Closed-Loop Insulin Therapy for People With Type 2 Diabetes Treated With an Insulin Pump: A 12-Week Multicenter, Open-Label Randomized, Controlled, Crossover Trial

Anne-Laure Borel,[1] Sandrine Lablanche,[2] Christine Waterlot,[3] Eloïse Joffray,[4] Céline Barra,[4] Nathalie Arnol,[4] Hafid Amougay,[5] and Pierre-Yves Benhamou[2]

ORIGINAL ARTICLE

OBJECTIVE

Continuous glucose monitoring (CGM) combined with continuous subcutaneous insulin infusion (CSII) achieves better glycemic control than multi-injection therapy in people with type 2 diabetes. The effectiveness of closed-loop therapy needs to be further evaluated in this population.

RESEARCH DESIGN AND METHODS

The study objective was to measure the impact of a hybrid closed-loop device (DBLG1) compared with CSII + CGM on glycemic control in people with type 2 diabetes previously treated with CSII. The randomized, controlled, crossover, two-period, open-label, and multicenter study was conducted from August 2022 to July 2023 in 17 individuals (9 to receive 6 weeks of CSII + CGM first and 8 to receive 6 weeks of closed-loop therapy first). The primary end point was the percentage time in range (TIR: 70–180 mg/dL). Secondary outcomes were other CGM-glucose metrics, physical activity, and sleep objectively measured using 1-week actimetry.

RESULTS

Data were analyzed using a modified intention-to-treat approach. Mean age was 63 (SD 9) years and 35% were women. Mean HbA_{1c} at inclusion was 7.9% (SD 0.9). TIR increased to 76.0% (interquartile range 69.0–84.0) during the closed-loop condition vs. 61.0% (interquartile range 55.0–70.0) during the CSII + CGM condition; mean difference was 15.0 percentage points (interquartile range 8.0–22.0; $P < 0.001$). Analyses of secondary end points showed a decrease in time above range, in glucose management indicator, in glucose variability, and an increase in daily insulin dose. Actimetric sleep analysis showed an improvement in sleep fragmentation during closed-loop treatment.

CONCLUSIONS

Closed-loop therapy improved glycemic control more than did CSII + CGM in people with type 2 diabetes.

[1]Department of Endocrinology, Diabetology and Nutrition, Centre hospitalier Grenoble Alpes, INSERM U1300, Université Grenoble Alpes, Grenoble, France
[2]Department of Endocrinology, Diabetology and Nutrition, Centre hospitalier Grenoble Alpes, INSERM U1055, Université Grenoble Alpes, Grenoble, France
[3]Department of Endocrinology and Diabetology, Centre Hospitalier Métropole Savoie, Chambéry, France
[4]ICADOM, Meylan, France
[5]Department of Endocrinology and Diabetology, Centre Hospitalier Annecy Genevois, Annecy, France

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The prevalence of type 2 diabetes has risen steadily since the 1980s. The International Diabetes Federation estimated that in 2021, 537 million people in the world had diabetes, and this number is projected to reach 643 million by 2030 and 783

million by 2045 (1). People who live with type 2 diabetes have a higher risk of organ dysfunction and failure, especially the kidneys, eyes, and nerves. It is estimated that people with type 2 diabetes have an excess mortality risk from any cause of 15% compared to general population and that this mortality risk increases substantially with poorer glycemic control, severe renal complications, impaired renal function, and younger age at diagnosis (2).

Type 2 diabetes is a progressive disease. Treatment needs to be intensified over time until insulin replacement becomes necessary. In France, the Echantillon National Témoin Représentatif des personnes Diabétiques, 3rd edition (ENTRED3) epidemiological study showed that 22.5% of people living with type 2 diabetes are treated with insulin (3). Several studies have shown improvements in glycemic control with continuous subcutaneous insulin infusion (CSII) when people with type 2 diabetes reach the stage of requiring multiple daily insulin injections (4,5). In addition, using continuous glucose monitoring (CGM) or flash CGM (FGM) in adults with type 2 diabetes has also improved glycemic control (6).

In people with type 1 diabetes, closed-loop therapy has been shown to be superior to glucose sensor-augmented pump therapy or any other treatment modality. Closed-loop systems allow more time to be spent in range (TIR, 70–180 mg/dL), reduce glycemic variability, and reduce the risk of hypoglycemia (7–11).

Insulin delivery by closed-loop therapy in type 2 diabetes has been tested in eight randomized controlled trials (RCTs) to date. Five of these were conducted in hospitalized individuals with treatment exposure times of <20 days (12–16). Three were conducted in outpatients with an exposure duration of 20 days (17), 8 weeks (18), and 12 weeks (19), respectively. Four trials were multicenter (13,14,17,19). One trial was conducted in people requiring nutritional support (14), another during the perioperative period of elective surgery (16), and another in people treated with dialysis (17). All of these trials (18) involved comparison with conventional insulin therapy using single or multiple daily insulin injections. A recent meta-analysis RCTs showed that closed-loop insulin delivery enabled an improvement in TIR of 337 min per 24 h (Hedges g = 1.22%, 95% CI 0.84%–1.6%, $P < 0.01$), with a reduction in time spent in hyperglycemia (time above range [TAR]), and no difference in time spent in hypoglycemia (time below range [TBR]) (20).

