpellier, and the Sansum Diabetes Research Institute (SDRI; Santa Barbara, CA) (20). We now report a subsequent multisite randomized crossover trial comparing the safety of CLC to sensor-augmented pump therapy in a supervised transitional outpatient setting. The first results from this study were presented at the 73rd Scientific Sessions of the American Diabetes Association (21).

RESEARCH DESIGN AND METHODS

This study combined four identical protocols sharing the same DiAs artificial pancreas technology conducted at UVA, SDRI, and the Universities of Padova and Montpellier. The primary objective of the study was to estimate the effect size of hypoglycemia risk reduction on CLC versus open loop (OL; defined as CGM-augmented insulin pump treatment) in an outpatient setting. Specifically, we expected that compared with OL, CLC will result in a moderate effect size of ~0.4 in terms of reduction of the risk for hypoglycemia as measured by the low BG index (LBGI) (22) computed from CGM data. Secondary objectives included comparing markers of frequency of hypoglycemia, time within the target range of 3.9–10 mmol/L, and average glycemic control on CLC versus OL. We also collected engineering data logs and evaluated DiAs system functioning, the operation of the DiAs remote monitoring system (23), and the interdevice connections between DiAs and the CGM and between DiAs and the insulin pump. Overall, the purpose of this study was to investigate the effect size of hypoglycemia risk reduction and provide design support for a subsequent larger multicenter trial of CLC at home.

Subjects

First we recruited two pilot subjects for initial testing of the system. Their data were not used in the analysis, but one of these subjects participated later in the primary study as well. The primary study recruited 21 subjects, 1 of whom failed screening due to hypothyroidism, leaving 20 subjects to initiate the study. All participants were adults (ages 21–65 years) with clinical diagnosis of type 1 diabetes. All were experienced insulin pump users and were required to have prestudy HbA_{1c} of 6–9%; predefined insulin pump parameters for basal rates, carbohydrate ratios, and correction factors; and proper mental status/cognition. The exclusion criteria were directed toward safety and included recent history of diabetic ketoacidosis or severe hypoglycemia; pregnancy, breast feeding, or intention of becoming pregnant (females); uncontrolled arterial hypertension; and conditions that may increase the risk of hypoglycemia or infections. The demographic characteristics of the participants were average age of 46 (±10) years and baseline HbA_{1c} of 7.4 (±0.7). There were 5 females and 15 males.

Subject Experience and Training

Subject experience with CGM was heterogeneous prior to the study; some had used CGM for several weeks while others had no experience prior to the CGM training preceding the trial. To initiate CGM, subjects met with a qualified member of the study team and participated in an outpatient training visit 48–72 h prior to hotel admissions to initiate two CGM systems. The subject was trained on sensor insertion and supervised during the initial CGM sensor placements on the abdomen and on use of the study glucometer. The subject was instructed to obtain finger-stick BG, avoiding alternative sites, when obtaining blood values and was told that all finger sticks should be preceded by hand washing with warm water and a dry towel. The subject was taught how to calibrate the CGM systems per manufacturer guidelines and was informed that all treatment decisions should be based on finger-stick values and not on CGM values. As a precaution, the subject was taught to look for skin irritation after sensor removal and was reminded to avoid products containing acetaminophen while the CGM was in use. The visit lasted 1–3 h, depending on prior knowledge of the device. Then the subject was given an instruction sheet with 24-h contact information of the research team to address any problems or questions; unlimited additional appointments and calls to the study team were available.

Study Design

To achieve its primary objective, this study had a nonblinded, randomized crossover design, with each patient

participating in random order in two 40-h outpatient admissions: *1*) experimental involving integrated CLC and *2*) control using OL CGM-augmented insulin pump treatment. Both the CLC and OL admissions of the study used the DiAs system running in closed-loop or OL mode, respectively.

Procedure

All protocols were approved by the review boards of the participating institutions. In addition, the U.S.-based studies received Food and Drug Administration approval (IDE #G120210) and the European studies received appropriate national-level certifications. All studies were registered with ClinicalTrials.gov: NCT01714505 (UVA/SDRI), NCT01727817 (Padova), and NCT01742741 (Montpellier). Prior to general enrollment, two pilot subjects were run in a shorter 24-h protocol, which allowed initial testing of the study technology. After consent and screening, outpatient visits were scheduled 24–72 h prior to the CLC and OL admissions to initiate two CGM systems for each session. The CLC and OL sessions had identical timelines and proceeded as follows: patients arrived at the outpatient facility (hotel or guesthouse) at ~1700 h on session day 1, a baseline self-monitoring of BG (SMBG) value was obtained, the subject's own insulin pump was replaced by the study pump, and the study physician selected one sensor as a primary to be connected to DiAs (see STUDY TECHNOLOGY below). The subject was then introduced to DiAs operation; the orientation took ~20–30 min to complete. The DiAs user manual and advice from the study team were available at all times. After this introduction, the subject interacted with the system using the DiAs graphical user interface (GUI); the communication between CGM and the control of the pump were done exclusively through the DiAs GUI during both CLC and OL sessions. Remote monitoring was initiated. In the experimental sessions, CLC was activated at ~1900 h. Subjects were discharged by 0900 h on session day 3, spending 40 h in the study for each CLC or OL session.

