The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 31, 2019 VOL. 381 NO. 18

Six-Month Randomized, Multicenter Trial of Closed-Loop Control in Type 1 Diabetes

S.A. Brown, B.P. Kovatchev, D. Raghinaru, J.W. Lum, B.A. Buckingham, Y.C. Kudva, L.M. Laffel, C.J. Levy, J.E. Pinsker, R.P. Wadwa, E. Dassau, F.J. Doyle III, S.M. Anderson, M.M. Church, V. Dadlani, L. Ekhlaspour, G.P. Forlenza, E. Isganaitis, D.W. Lam, C. Kollman, and R.W. Beck, for the iDCL Trial Research Group*

ABSTRACT

BACKGROUND

Closed-loop systems that automate insulin delivery may improve glycemic outcomes in patients with type 1 diabetes.

METHODS

In this 6-month randomized, multicenter trial, patients with type 1 diabetes were assigned in a 2:1 ratio to receive treatment with a closed-loop system (closed-loop group) or a sensor-augmented pump (control group). The primary outcome was the percentage of time that the blood glucose level was within the target range of 70 to 180 mg per deciliter (3.9 to 10.0 mmol per liter), as measured by continuous glucose monitoring.

RESULTS

A total of 168 patients underwent randomization; 112 were assigned to the closed-loop group, and 56 were assigned to the control group. The age range of the patients was 14 to 71 years, and the glycated hemoglobin level ranged from 5.4 to 10.6%. All 168 patients completed the trial. The mean (±SD) percentage of time that the glucose level was within the target range increased in the closed-loop group from 61±17% at baseline to 71±12% during the 6 months and remained unchanged at 59±14% in the control group (mean adjusted difference, 11 percentage points; 95% confidence interval [CI], 9 to 14; P<0.001). The results with regard to the main secondary outcomes (percentage of time that the glucose level was >180 mg per deciliter, mean glucose level, glycated hemoglobin level, and percentage of time that the glucose level was <70 mg per deciliter or <54 mg per deciliter [3.0 mmol per liter]) all met the prespecified hierarchical criterion for significance, favoring the closed-loop system. The mean difference (closed loop minus control) in the percentage of time that the blood glucose level was lower than 70 mg per deciliter was −0.88 percentage points (95% CI, −1.19 to −0.57; P<0.001). The mean adjusted difference in glycated hemoglobin level after 6 months was −0.33 percentage points (95% CI, −0.53 to −0.13; P=0.001). In the closed-loop group, the median percentage of time that the system was in closed-loop mode was 90% over 6 months. No serious hypoglycemic events occurred in either group; one episode of diabetic ketoacidosis occurred in the closed-loop group.

CONCLUSIONS

In this 6-month trial involving patients with type 1 diabetes, the use of a closed-loop system was associated with a greater percentage of time spent in a target glycemic range than the use of a sensor-augmented insulin pump. (Funded by the National Institute of Diabetes and Digestive and Kidney Diseases; iDCL ClinicalTrials.gov number, NCT03563313.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Kovatchev at the University of Virginia Center for Diabetes Technology, 560 Ray C. Hunt Dr., 2nd Flr., Charlottesville, VA 22903, or at boris@virginia.edu.

*A list of the members of the iDCL Trial Research Group is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Brown, Kovatchev, and Beck contributed equally to this article.

This article was published on October 16, 2019, at NEJM.org.

N Engl J Med 2019;381:1707-17.
DOI: 10.1056/NEJMoa1907863

A Quick Take is available at NEJM.org

Despite advances in care, attaining good glycemic outcomes in patients with type 1 diabetes remains challenging; the targets set by the American Diabetes Association are met in only a minority of patients.[1,2] The use of a closed-loop system (also referred to as an "artificial pancreas") that automates aspects of insulin delivery offers the potential to attain the desired glycemic outcomes.[3,4] Meta-analyses have suggested that closed-loop systems are effective.[5-7]

Currently, one closed-loop system, the Medtronic MiniMed 670G, is in commercial use in the United States, but randomized trials are needed to assess its efficacy and safety.[8] Such a system, which modulates basal insulin delivery but does not administer automated boluses, is referred to as a "hybrid" closed-loop system.

We now report the results of the International Diabetes Closed Loop (iDCL) trial, a randomized trial assessing the efficacy and safety of a closed-loop system (Control-IQ, Tandem Diabetes Care) as compared with a sensor-augmented pump. This closed-loop system uses an algorithm with a dedicated hypoglycemia safety module, automated correction boluses, and overnight intensification of basal insulin delivery designed to consistently target near-normal glycemia each morning.