The study objective was to assess whether a hybrid closed-loop device (DBLG1) will allow better glycemic control than CSII + CGM in individuals with type 2 diabetes previously treated with CSII in their usual living conditions.

RESEARCH DESIGN AND METHODS

Design

We conducted an interventional, randomized, controlled, cross-over, open-label, multicenter, 13-week study. A relatively small number of individuals with type 2 diabetes benefit from insulin therapy administrated by CSII. For a first study in this population, a crossover study was chosen to achieve a greater statistical power with a limited number of patients included. Data were collected from August 2022 to July 2023. The study protocol was approved by the ethics committee (CPP Ouest I, Tours, France, ID-RCB 2020-A03429-30) and is provided in the Supplementary Material. The safety aspects of the trial were overseen by an independent data and safety monitoring board. All individuals who were included signed informed consent forms after receiving verbal and written information with a time of reflection of several days. The study was registered at ClinicalTrials.gov (NCT05369871). The study is reported according to the Consolidated Standards of Reporting Trials (CONSORT) extension for crossover studies guidelines.

Sample

We recruited outpatients with type 2 diabetes monitored in three hospitals in France, including one university hospital. They were previously treated with CSII in routine clinical care via collaboration with a home care service provider (Agiradom, France). In France, CSII therapy can be administered and reimbursed to patients with type 2 diabetes if they do not have a good glycemic control on multidaily injection therapy. These participants lived at home and were autonomous in their daily activities. They were also autonomous in managing their CSII + FGM therapy at home. Participant eligibility was assessed using clinical and treatment data collected by the home care provider. Inclusion was done in each hospital center.

Inclusion criteria were age >18 years, body weight ≤150 kg, type 2 diabetes diagnosed by a diabetologist, treated with an insulin pump for at least 6 months and stable pharmacological treatment of diabetes for at least 6 months, equipped with a CGM or FGM system, total daily insulin dose <160 IU/24 h, and HbA_{1c} <10%.

Criteria for noninclusion were type 1 diabetes, insulin requirements <8 IU/24 h, a disease that could impact on the physiology of diabetes (i.e., involving interactions with glucose or insulin that could interfere with the medical device, such as corticosteroid treatment), severe uncorrected hearing, visual acuity problems, pancreatectomy, severely impaired pancreas function, renal failure with clearance <30 mL/min/m^2, impaired hypoglycemia perception, highly unstable diabetes (patient experiencing problematic hypoglycemia despite up-to-date and appropriate diabetes management), pancreas or islet transplantation, severe neuropathy associated with HbA_{1c} >9%, or severe proliferative retinopathy/maculopathy associated with HbA_{1c} >9% (because of the risk of worsening in the event of rapid correction of glycemic control).

Primary End Point

The primary end point was the difference in percentage TIR [70–180] mg/dL measured using the Dexcom G6 model CGM sensor (Dexcom, San Diego, CA) between 6 weeks of hybrid closed-loop therapy (C for "closed") and 6 weeks of CSII + CGM (O for "open"). The analysis was performed on data from the last 3 weeks of each 6-week condition.

Secondary End Points

The secondary end points were the differences hybrid closed-loop therapy and CSII + CGM for the following variables:

- daily glycemic variability measured by the coefficient of variation and SD of glycemia,
- hyperglycemia measured by the percentage TAR (>180 mg/dL),
- hypoglycemia measured by the percentage TBR (<70 mg/dL),
- average daily insulin dose,
- glucose management indicator (GMI) corresponding to estimated HbA_{1c},
- daily physical activity measured in MET by 1-week actimetry,

- sleep duration and sleep fragmentation measured by 1-week actimetry,
- satisfaction with diabetes treatment measured by the Diabetes Treatment Satisfaction Questionnaire (DTSQs),
- treatment safety (prospective collection of severe adverse events), and
- satisfaction with the therapy system assessed using a usability questionnaire.