Meals

The mealtimes were not fixed. The approximate mealtime windows were breakfast (0700–0800 h), lunch (1200–1300 h), dinner (1830–2030 h), and optional snack (2200–2300 h). Meal boluses were requested by the subject through the DiAs user interface; the subject entered estimated carbohydrate amount for the meal. During CL, DiAs recommended a bolus that was part of the control cycle, not a separate bolus calculator. To compute bolus amount, the controller took into account a number of factors, such as insulin on board (IOB) and necessary corrections. During OL the subjects used the usual pump bolus calculator to decide on premeal insulin. Upon confirmation of the bolus by the subject, DiAs injected the meal insulin. There were no dietary restrictions, but the meal content was consistent between CLC and OL admissions (e.g., on both admissions, subjects went to the same restaurant and ordered the same dinner). Meals were ordered for delivery, or staff accompanied the subjects to nearby restaurants. All subjects had at least one restaurant dinner during each session; most had a restaurant lunch as well. Alcohol was permitted but had to be consistent across the CLC and OL sessions.

Outpatient Walk

Within 1 h after lunch on session day 2, subjects were asked to take a 45-min walk in town, accompanied by at least one study staff member. During the walks, the system was observed remotely by the study technician. The walking intensity was consistent across the CLC and OL sessions for each patient.

Safety and Self-Monitoring

A nurse and a technician were located in nearby rooms to provide assistance. SMBG finger sticks were collected using a home BG meter at mealtime, 2 h postmealtime, and at bedtime. If the subject ate a snack, a finger stick was collected at that time as well. There were no finger sticks overnight (2300–0700 h) unless required by the safety protocol, which was activated if CGM read below 4.4 mmol/L (80 mg/dL) or above 14.4 mmol/L (260 mg/dL), if the two sensors disagreed by more than 20%, or if the DiAs hypoglycemia or hyperglycemia red-light warning was triggered (17). Hypoglycemia (defined as SMBG $<$3.9 mmol/L) was treated with ~16 g of fast-acting carbohydrate (e.g., glucose tablets or juice). DiAs hyperglycemia red-light warnings prompted checking the insulin pump for occlusion or malfunction. Any SMBG reading above 13.9 mmol/L (250 mg/dL) was followed by a β-hydroxybutyrate test (finger stick Precision Xtra β-ketone measurement); confirmed β-hydroxybutyrate level above 1.0 mmol/L was a criterion for discontinuation of the trial. In such a case, the subject could be rescheduled. Finger sticks were also used to calibrate the CGM systems per manufacturer instructions, up to every 6 h for sensor disagreement of more than 20%.

Study Technology

Central to this study was the previously introduced DiAs artificial pancreas platform (16), which uses an Android smartphone as a computing and communication hub. DiAs received CGM data from one of the two Dexcom G4 Platinum sensors (Dexcom Inc., San Diego, CA) via a communication box converting the USB signal of the G4 receiver into wireless Bluetooth. Criteria for choosing the primary sensor included closeness of the CGM reading to the initial study session SMBG reading, CGM signal reliability, and subject input about the performance and consistency of the CGM readings. In the event of primary sensor failure, the system was transitioned to the secondary sensor. Additionally, on study day 2 of the OL admission, the system was challenged with a switch from primary to secondary sensor and then back to the primary sensor. DiAs controlled a t:slim insulin pump (Tandem Diabetes Care, San Diego, CA) via wireless Bluetooth low-energy signal; the pump's own user interface was disabled and the pump communications were modified to accommodate closed-loop operation. Upon admission, DiAs was programmed with each subject's insulin pump parameters, including carbohydrate ratio, correction factor, and basal rate pattern, which ensured system individualization. DiAs is designed to switch between different controller configurations, including CLC; safety mode, where only the safety system is running to prevent hypoglycemia; OL pump mode, where DiAs acts as a pump companion; or OL sensor-alone mode. This study used OL mode for the OL sessions and closed-loop mode for the CLC sessions, switching to safety mode overnight in the U.S. studies as described below.