Methods

Trial Conduct and Oversight

We conducted a parallel-group, unblinded, randomized trial at seven university centers in the United States. The protocol, available with the full text of this article at NEJM.org, was approved by a central institutional review board, and written informed consent (or parental consent and assent from patients who were 14 to <18 years of age) was obtained as required. An investigational device exemption was approved by the Food and Drug Administration. An independent data and safety monitoring board provided trial oversight. The first, second, and last authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. Funding was provided by the National Institute of Diabetes and Digestive and Kidney Diseases. Tandem Diabetes Care provided the experimental closed-loop systems, supplies, and technical expertise with device issues. Tandem Diabetes Care reviewed the manuscript but was not otherwise involved in the trial design, conduct, data analysis, or manuscript preparation.

Trial Design and Patients

To be included in the trial, patients had to be at least 14 years old and have a clinical diagnosis of type 1 diabetes; they also had to have been treated with insulin for at least 1 year by means of a pump or multiple daily injections, without a restriction on the glycated hemoglobin level (complete eligibility criteria are described in Table S1 in the Supplementary Appendix, available at NEJM.org). The trial consisted of a 2-to-8-week run-in phase (with the duration dependent on whether the patient had used a pump or continuous glucose monitor previously) to collect baseline data and to train patients in the use of the devices, after which patients were randomly assigned in a 2:1 ratio to use a closed-loop system (closed-loop group) or a sensor-augmented pump (control group) for a 26-week period. The run-in phase could be skipped by patients who were already using a Dexcom continuous glucose monitor and an insulin pump (Fig. S1). Randomization was performed on the trial website with a computer-generated sequence and a permuted block design and was stratified according to site.

After randomization, each patient in the closed-loop group was trained in the use of the closed-loop system, which consisted of a pump (t:slim X2 insulin pump with Control-IQ Technology, Tandem Diabetes Care) and a continuous glucose monitor (Dexcom G6, Dexcom). This system is a third-generation descendant of DiAs — a mobile closed-loop system developed at the University of Virginia and subsequently implemented as inControl by TypeZero Technologies.[9,10]

Patients in the control group received a continuous glucose monitor; patients who had used a pump before participating in the trial used their personal pumps. For patients who received insulin by means of multiple daily injections, use of the pump was initiated during the run-in phase (without a low-glucose suspension feature). Patients in both treatment groups received blood glucose meters (Roche Accu-Chek Guide, Roche Diabetes Care) and ketone meters (Abbott Precision Xtra, Abbott Diabetes Care).

Patients in both groups attended follow-up visits at 2, 6, 13, and 26 weeks and were con-

tacted by telephone at 1, 4, 9, 17, and 21 weeks. Data from the devices were downloaded and reviewed at each visit and during telephone contacts. Glycated hemoglobin was measured at each trial site (either with the use of a point-of-care device or by a local laboratory) at screening, randomization, and after 13 and 26 weeks. Glycated hemoglobin also was measured at randomization and after 13 and 26 weeks at a central laboratory at the University of Minnesota Advanced Research and Diagnostic Laboratory.

Reporting of adverse events was solicited throughout the trial. Reportable adverse events included serious adverse events, adverse events occurring in association with a trial device or procedure, severe hypoglycemia (defined as hypoglycemia leading to the need for assistance because of altered consciousness), diabetic ketoacidosis as defined by the Diabetes Control and Complications Trial,[11] or hyperglycemia with ketonemia for which a health care provider was contacted.

In March 2019, use of the Control-IQ software by the closed-loop group was temporarily suspended as a precaution after a software error was found (no serious adverse events occurred); in certain instances, this error led to erroneous discontinuation of insulin delivery for up to several hours or to an erroneous bolus being given when insulin delivery restarted. Patients continued to use the system in open-loop mode until a software update was deployed to patients at home with the use of a Web-based software updater. This suspension affected 33 patients in the closed-loop group for up to 4 weeks (median, 14 days). The analyses included all data recorded during this period, even if the closed-loop mode was not in use.

OUTCOMES

The primary outcome was the percentage of time that the glucose level, as measured by the continuous glucose monitor, was in the target range of 70 to 180 mg per deciliter (3.9 to 10.0 mmol per liter). The main secondary outcomes, which were tested in a hierarchical fashion to maintain a type I error rate of 5%, were the percentage of time that the glucose level was greater than 180 mg per deciliter, the mean glucose concentration, the glycated hemoglobin level at 26 weeks, the percentage of time that the glucose level was less than 70 mg per deciliter, and the percentage of time that the glucose level was less than 54 mg per deciliter (3.0 mmol per liter). Continuous glucose-monitoring data, from randomization through the 26-week follow-up visit, were included in the calculation of each metric, regardless of whether the closed-loop system was active. Additional secondary outcomes, for which the type I error was controlled with the use of the false discovery rate, are listed in the statistical analysis plan. Safety outcomes included the frequency of severe hypoglycemia, diabetic ketoacidosis, and other serious adverse events.