To apply the recent recommendations (21) published after the end of the study concerning the reporting of results in studies involving CGM data, we analyzed the following variables that were not prespecified in the protocol:

- TBR (very low glucose or level 2 hypoglycemia), that is, $<$54 mg/dL
- TAR (very high glucose or level 2 hyperglycemia), that is, $>$250 mg/dL
- Mean sensor glucose (mg/dL)

Hybrid Closed-Loop System

We used the DBLG1 system, which is composed of an Accu-Chek Insight insulin pump (Roche, Basel, Switzerland) and the DEXCOMG6 CGM system. Transmission is via Bluetooth Low Energy technology and the system uses the Diabeloop application (Regulation v2017.04.20; Diabeloop, Paris, France) installed on an android smartphone (Motorola Moto E XT1524, Motorola, Chicago, IL). The data were computed and accessible in real-time to participants and physicians through the YourLoops web platform (Diabeloop, Paris, France). DBLG1 is a hybrid loop algorithm on which the patient needs to input meals by the amount of carbohydrates ingested or by selecting meal size (small, medium, or large). The physical activity also needs to be declared. Previous work has shown that the most frequent adjustments to the algorithm parameters were generally made within the first 2 weeks, and that glucose measurements were stable after 1 or 2 weeks of active hybrid closed loop (22). We therefore chose to analyze the data after the adjustments to the algorithm settings during the first 2 weeks.

CSII + CGM System

During the CSII + CGM period, participants used their usual insulin pump therapy. They were equipped with a DexcomG6 CGM and had access to continuous glucose data. The use of "hypoglycemia" and "hyperglycemia" alarms was set at the same thresholds for all participants, with an hypoglycemia alarm set at 60 mg/dL for at least 25 min and an hyperglycemia alarm set at 320 mg/dL for at least 20 min.

Study Schedule

The study schedule is shown in Supplementary Fig. 1. Details of each visit are provided in the Supplementary Appendix.

During the closed-loop period, patients began treatment with the new CSII system and the YourLoops software. To enable them to adapt to the new equipment in the event of unexpected shutdown of the closed-loop at a later date, they were left for 7 days with the new CSII system and the loop open, after which the loop was closed. The patient received a call from the nurse on day (D) 1 and D2 when the loop was closed, and then once a week. The doctor looked at the data at D1, D2, D7, and D14 to adjust the algorithm parameters if necessary. The doctor did not intervene in the settings for the following 3 weeks. For the CSII + CGM control period, participants continued their treatment with their usual CSII system, with weekly contacts with a nurse and data visualization on YourLoops at D1, D2, D7, and D14 by the doctor to adjust pump parameters if necessary.

Randomization

Randomization was performed electronically via eCRF, according to a randomization list preestablished by the statistician. The randomization list was stratified by center, by block size 2, using the "proc plan" function of SAS 9.4 software (SAS institute, Cary, NC). The investigator and patient were open about the arm allocated to the patient (O/C or C/O).

Statistical Analysis

We were unable to perform a formal sample size calculation because of lack of relevant data in the literature at the time of study conception. Therefore, the number of people to be included was chosen according to inclusion capacity of each of the three centers, which was estimated at 30 individuals. We anticipated a 30% refusal to participate in the study; therefore, the number of people to be included was set at 20.

Qualitative variables are described by number and percentage. Quantitative variables are reported by means and SDs and differences between periods by mean and 95% CI if the data were normally distributed. Quantitative variables and differences between periods are reported by median and interquartile range (IQR) if the data were not normally distributed. The number and percentage of missing data are reported.

The populations to be analyzed were defined as follows: the modified intention-to-treat (mITT) population was defined as all participants exposed to the second period for at least 24 h, in each arm. The per-protocol population corresponded to the mITT population with no major protocol deviations. A major protocol deviation was defined as stopping the closed-loop for $>$75% of the planned closed-loop time or completely stopping the planned treatment (closed loop or CSII + CGM treatment). The per-protocol and mITT populations were identical; therefore, only mITT analyses are presented.

The effect of the hybrid closed-loop versus the CSII + CGM on the primary and secondary end points of the study was investigated using specific crossover analyses. These analyses allowed us to study the treatment effect, the order effect, and to control for a possible order × treatment interaction. A significant interaction would mean that the treatment effect depended on the order of administration of the conditions studied. In such cases, only the first period of the crossover was analyzed.

The treatment effect was analyzed by a Student *t* test if the distribution of interperiod difference values was normally distributed or by a Mann-Whitney test if the distribution of interperiod difference values was not normally distributed. The distribution was assessed visually and using the Shapiro-Wilk test. The comparison was adjusted for treatment order.

The treatment × center interaction was tested on the primary end point using a mixed model with the following factors: order, treatment, center, center × treatment (fixed factors), and subject factor nested within group factor (random factors).

All analyses were performed using SAS 9.4 statistical software (SAS institute, Cary, NC). The threshold of significance was set at 0.05.