Closed-Loop Operation

During the experimental CLC admission, DiAs ran a control-to-range algorithm, previously introduced as enhanced control-to-range (13). This algorithm had modular architecture (24) and included a safety supervision module (SSM) developed at UVA and responsible for prevention of hypoglycemia (25); IOB constraints developed at the University of California, Santa Barbara, and responsible for prevention of insulin stacking (26); and a range control module (RCM) developed in Pavia and Padova responsible for the optimization of glucose control, including calculation of premeal boluses and postprandial insulin corrections mitigating hyperglycemia to which an implicit insulin constraint was added to improve safety (27). The RCM is initialized individually for each person with his/her insulin pump parameters (basal rate, carbohydrate ratio, correction factor) and then works as a correction to this "nominal" insulin delivery profile. All modules were introduced previously and tested extensively in the clinic (13). Due to regulatory restrictions, in the U.S. studies, the RCM was turned off between 2300 and 0700 h, and the system was running in safety-only mode (SSM + IOB constraints) overnight. We should emphasize, however, that the prevention of hypoglycemia done by the SSM and IOB constraints was identical in the U.S. and in Europe.

OL Operation

During the control admission, DiAs ran in OL mode, serving as a CGM receiver and insulin pump handheld, but without running any algorithms.

Remote Monitoring

As with previous studies, a remote monitoring server collected deidentified data transmitted from one or more DiAs systems (23). The server provided a password-protected web-based user interface used by technical and clinical staff to monitor the status of a particular clinical trial subject in real time, which proved very useful as a risk mitigation approach. This setup allowed the simultaneous study of several patients; for example, all five subjects in Montpellier, Padova, and SDRI were studied at once.

Statistical Analysis

The objective of this study was to evaluate the effect size of CLC versus OL in terms of risk for hypoglycemia (LBGI). The LBGI reflects the frequency and extent of hypoglycemic episodes and presents the results in "risk space." Thus the LBGI is a weighted average of the number of hypoglycemic readings, with progressively increasing weights as BG levels go down. The increase of the weights follows a risk function; thus the LBGI has been associated with risk for hypoglycemia and prediction of severe hypoglycemic episodes (22). We used paired *t* tests to compare LBGI, carbohydrates used for hypoglycemia treatment, percentage of time in target range (3.9–10 mmol/L), and average BG on CLC versus OL. Nonparametric test (Wilcoxon) was used to compare the number of hypoglycemic episodes. Repeated-measures ANOVA with covariate average BG was used for CLC-OL comparisons accounting for differences in average glycemia and study site (U.S. versus Europe). In addition, we assessed sensor accuracy by computing mean absolute relative deviation of CGM from SMBG readings as well as correlation between CGM and SMBG values throughout the study.

RESULTS

Eighteen subjects completed the study; the protocol was discontinued for two patients as described in CLINICAL EVENTS. The percentage of valid data was high at 96.5%; pump occlusions and device communication failures necessitated discarding 3.5% of the data (569 out of 16,122 CGM readings). The remaining 15,553 CGM readings were used for the analyses below. The total time of DiAs system use was 700.4 h in OL mode during OL sessions and 697.6 h in closed loop during CLC sessions; thus the data amounts were well balanced for repeated-measures comparisons. There were no serious adverse events (see CLINICAL EVENTS below).

Safety (Primary Outcome)

Intention-to-treat analysis including all available data revealed the following (Table 1): the risk for hypoglycemia (LBGI) was significantly lower on CLC versus OL (0.64 vs. 1.12; $t = 3.4$; $P = 0.003$). With a pooled SD of 0.75, this yielded effect size of 0.64. Thus the primary goal of the study to achieve effect size of 0.4 was exceeded. Further, compared with OL, CLC reduced approximately twofold the frequency of hypoglycemic episodes (defined as BG <3.9 mmol/L), from 2.39 to 1.22 episodes requiring carbohydrate treatment per subject on OL versus closed loop ($P = 0.02$).

Efficacy (Secondary Outcome)

The reduction in hypoglycemia was achieved without a significant increase in time spent in hyperglycemia or an increase in glucose variability and with a marginal increase of 0.5 mmol/L (9 mg/dL; $P = 0.042$) in the patient's average glucose (Table 1). To test whether the reduction in hypoglycemia was influenced by this increase, we covaried LBGI with average BG in repeated-measures ANOVA. This analysis confirmed that the decrease in LBGI was still statistically significant ($F = 7.5$; $P = 0.015$) even if the increase in average BG is accounted for. The total amount of carbohydrate ingested per subject per session was lower on CLC versus OL (283.8 versus 312.3 g; $t = 2.4$; $P = 0.026$). This difference was primarily due to the fewer hypoglycemia treatments required on CLC. The analysis also identified some differences in closed-loop performance between the U.S. and Europe; while at both sites CLC cut the risk for hypoglycemia in half compared with OL and the U.S.-Europe difference in LBGI was not significant ($P = 0.29$), in Europe, the average BG was kept higher at 9.5 mmol/L (171 mg/dL) compared with 7.7 mmol/L (138.8 mg/dL) in the U.S. ($F = 6.5$; $P = 0.02$). This was explained by differences in subjects' standard basal-bolus therapy, which governs the action of the RCM.