Role of the Funding Source

The funding source, DIABELOOP, SA, participated in the study design. It did not participate in data acquisition, statistical analyses, results interpretation, or deciding

Table 1—Baseline participant characteristics

	All participants (N = 17)		O/C sequence (n = 9)		C/O sequence (n = 8)	
	Mean (SD) or median (IQR) or n (%)	Min; Max	Mean (SD) or median (IQR) or n (%)	Min; Max	Mean (SD) or median (IQR) or n (%)	Min; Max
Age (years)	63 (9)	47; 79	63 (6)	53; 75	63 (11)	47; 79
Male sex, n (%)	11 (64.7)		7 (77.8)		4 (50)	
Height (cm)	172 (9)	155; 190	174 (7)	160; 181	170 (11)	155; 190
Weight (kg)	97 (16)	73; 121	101 (16)	76; 121	91 (15)	73; 120
BMI (kg/m^2)	32.0 (4.0)	25.0; 40.0	32.9 (4.8)	25.0; 40.0	31.0 (3.0)	28.0; 37.0
Systolic blood pressure (mmHg)	145 (122–149)	112; 180	136 (125–154)	120; 180	145 (115–149)	112; 162
Diastolic blood pressure (mmHg)	70 (65–80)	55; 125	75 (69–81)	67; 125	65 (58–80)	55; 93
Type 2 diabetes characteristics						
HbA$_{1c}$ (%)	7.9 (0.9)	6.7; 9.7	7.8 (0.7)	6.7; 8.8	8.0 (1.1)	6.8; 9.7
HbA$_{1c}$ (mmol/mol)	63 (7)	50; 83	62 (6)	50; 73	64 (9)	51; 83
Diabetes duration (years)	24 (9)	13; 47	21 (6)	13; 32	28 (11)	16; 47
Duration of insulin pump treatment (years)	7 (3)	1; 15	5 (3)	1; 8	8 (4)	5; 15
Insulin pump therapy						
Glycemic target (mg/dL)	110 (110–110)	100; 150	110 (100–110)	100; 120	110 (110–125)	100; 150
No. of bolus/day	3.2 (1.8)	0.3; 5.4	3.2 (1.7)	0.3; 5.2	3.3 (2.0)	0.3; 5.4
Daily bolus insulin (IU/day)	37.6 (28.6)	0.6; 90.5	39.5 (31.4)	4.2; 90.5	35.6 (26.9)	0.6; 69.6
Daily basal insulin (IU/day)	40.4 (14.5)	11.8; 68.6	45.3 (15.8)	19.7; 68.6	34.9 (11.4)	11.8; 48.4
Daily total insulin (IU/day)	78.1 (35.9)	23.9; 156.2	84.8 (41.6)	23.9; 156.2	70.5 (29.2)	28.2; 111.2
CGM						
TIR, 70–180 mg/dL (%)	58.9 (20.1)	18.0; 86.0	55.5 (18.3)	31.7; 86.0	63.2 (23.0)	18.0; 85.4
TAR, >180 mg/dL (%)	40.4 (20.4)	13.8; 81.5	44.1 (18.3)	14.0; 68.3	35.6 (23.4)	13.8; 81.5
TBR, <70 mg/dL (%)	0.5 (0.0–0.9)	0.0; 3.5	0.0 (0.0–0.5)	0.0; 0.9	0.8 (0.5–1.9)	0.5; 3.5
Mean daily variation coefficient (%)	29.8 (3.8)	21.1; 34.4	28.6 (4.2)	21.1; 32.6	31.4 (2.7)	27.2; 34.4
Mean daily SD (g/L)	0.54 (0.10)	0.37; 0.71	0.53 (0.10)	0.37; 0.66	0.54 (0.12)	0.38; 0.71
Mean daily GMI (%)	7.7 (1.0)	6.5; 10.1	7.9 (0.9)	6.8; 9.3	7.5 (1.3)	6.5; 10.1
Mean daily CGM use (% of 24 h)	81.1 (67.0–91.0)	25.3; 100.0	79.0 (58.3–88.0)	30.6; 97.6	83.3 (75.8–94.1)	25.3; 100.0
Other antidiabetes medications						
Metformin, n (%)	11 (64.7)		8 (88.9)		3 (37.5)	
GLP-1 agonists, n (%)	7 (41.2)		4 (44.4)		3 (37.5)	
SGLT2 inhibitors (yes), n (%)	5 (29.4)		3 (33.3)		2 (25.0)	
Diabetes complications						
No. diabetes-related hospitalization during the last year	0.0 (0.0-0.0)	0.0; 1.0	0.0 (0.0-0.0)	0.0; 0.0	0.0 (0.0-0.0)	0.0; 1.0
Retinopathy, n (%)	6 (35.3)		4 (44.4)		2 (25.0)	
Nephropathy, n (%)	6 (35.3)		4 (44.4)		2 (25.0)	
If yes, dialysis, n (%)	0 (0)		0 (0)		0 (0)	
Diabetic foot injury, n (%)	2 (11.8)		1 (11.1)		1 (12.5)	
Cardiovascular history, n (%)	10 (58.8)		5 (55.6)		5 (62.5)	
Heart attack	3 (17.6)		2 (22.2)		1 (12.5)	
Cerebrovascular accident	0 (0)		0 (0)		0 (0)	
Hypertension	6 (35.3)		3 (33.3)		3 (37.5)	
Heart failure	0 (0)		0 (0)		0 (0)	
Other	1 (5.9)		0 (0)		1 (12.5)	
Other medical history, n (%)						
Depressive disorders	4 (23.5)		1 (11.1)		3 (37.5)	
Liver cirrhosis	1 (5.9)		1 (11.1)		0 (0)	
Arrhythmia	2 (11.8)		1 (11.1)		1 (12.5)	
Cancer	2 (11.8)		1 (11.1)		1 (12.5)	
Other	3 (17.6)		2 (22.2)		1 (12.5)	