Table 2 presents subject-level data for all participants who completed the study, including, under both closed-loop and OL conditions, the following metrics: average BG (SD), time in target 3.9–10 mmol/L, episodes of hypoglycemia, and LBGI score. Supplementary Data includes the glucose, insulin delivery, and SMBG traces for all subjects.

Finally, throughout the study, sensor accuracy was very good with a mean absolute relative deviation (CGM from SMBG) of 11.5% and correlation $r = 0.95$ between CGM and SMBG data points.

Clinical Events

One subject during CLC experienced gradually rising CGM readings after bedtime. The safety protocol was activated after DiAs CGM read >260. An

Table 1—Summary of study outcomes

Metric	OL	Closed loop	*P* level
Primary outcomes: reduction in hypoglycemia			
LBGI	1.12	0.64	0.003
Percentage of time below 3.9 mmol/L (70 mg/dL)	1.25	0.70	>0.1
Number of hypoglycemic episodes/person/session requiring carbohydrate treatment	2.39	1.22	0.021
Grams of carbohydrate/person/session used for treatment of hypoglycemia	39.7	17.6	0.022
Secondary outcomes: glucose control			
Percentage of time in the target range of 3.9–10 mmol/L (70–180 mg/dL)	70.7	66.1	>0.1
Percentage of time above 180 mg/dL	28.0	33.1	>0.1
Average BG	8.45 mmol/L (152.1 mg/dL)	8.96 mmol/L (161.3 mg/dL)	0.042
Glucose variability (SD)	2.44 mmol/L (43.9 mg/dL)	2.49 mmol/L (44.9 mg/dL)	>0.1
Total meal carbohydrate content/person/session	272.5 g	266.2 g	>0.1
Total insulin delivered/person/session	62.6 units	59.2 units	>0.1

SMBG reading of 282 mg/dL and β-hydroxybutyrate level of 0.3 mmol/L prompted a pump-site change. The pump tubing was noted to be kinked. The patient was given 2 units of insulin via subcutaneous injection and was transitioned back to closed-loop safety-only mode at 0515 h, with 0700-h SMBG of 6.8 mmol/L (122 mg/dL). Another subject with similarly rising CGM readings overnight at 0014 h had an SMBG of 14.2 mmol/L (255 mg/dL) with a β-hydroxybutyrate level of 0.6 mmol/L without symptoms. No abnormalities with the tubing or site were observed. The patient was given 2 units of insulin via subcutaneous injection, the tubing and pump site were changed, and the subject was transitioned back to closed-loop safety-only mode. By 0214 h, SMBG was 10.2 mmol/L (184 mg/dL) and the β-hydroxybutyrate level had normalized at 0.1 mmol/L. Morning SMBG at 0734 h was 6.6 mmol/L (118 mg/dL). One patient experienced a prolonged duration of no basal rate administration per the CLC algorithm after dinner, with an SMBG of 10 mmol/L (181 mg/dL) just prior to entering safety-only mode overnight. Closed loop was overridden, and the subject was placed in OL to administer a 0.88-unit insulin bolus. Closed loop was subsequently reinitiated, and the patient transitioned to safety-only mode at 2300 h. One subject experienced several episodes of system malfunction during closed loop (0825–0838 h, no CGM; 0854–0916 h, system stopped; 1025–1044 h, no CGM; 1053–1108 h, no insulin delivery). The DiAs smartphone was replaced, closed loop was reinitiated, and the communications problems were resolved.

There were two discontinuations of the study. One subject arrived at the hotel with a baseline SMBG of 2.5 mmol/L (45 mg/dL). The study was cancelled, and the patient was stabilized with glucose administration prior to

Table 2—Patient-level outcomes for all subjects finishing the study

		OL control					CLC				
		BG (mmol/L)					BG (mmol/L)				
Subject ID	Site	Mean	SD	% Target	# Hypo	LBGI	Mean	SD	% Target	# Hypo	LBGI
23101	1	6.92	1.52	98.00	3	1.27	8.31	2.13	76.60	1	0.44
23102	1	6.50	1.67	93.91	2	1.58	6.81	2.04	87.72	1	1.48
23104	1	8.48	2.62	70.96	0	0.71	7.64	1.88	87.50	1	0.74
23105	1	8.48	2.49	71.56	4	1.32	8.56	2.45	65.19	2	0.63
23106	1	7.85	2.48	77.60	3	1.72	9.23	2.37	60.85	5	0.57
23202	2	7.60	2.49	74.19	4	2.27	8.05	2.22	82.09	0	0.41
23203	2	6.70	3.27	88.15	9	2.95	6.07	1.79	88.47	4	3.08
23204	2	7.40	2.61	79.67	3	1.70	8.76	2.50	78.37	3	0.29
23301	3	9.21	2.37	68.09	2	0.46	10.02	3.59	62.94	0	0.19
23302	3	11.69	2.51	22.17	1	0.14	9.98	2.32	49.89	1	0.12
23303	3	9.14	2.47	49.54	2	0.64	10.00	2.61	49.01	2	0.31
23304	3	13.05	3.60	20.59	2	0.09	13.36	3.18	12.25	1	0.02
23305	3	8.05	2.53	78.30	5	1.22	9.20	2.91	60.74	0	0.77
23401	4	9.05	2.26	65.68	1	0.18	8.94	2.85	67.44	0	0.44
23402	4	9.59	2.35	61.36	1	0.39	9.18	3.24	67.34	0	0.64
23403	4	7.50	1.97	86.13	1	1.16	9.70	2.75	61.32	0	0.27
23404	4	6.59	1.77	93.83	0	1.52	7.95	2.11	80.05	1	1.17
23405	4	8.27	2.89	73.62	0	0.83	9.52	1.92	52.65	0	0.02