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Table 1—Continued

	All participants (*N* = 17)		O/C sequence (*n* = 9)		C/O sequence (*n* = 8)	
	Mean (SD) or median (IQR) or *n* (%)	Min; Max	Mean (SD) or median (IQR) or *n* (%)	Min; Max	Mean (SD) or median (IQR) or *n* (%)	Min; Max
DTSQs						
Treatment satisfaction scale total	32 (3)	26; 36	32 (3)	28; 36	32 (3)	26; 35
Perceived frequency of						
Hyperglycemia (*n*/day)	1.0 (1.0–2.0)	0.0; 4.0	1.0 (1.0–3.0)	0.0; 4.0	1.5 (0.5–2.0)	0.0; 4.0
Hypoglycemia (*n*/day)	1.0 (0.0–2.0)	0.0; 5.0	1.0 (0.0–1.0)	0.0; 2.0	1.5 (0.5–3.0)	0.0; 5.0

Data are mean (SD) or median (IQR) for normally and not normally distributed data, respectively, and minimum; maximum for continuous data. Qualitative data are *n* (%). There was one missing data value for blood pressure and one missing data value for CCM metrics at baseline. GLP-1, glucagon-like peptide 1; Min, minimum; Max, maximum; SGLT2, sodium–glucose cotransporter 2.

to submit the manuscript. It did not write the report, except for Fig. 2, which was featured by a member of DIABELOOP.

RESULTS

The study screened 77 individuals, and 20 were included. Three individuals (15%) withdrew (one due to "anxiety about new equipment," another due to "constraints related to the study and the closed-loop system," and the last due to "family event"), so 17 individuals were analyzed. The study flowchart is presented in Supplementary Fig. 2. Participant characteristics are presented in Table 1. Mean age of the 17 participants included in the mITT was 63 (SD 9) years, and 64.7% were men. Mean time since diagnosis of diabetes was 24 (SD 9) years and mean treatment time with CSII was 7 (SD 3) years. Mean baseline HbA_{1c} was 7.9% (SD 0.9) or 63 (SD 7) mmol/mol, and mean baseline TIR was 58.9% (SD 20.1). All participants but one used the "small/medium/large meal" function to quantify food intake during the hybrid closed-loop period. One participant used functional insulin therapy to calculate meal bolus doses. The percentage of time spent with active hybrid closed-loop system during the "closed-loop" period was 98% (IQR 95–99) overall, with 99.0% (IQR 97.5–99.0) for the C/O sequence and 97.0% (IQR 89.0–98.0) for the O/C sequence ($P = 0.026$).

Primary Outcome

Median (IQR) TIR was 61.0% (55.0–70.0) during CSII + CGM and 76.0% (69.0–84.0) during the closed-loop periods; median difference of TIR between the two periods of treatment was 15.0 percentage points (IQR 8.0–22.0; treatment effect $P < 0.001$) (Table 2). There was no significant order × intervention ($P = 0.18$) or treatment × center ($P = 0.86$) interaction. Figure 1 shows the individual results of the participants. Despite the absence of order × intervention interaction, the magnitude of improvement with the closed-loop is visually more marked in the O/C versus C/O arm, suggesting retention of the closed-loop benefit on the CSII + CGM sequence in the C/O arm. To assess the impact on results of excluding the period of adaptation of the algorithm to the participant during the first 15 days, we evaluated the difference between the two periods for the total time spent in hybrid closed-loop compared with the total period under CSII + CGM. The difference between the two treatment modalities remains significant in favor of the hybrid closed-loop, albeit of lesser magnitude (6.2 percentage points [SD 7.4], $P = 0.004$) (Supplementary Table 1).

Secondary Outcomes

The comparison between CSII + CGM and closed-loop periods for the secondary outcomes is reported in Table 2. TAR was shorter during the closed-loop than in the CSII + CGM periods, with no difference in TBR. The glycemic variability, assessed by the variation coefficient and SD, and GMI were lower during the closed-loop than the CSII + CGM periods. The time of CGM use (percentage of 24 h) was high in both conditions with 99.0% (IQR 96.9–99.0) during closed-loop and 95.0% (IQR 93.0–98.0) during CSII + CGM, mean difference 2.0 percentage points (IQR 0.0–5.0; $P = 0.016$). The global results of the CGM during the closed-loop and CSII + CGM are shown in Fig. 2.

The total daily insulin dose was higher during the closed-loop than during the CSII + CGM periods. Total DTSQs score did not differ between conditions. The perceived frequency of hyperglycemia was lower with the closed-loop, but the perceived frequency of hypoglycemia did not differ between conditions.