Site 1, UVA; site 2, SDRI; site 3, Padova; site 4, Montpellier; % target, percentage of time within the target range of 3.9–10 mmol/L; # hypo, number of hypoglycemic episodes requiring treatment.

discharge. That same subject on a subsequent OL admission was dosed 9.1 units of insulin at 2020 h for a dinner meal with 90 g of carbohydrate and an SMBG of 11.8 mmol/L (213 mg/dL). By 2330 h, his SMBG was 2.6 mmol/L (47 mg/dL), with mild symptoms. Per protocol, the study was stopped and he was stabilized with glucose administration prior to discharge. He was subsequently discontinued from the study and referred back to his endocrinologist due to inappropriate pump parameters. For another subject, the study was discontinued due to hyperglycemia during a period of no active CLC resulting in β-ketone levels of 1.5 mmol/L—above the protocol threshold of 1 mmol/L. Overall, both patients and investigators emphasized the perceived safety benefits of CLC in terms of hypoglycemia reduction; some mentioned that they would have expected earlier reactions of the RCM in case of sustained glucose levels above target range. Further subject-level information is included in Supplementary Data, presenting all traces and events in the study.

CONCLUSIONS

Following several years of inpatient testing, the first early feasibility outpatient studies of portable artificial pancreas were conducted in 2011–2013 (14,15,19,20). Two of these studies introduced and tested a new CLC platform—the DiAs based on an Android smartphone—which opened the possibility for mobile closed-loop technology (19,20). The next logical step was assessment of the safety of such a platform in conditions as close to free living as possible in pilot studies. The results reported here represent the first randomized crossover trial of supervised outpatient CLC intended to estimate the effect of a modular control algorithm specifically tuned to reduce hypoglycemia and ensure the safety of the patient. This controller was compared with sensor-augmented insulin pump therapy in trials run at two research centers in the U.S. (UVA and SDRI) and two centers in Europe (Padova and Montpellier). Despite its relatively small size (five patients per site), this study achieved its goals and collected 1,400 h of CGM, insulin infusion, and system functioning data in OL and closed-loop mode of operation that will be used to power further investigations and to refine the DiAs control system for larger subsequent clinical trials of artificial pancreas at home. We can derive the following conclusions from this pilot investigation.

Although the study enrolled patients without history of severe hypoglycemia who were at relatively low risk for hypoglycemia, CLC achieved further significant reduction in the risk for hypoglycemia when compared with state-of-the-art OL therapy in outpatient conditions. The primary outcome of the study—effect size of reduction of the risk for hypoglycemia on CLC—exceeded expectations and was supported by significant reduction in the frequency of hypoglycemic episodes and the amount of rescue carbohydrates used for treatment of hypoglycemia. The trade-off of these improvements was a marginal increase of average BG on CLC (0.5 mmol/L) and a nonsignificant 5% increase in the time spent above 10 mmol/L. There were two reasons for such an increase. First, the control algorithm was conservatively tuned to reduce hypoglycemia, having dedicated SSM and IOB constraints. Second, the control condition was very demanding: experienced insulin pump users with good baseline control (average HbA_{1c} = 7.4) were given full access to the information from two continuous glucose sensors and were placed in a setting where tight glucose control was their primary assignment. In other words, the algorithm performance was comparable to the best results people could achieve if provided with even more information than the information available to the algorithm (which had access to only one sensor). We have to acknowledge, however, that the study protocol did not include extensive CGM training for all subjects, which is a limitation that could have influenced the interpretation of CGM alarms. Indeed, in this relatively short trial, the training of the subjects with CGM included only a CGM training session followed by 48–72 h of CGM use at home prior to the study as described in RESEARCH DESIGN AND METHODS. However, we confirmed that all study participants had prior experience with CGM, and approximately half were long-term CGM users.

To put these results in perspective, contemporary outpatient studies of CLC achieved similar results in prevention of hypoglycemia and also showed improved average glycemia overnight in supervised outpatient conditions (14) and at home (15). Thus, in terms of hypoglycemia, our results are consistent with the literature but, on the negative side, did not confirm improved average glucose control. On the positive side, the system we tested was portable, running CLC on a smartphone (as opposed to laptop computers), which permitted running CLC around the clock, not only overnight. The study design attempted to mimic real-life conditions as closely as possible for a pilot investigation. Beside the study location (guesthouse or a hotel) and the availability of the study team, the subjects were free to carry out everyday activities; there were no meal restrictions, light but extended physical activity was required, and alcohol was permitted. For added safety during these first transitional studies, the subjects were accompanied by medical personnel when walking in town and were not able to go independently to work or to visit events. A typical walk or restaurant visit was within a mile from the hotel room; vigorous exercise was not permitted. In this context, we tried to make OL versus closed-loop comparisons as unbiased as possible, matching the daily regimen, the restaurants and restaurant orders, the walk session of the experimental and control admissions, and randomizing the order of the admissions. Nevertheless, there were confounding factors that could not be controlled. For example, one of the first admissions at UVA was on the day of the 2012 U.S. presidential elections, which resulted in late-night waiting for the results and additional emotional stress to some of our study participants. Despite the uncontrolled diet and these confounds, the control performance in outpatient conditions was comparable to the in-hospital performance of our standard control-to-range algorithm (13), with average glucose of 8.3 (inpatient) vs. 8.9 (outpatient) mmol/L and LBGI of 0.73 (inpatient) vs. 0.64 (outpatient). In this previous inpatient study, we also tested the enhanced control-to-range algorithm used here, but with more aggressive tuning, which resulted in lower average glucose of 6.7 mmol/L but also in higher risk for hypoglycemia (LBGI = 1.05) (13). These post hoc comparisons allow us to

speculate that the transition of CLC from strictly controlled inpatient conditions to a relaxed outpatient setting would not result in significant deterioration of control performance. This is an encouraging finding, but further larger studies are needed to confirm that outpatient CLC is indeed a viable treatment for type 1 diabetes.

In terms of technology, we confirmed that a contemporary smartphone is capable of running outpatient CLC. In addition, a contemporary CGM is sufficiently accurate to provide data for control-to-range automation. To expand on this point, a well-designed control algorithm uses several consecutive CGM values, computes trends (typically via model prediction), and uses additional data sources, such as information from the insulin pump. Thus the overall accuracy of the sensor in CLC applications could be lower than the accuracy required for abrupt decisions, such as insulin dosing or pump shutoff based on a single CGM value. In view of future long-term home use, there were indications from some patients that the existing DiAs GUI could benefit from some modifications, e.g., easier reading of the display and clearer feedback when a bolus is being delivered. Surprisingly, some patients requested access to more information than currently provided, whereas providing too much data was expected by the investigators to be a burden for patients. This suggests that individualization of the system GUI should be considered for longer-term home use. Although the system now has an audible hypoglycemia alarm, more nuanced sound indicators would be appreciated in addition to "traffic light" warnings. Limited battery life (below 12 h) was considered unacceptable for long-term home use. Real-time remote monitoring remains an indispensable feature, adding a valuable layer of confidence and safety, particularly useful for detecting interruption of interdevice connections. We should also emphasize that that this was a pilot-feasibility study that had to deal not only with first-in-class technology, but also with regulatory restrictions and clinical differences at both sides of the Atlantic. This led to certain compromises that are informative for future research, such as switching the controller into safety mode overnight in the U.S. due to FDA request. However, these compromises did not alter the architecture of the control system—as noted above, DiAs is designed to switch between various control configurations, and we anticipate that various modes of operation will be switched by DiAs users during normal use. We believe that such flexibility is mandatory for a viable outpatient artificial pancreas.

In conclusion, CLC running on a smartphone (DiAs) in supervised outpatient conditions reduced hypoglycemia and hypoglycemia treatments when compared with sensor-augmented pump therapy. This was accompanied by a marginal increase in average glycemia due to a possible overemphasis on hypoglycemia safety, indicating that further optimization of the balance between prevention of hypoglycemia and improvement in average glycemia is needed for this control algorithm. Operation of the DiAs system by the patient was feasible without adverse events. The weakest system elements were the interdevice communications and limited battery life, which need further enhancement and robustness testing. This is well understood, and work is ongoing to improve the wireless connections between the CGM system, DiAs, and the insulin pump and to optimize the power needs of the system before long-term home use of CLC is attempted.