The mean daily physical activity and the mean total sleep time did not differ between conditions. The order × treatment interaction was significant for the sleep fragmentation index. We therefore compared the sleep fragmentation index between closed-loop and CSII + CGM for only the first period of the sequence. The Mean sleep fragmentation index was lower with the closed-loop system than with CSII + CGM (18.2 [SD 5.0] vs. 23.6 [SD 4.9], $P = 0.047$, respectively).

Adverse Events

Adverse events are reported in Supplementary Table 2. One serious adverse event was attributable to the study. It occurred in a participant who presented with severe hyperglycemia that needed the on-call physician intervention. Hyperglycemia was caused by a folded insulin pump cannula while the participant was in the closed-loop period of the study. Under physician monitoring, the remission of the hyperglycemia occurred without hospitalization. Of note, no severe hypoglycemic events occurred. All adverse events and Common Terminology Criteria for Adverse Events (CTCAE) grades are detailed in Supplementary Table 3.

In addition, body weight was measured at baseline and at the end of both treatment periods. There was no change in weight between the beginning and end of the study neither for the entire population nor for each group: C/O or O/C (Supplementary Table 4).

Table 2—Main and secondary outcomes for the differences between closed-loop system and CSII with CGM

	N	Closed loop	CSII + CGM	Difference of closed loop minus CSII + CGM	*P* value treatment effect	Statistical test for treatment effect	*P* value for normality test of the treatment effect	*P* value for interaction test order x intervention
Main outcome								
TIR 70–180 mg/dL (%)	17	76.0 (69.0–84.0)	61.0 (55.0–70.0)	15.0 (8.0–22.0)	<0.001	Mann-Whitney	0.013	0.18
Secondary outcomes								
CGM metrics								
Mean sensor glucose (mg/dL)	17	158.8 ± 17.3	172.2 ± 20.8	−13.2 (−20.8 to −5.6)	0.002	Student	0.12	0.19
TAR >180 mg/dL (%)	17	24.0 (16.0–30.0)	38.0 (30.0–45.0)	−15.0 (−22.0 to −8.0)	<0.001	Mann-Whitney	0.007	0.18
Level 2 hyperglycemia, >250 mg/dL	17	2.3 (1.0–5.3)	7.0 (3.7–9.6)	−3.3 (−6.9 to 0.7)	0.014	Student	0.71	0.16
TBR <70 mg/dL (%)	17	0.1 (0.0–0.4)	0.3 (0.2–1.0)	−0.2 (−0.2 to 0.0)	0.13	Mann-Whitney	0.001	0.38
Level 2 hypoglycemia, <54 mg/dL	17	0.00 (0.00–0.05)	0.00 (0.00–0.02)	0.00 (−0.02 to 0.03)	0.89	Mann-Whitney	<0.001	0.81
Variation coefficient (%)	17	23.0 (3.3)	25.1 (2.9)	−2.1 (95% CI −3.6 to 0.7)	0.006	Student	0.30	0.83
SD (g/L)	17	0.43 (0.11)	0.50 (0.08)	−0.07 (95% CI −0.11 to 0.02)	0.005	Student	0.20	0.54
GMI (%)	17	7.1 (0.4)	7.4 (0.5)	−0.3 (95% CI −0.5 to 0.1)	0.002	Student	0.12	0.16
CGM use (% of 24 h)	17	99.0 (96.9–99.0)	95.0 (93.0–98.0)	2.0 (0.0–5.0)	0.016	Mann-Whitney	0.006	0.65
Insulin doses								
Daily total insulin (IU/day)	17	103.7 (76.1–122.8)	78.0 (59.3–95.3)	10.0 (3.3–30.6)	0.003	Mann-Whitney	<0.001	0.36
DTSQs								
Treatment satisfaction scale total	17	31.0 (28.0–35.0)	32.0 (28.0–35.0)	−1.0 (−6.0 to 4.0)	0.89	Student	0.15	0.43
Perceived frequency of								
Hyperglycemia (*n*/day)	17	1.0 (1.0–3.0)	3.0 (1.0–5.0)	−2.0 (−3.0 to 1.0)	0.045	Student	0.19	0.65
Hypoglycemia (*n*/day)	17	1.0 (0.0–2.0)	1.0 (0.0–2.0)	0.0 (−1.0 to 1.0)	0.84	Student	0.15	0.27
Actimetry								
Mean daily physical activity (METs)	16	1.07 (1.04–1.09)	1.06 (1.05–1.08)	0.01 (−0.01 to 0.02)	0.16	Mann-Whitney	0.044	0.50
Mean daily total sleep time (min)	16	369 (64)	371 (72)	−2 (−51 to 47)	0.93	Student	0.21	0.64
Mean daily sleep fragmentation index	16							0.038

Results are expressed as means and SD and differences between periods by means and 95% CIs if the data are normally distributed. Quantitative variables and differences between periods are reported by median and interquartile range if the data are not normally distributed. Mean differences represent the means of the individual differences between the two periods of the study. If the differences were normally distributed, a Student test was realized to look for treatment effect; if not, a Mann-Whitney test was realized.