Acknowledgments. The authors thank Tandem Inc. and Dexcom Inc. for providing access to their technology; the UVA engineering team, Stephen Patek and Colleen Karvetski who designed the SSM of the control algorithm; Mary Oliveri (UVA) who was the primary contact for the U.S. regulatory submission; Christian Wakeman (UVA) who orchestrated all data and maintained the primary database for this project; Giuseppe De Nicolao (University of Pavia) who designed the RCM of the control algorithm; Wendy Bevier (SDRI) who coordinated the clinical studies in Santa Barbara; and the team at Clinical Investigation Center INSERM 1001, Montpellier, Hugues Chevassus and Isabelle Gabillaud who organized and led the investigative nurse team.

Funding. This study was supported by the JDRF Artificial Project (22-2011-649) and by National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases grant R01-DK-085623. Technology development was supported by Paul and Dianne Manning, Charlottesville, VA, and by the Frederick Banting Foundation, Richmond, VA.

Duality of Interest. B.P.K., P.K.-H., and M.D.B. hold patents or patent applications related to the study technology. B.P.K. serves on advisory boards for Animas and Sanofi and has received research grant/material support from Abbott, Animas, Dexcom, Insulet, LifeScan, Tandem, and Sanofi. E.R. serves as consultant/advisor to A. Menarini Diagnostics, Abbott, Cellnovo, Dexcom, Eli Lilly, Johnson & Johnson (Animas and LifeScan), Medtronic, Novo Nordisk, Roche Diagnostics, and Sanofi and has received research grant/material support from Abbott, Dexcom, Insulet, and Roche Diagnostics. H.C.Z. serves as consultant/advisor to Animas, Cellnovo, Insulet, MannKind, and Roche and has received research grant/product support from Animas, Abbott, Dexcom, Eli Lilly, GluMetrics, Insulet, LifeScan, Medtronic, Novo Nordisk, Roche, and Sanofi. S.M.A. has received grant/material support from Animas and Becton Dickinson. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. B.P.K. designed the study protocol, contributed to the technology design and to the clinical execution of the study, wrote the manuscript, and was the principal investigator of the project. E.R., C.C., and H.C.Z. directed the clinical trials in Montpellier, Padova, and California, respectively; designed the study protocol; contributed to the study approval and the clinical execution; and wrote the manuscript. P.K.-H. was the chief engineer of DiAs responsible for the technical aspects of the outpatient platform functioning. S.M.A. and S.A.B. wrote the study protocol, were the study physicians overseeing the execution of the clinical studies in Virginia, interpreted data, and edited the manuscript. D.R.C. coordinated all clinical aspects of the project design and execution, including on-site project management at UVA and SDRI. M.D.B. designed the safety supervising module, ensured the regulatory approval of the entire CLC system, and analyzed the data from this project. L.B.M. developed all system communication protocols and was the chief technician on site during all studies in Virginia. A.F. conducted the clinical trials in France and reviewed the manuscript. J.P. was the primary designer of the remote monitoring system and was responsible for the technical execution of the study in France. D.B., F.B., S.G, and A.A. were the study physicians responsible for the execution of the clinical studies in Padova. S.D.F. was responsible for technical aspects of the system functioning during the clinical studies in Padova. L.M. was the primary designer of the RCM used in this study and edited and revised the manuscript. F.D.P., C.T., and M.M. were responsible for the implementation and the in silico testing of the RCM. E.D. designed the IOB module of the closed-loop system; supervised the University of California, Santa Barbara, engineering team; and edited and revised the manuscript. F.J.D. was the principal investigator of the project in California; designed the IOB module of the closed-loop system; supervised the University of California, Santa Barbara, engineering team; and edited and revised the manuscript. B.P.K. 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.

Prior Presentation. This study was presented in abstract form at the 73rd Scientific Sessions of the American Diabetes Association, Chicago, IL, 21–25 June 2013, and at the 74th Scientific Sessions of the American Diabetes Association, San Francisco, CA, 13–17 June 2014.

References

1. Cobelli C, Renard E, Kovatchev BP. Artificial pancreas: past, present, future. Diabetes 2011; 60:2672–2682
2. Weinzimer SA, Steil GM, Swan KL, Dziura J, Kurtz N, Tamborlane WV. Fully automated closed-loop insulin delivery versus semiautomated hybrid control in pediatric patients with type 1 diabetes using an artificial pancreas. Diabetes Care 2008;31:934–939
3. Clarke WL, Anderson SM, Breton MD, Patek SD, Kashmer L, Kovatchev BP. Closed-loop artificial pancreas using subcutaneous glucose sensing and insulin delivery and a model predictive control algorithm: the Virginia experience. J Diabetes Sci Tech 2009;3:1031–1038
4. Bruttomesso D, Farret A, Costa S, et al. Closed-loop artificial pancreas using subcutaneous glucose sensing and insulin delivery and a model predictive control algorithm: preliminary studies in Padova and Montpellier. J Diabetes Sci Tech 2009;3:1014–1021
5. Hovorka R, Allen JM, Elleri D, et al. Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial. Lancet 2010;375:743–751
6. El-Khatib FH, Russell SJ, Nathan DM, Sutherlin RG, Damiano ER. A bihormonal closed-loop artificial pancreas for type 1 diabetes. Sci Transl Med 2010;2:27ra27
7. Dassau E, Zisser H, Percival MW, Grosman B, Jovanovič L, Doyle FJ III. Clinical results of automated artificial pancreatic β-cell system with unannounced meal using multi-parametric MPC and insulin-on-board. Diabetes 2010;59(Suppl. 1):A94
8. Atlas E, Nimri R, Miller S, Grunberg EA, Phillip M. MD-logic artificial pancreas system: a pilot study in adults with type 1 diabetes. Diabetes Care 2010;33:1072–1076
9. Renard EM, Farret A, Place J, Cobelli C, Kovatchev BP, Breton MD. Closed-loop insulin delivery using subcutaneous infusion and glucose sensing, and equipped with a dedicated safety supervision algorithm, improves safety of glucose control in type 1 diabetes. Diabetologia 2010;53(Suppl. 1):S25
10. Hovorka R, Kumareswaran K, Harris J, et al. Overnight closed loop insulin delivery (artificial pancreas) in adults with type 1 diabetes: crossover randomised controlled studies. BMJ 2011; 342:d1855
11. Dassau E, Zisser H, Harvey R, et al. Clinical evaluation of a personalized artificial pancreas. Diabetes Care 2013;36:801–809
12. Kovatchev BP. Closed loop control for type 1 diabetes. BMJ 2011;342:d1911
13. Breton M, Farret A, Bruttomesso D, et al.; International Artificial Pancreas Study Group. Fully integrated artificial pancreas in type 1 diabetes: modular closed-loop glucose control maintains near normoglycemia. Diabetes 2012;61:2230–2237
14. Phillip M, Battelino T, Atlas E, et al. Nocturnal glucose control with an artificial pancreas at a diabetes camp. N Engl J Med 2013;368: 824–833
15. Nimri R, Muller I, Atlas E, et al. Night glucose control with MD-Logic artificial pancreas in home setting: a single blind, randomized crossover trial-interim analysis. Pediatr Diabetes 2013;15:91–99
16. Keith-Hynes P, Guerlain S, Mize B, et al. DiAs user interface: a patient-centric interface for mobile artificial pancreas systems. J Diabetes Sci Tech 2013;7:1416–1426
17. Kovatchev BP, Breton MD, Keith-Hynes PT, Patek SD. Unified platform for monitoring and control of blood glucose levels in diabetic patients. International application no. PCT/US2012/043910. 23 June 2012
18. O'Grady MJ, Retterath AJ, Keenan DB, et al. The use of an automated, portable glucose control system for overnight glucose control in adolescents and young adults with type 1 diabetes. Diabetes Care 2012;35:2182–2187
19. Cobelli C, Renard E, Kovatchev BP, et al. Pilot studies of wearable outpatient artificial pancreas in type 1 diabetes. Diabetes Care 2012;35: e65–e67
20. Kovatchev BP, Renard E, Cobelli C, et al. Feasibility of outpatient fully integrated closed-loop control: first studies of wearable artificial pancreas. Diabetes Care 2013;36: 1851–1858
21. Kovatchev BP, Cobelli C, Renard E, Zisser H. Efficacy of outpatient closed-loop control (CLC). Presented at the 73rd Scientific Sessions of the American Diabetes Association, 21–25 June 2013, Chicago, IL
22. Kovatchev BP, Cox DJ, Gonder-Frederick LA, Young-Hyman D, Schlundt D, Clarke W. Assessment of risk for severe hypoglycemia among adults with IDDM: validation of the low blood glucose index. Diabetes Care 1998;21:1870–1875
23. Place J, Robert A, Ben Brahim N, et al. DiAs web monitoring: a real-time remote monitoring system designed for artificial pancreas outpatient trials. J Diabetes Sci Tech 2013;7:1427–1435
24. Patek SD, Magni L, Dassau E, et al. Modular closed-loop control of diabetes. IEEE Trans Biomed Eng 2012;59:2986–2999
25. Hughes CS, Patek SD, Breton MD, Kovatchev BP. Hypoglycemia prevention via pump attenuation and red-yellow-green "traffic" lights using continuous glucose monitoring and insulin pump data. J Diabetes Sci Technol 2010;4:1146–1155
26. Ellingsen C, Dassau E, Zisser H, et al. Safety constraints in an artificial pancreatic beta cell: an implementation of model predictive control with insulin on board. J Diabetes Sci Technol 2009;3:536–544
27. Soru P, De Nicolao G, Toffanin C, et al.; AP@home Consortium. MPC based artificial pancreas: strategies for individualization and meal compensation. Annu Rev Contr 2012;36: 118–128