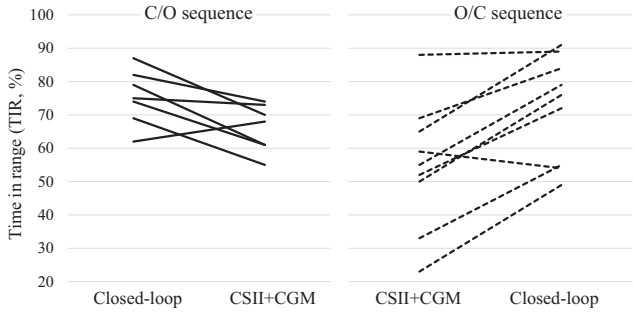

Figure 1—Time in range during the closed-loop and the CSII + CGM periods.

Usability

The device, including insulin pump therapy, CGM sensor, and algorithm terminal, was found to be easy to use and easy to learn by approximately three-quarters of the participants. The remaining one-quarter of participants found the application difficult to use and two of those three dropped out because of the constraints of the "hybrid closed-loop" device. Detailed responses to the usability questionnaires and comments related to the device are reported in Supplementary Tables 5–7.

CONCLUSIONS

The results of this work showed that, in patients with type 2 diabetes already receiving intensive insulin therapy administered with CSII combined with CGM, implementation of a hybrid closed-loop system improved the median TIR by 15.0 percentage points (IQR 8.0–22.0). This improvement was associated with a reduction in TAR, glucose variability, and GMI and with an increase in the total daily insulin dose. Moreover, the improvement in glycemic control was not achieved at the expense of an increase in TBR. In addition, quality of sleep was better in the closed-loop than the CSII + CGM condition because of a reduction in sleep fragmentation.

CSII has been shown to improve glycemic control in people with type 2 diabetes (4,5). In addition, the use of a FGM or a CGM system also improves HbA_{1c} and TIR in people with type 2 diabetes treated with insulin (insulin pump or multiple daily injections) (6,23). In this context, the added value of a hybrid closed-loop to improve an already intensive treatment with CSII + CGM might not have brought any additional benefit. Previous studies showing benefits of closed-loop therapy in type 2 diabetes have focused on particular situations in which glycemic control is jeopardized: perioperative period (16), dialysis (17), under nutritional support (14), or any medical condition leading to insulin treatment during hospitalization (13). In one study under usual living conditions (18), a fully closed-loop system was compared with standard insulin therapy in a single-center RCT with parallel arms in which 28 people without prior insulin treatment were included. The TIR increased in both groups with an additional benefit in the closed-loop arm. As in our study, the TAR range was lower in the closed-loop arm, with no difference in TBR, and the daily insulin doses were higher in the closed-loop arm. Another multicenter RCT with parallel arms (19) included individuals with uncontrolled insulin-treated type 2 diabetes who depended on a home nurse for insulin injections. They were randomized to a hybrid closed-loop intervention group, managed by a home nurse every 3 days combined with 7–10 days of remote medical supervision, compared with usual treatment group managed by a home nurse every day. TIR improved in the closed-loop arm from 34% (SD 21.3) to 63.0% (SD 9.4), with no increase in TBR.

These studies demonstrated that the closed-loop system increased TIR and reduced time in hyperglycemia without increasing the risk of hypoglycemia in people with type 2 diabetes. In addition to monitoring HbA_{1c} levels, use of these new glycemic control metrics, derived from CGM, is now recommended to monitor patients with type 1 diabetes and type 2 diabetes because they more efficiently capture the glucose variability and the risk of hypoglycemia (24–26). TIR and TAR are correlated with occurrence of albuminuria (27), retinopathy (28), and carotid atherosclerosis (29). In our study, the 70% recommended TIR threshold was

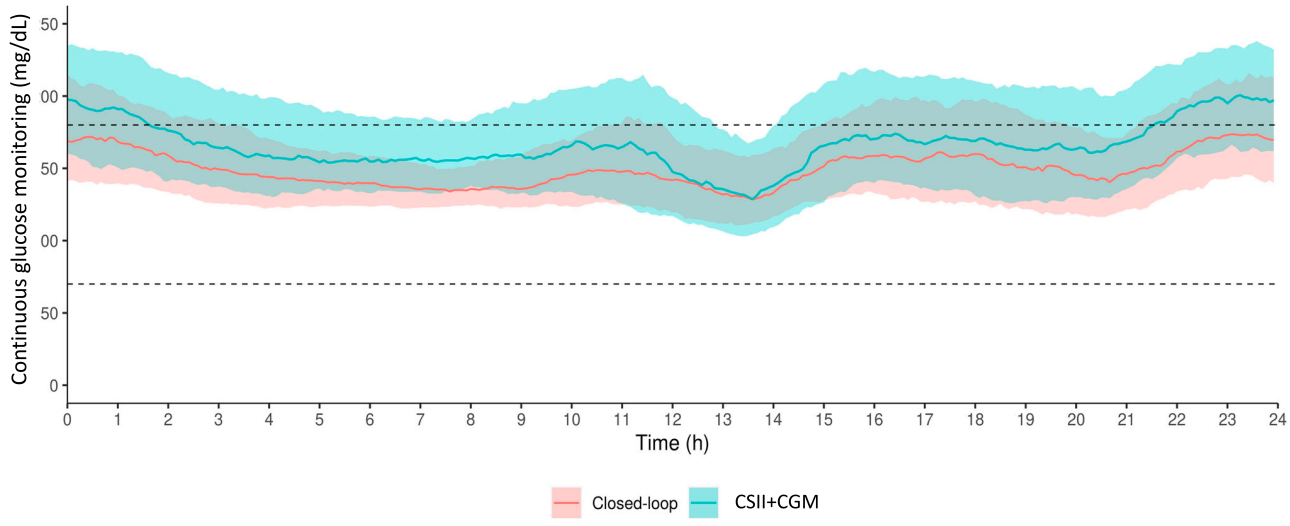

Figure 2—Glucose control during the closed-loop and the CSII + CGM periods. The shaded areas show the 95% CI.

reached in ~75% of the participants with the hybrid closed-loop and the glycemic variability decreased (30).

People living with diabetes have poorer quality of sleep than people without diabetes, partly due to greater sleep fragmentation (31,32) caused by nocturnal hypoglycemia, and/or nocturnal hyperglycemia, leading to polyuria and hence nocturia. Hyperglycemia has been linked to an increased arousal index (32) as well as glycemic variability (31). Therefore, a secondary outcome of our study was to objectively determine the effect of the closed-loop system on sleep quality by using actimetry. Despite interaction with the treatment sequence, sleep fragmentation was reduced, suggesting that the hybrid closed-loop system improved sleep quality. These data are exploratory, given the small number of participants. However, this additional positive effect of hybrid closed-loop therapy should be confirmed in longer duration studies.

Our findings must be interpreted in the light of some limitations. First, the inclusion conditions limited the daily insulin dose to 160 IU/24 h and body weight to 150 kg. These criteria were due partly to the size of the insulin pump reservoir and partly to the algorithm, which was designed not to exceed a cumulative dose of 160 IU/24 h. Therefore, individuals with major insulin requirements were not included, limiting the generalizability of our findings. This problem could be addressed by using more concentrated U500 insulin and adapting the algorithm accordingly. Indeed, beyond the practical advantage of reducing the need to refill the insulin pump tank more than once a day, U500 is more effective for the glycemic control of people with high insulin resistance (33).

The second limitation is the relatively short duration of exposure to the closed-loop period of 6 weeks, including 1 week of open treatment with the new CSII and 2 weeks of adjustment of the closed-loop parameters, which requires close medical follow-up. Given the time needed to adapt to the new equipment and treatment modalities, although glycemic control was improved, participants did not necessarily feel the benefit of the hybrid closed-loop, as reflected by the lack of difference in satisfaction between treatment modalities. A longer-term study could provide a better assessment of the impact of this hybrid closed-loop treatment on satisfaction and quality of life, once the learning curve has been overcome. It would also enable a more reliable assessment of safety and efficacy. In addition, although patients were above the target of 70% CGM use time in clinical routine at the start of the study, their participation in the study with the frequent nurse's calls most likely increased CGM use time from 81 to 95% during the control period and to 99% during the closed-loop period. We were careful to have the same number of patient interactions during both periods, so as not to induce follow-up bias between the two arms. However, the fact that the study was not blinded may explain why CGM time was slightly higher during the closed-loop period, as patients were probably more attentive to their treatment during under hybrid closed-loop, which was new to them. We verified, in a post hoc analysis, that this difference had no impact to the results for TIR (Pearson correlation between TIR and time with active CGM on the whole sample was $r = -0.18$, $P = 0.49$).

Finally, the relatively small number of patients ($n = 17$) who completed the study, and the use of CSII + CGM as a comparator, to assess the benefit of a hybrid closed-loop in patients with type 2 diabetes, limits the generalizability of the results; indeed, CSII treatment is not generally a reimbursed treatment outside France. Our study should therefore be seen as a proof of concept that highlights which insulin delivery modality could provide the best glycemic control in patients with type 2 diabetes.

In summary, this study showed that a hybrid closed-loop therapy further improves glycemic control in people with type 2 diabetes already optimally treated with CSII + CGM. Long-term studies are now required to measure the benefits of closed-loop therapy on long-term glycemic control, quality of life, treatment satisfaction, and prevention of diabetes-related complications.

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