STATISTICAL ANALYSIS

We calculated that a sample size of 123 patients and randomization in a 2:1 ratio (closed-loop:control) would provide 90% power with a type I error rate (two-sided) of 5% to reject the null hypothesis of no between-group difference in the percentage of time with the glucose level in the target range, under the assumption that the percentage of time in the target range in the closed-loop group would be 7.5 percentage points higher than that in the control group, with a standard deviation of 12%. The sample size was increased to 168 for an enhanced regulatory safety assessment of the closed-loop system.

Statistical analyses were performed on an intention-to-treat basis, and all patients were included in the primary analysis and all secondary analyses unless otherwise noted. For the primary analysis, the percentage of time that the glucose level was in the target range was compared between the two groups with a linear mixed-effects regression model. Analyses of the secondary outcomes that were measured with the continuous glucose monitor, glycated hemoglobin level, insulin measures, body weight, and body-mass index paralleled the primary analysis. Modification of the treatment effect according to baseline variables was assessed by including an interaction term in the models described above. The analyses of the data at 13 weeks paralleled those of the data at 26 weeks. All models and reported treatment-group differences included adjustment for the baseline level of the dependent variable, age, previous use of a continuous glucose monitor and pump, and clinical center (random effect).

Descriptive statistics include means with stan-

dard deviations and medians with interquartile ranges, depending on the distribution of data. All P values are two-tailed. Analyses were performed with SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS AND FOLLOW-UP

Between July 12, 2018, and October 9, 2018, a total of 168 patients (50% of whom were female) were randomly assigned to either the closed-loop group (112 patients) or the control group (56 patients) (Table 1). The patients' ages ranged from 14 to 71 years, the duration of diabetes from 1 to 62 years, and the baseline glycated hemoglobin level from 5.4 to 10.6%. Insulin pumps were used by 133 patients (79%), and multiple daily insulin injections were used by 35 (21%); 118 (70%) were using continuous glucose monitoring, and 102 (86%) of these were using pumps. The closed-loop and control groups appeared balanced with regard to baseline characteristics. All 168 patients completed the trial (Fig. S2).

Overall, 100% of follow-up visits and 99.9% of telephone contacts were completed. There were 68 unscheduled visits in the closed-loop group (37 to obtain supplies related to the trial, 28 related to a trial device issue, and 3 for other reasons) and 13 in the control group (Table S2).

EFFICACY OUTCOMES

In the primary analysis, the mean percentage of time with glucose levels within the target range increased from 61±17% at baseline to 71±12% during the 6 months in the closed-loop group and remained unchanged at 59±14% in the control group (mean difference [closed loop minus control], 11 percentage points; 95% confidence interval [CI], 9 to 14; P<0.001) (Table 2). This mean difference amounted to 2.6 more hours per day spent in the target range in the closed-loop group. The treatment effect was evident in the first month and was consistent over the 6 months (Fig. 1A). All five secondary outcomes included in the hierarchical analysis plan (percentage of time that the glucose level was >180 mg per deciliter, mean glucose level, glycated hemoglobin level, percentage of time that the glucose level was <70 mg per deciliter, and percentage of time that the glucose level was <54 mg per deciliter) met the prespecified criterion for significance in favor of the closed-loop system (Table 2). The mean difference in the glycated hemoglobin level at 26 weeks was −0.33 percentage points (95% CI, −0.53 to −0.13; P=0.001) (Fig. 2A); the mean difference in the percentage of time that the glucose level was greater than 180 mg per deciliter was −10 percentage points (95% CI, −13 to −8; P<0.001), a difference that amounted to 2.4 hours per day; and the mean difference in the percentage of time that the glucose level was less than 70 mg per deciliter was −0.88 percentage points (95% CI, −1.19 to −0.57; P<0.001), a difference that amounted to 13 minutes per day (Fig. 2B and Table 2). (Additional details of the results of these analyses are provided in Fig. S3.)

Similar results favoring the closed-loop system were seen for the other secondary outcomes that were based on continuous glucose-monitoring data (hyperglycemia, hypoglycemia, and glucose-level variability), as well as for secondary outcomes derived from the glycated hemoglobin level; in addition, the results at 13 weeks were similar to those at 26 weeks (Tables S3 through S5). The mean percentage of time that the glucose level was in the target range was 70% in the closed-loop group and 59% in the control group during the daytime (6 a.m. to midnight) and was 76% and 59%, respectively, during the nighttime (midnight to 6 a.m.). The greatest difference in the median percentage of time in the target range occurred at 5 a.m. (89% in the closed-loop group vs. 62% in the control group), and the greatest differences in the mean glucose level occurred at 5 a.m. and 6 a.m. (139 mg per deciliter [7.7 mmol per liter] in the closed-loop group vs. 166 mg per deciliter [9.2 mmol per liter] in the control group at both time points). This diurnal pattern, shown in Figure 1B, is a result of the increased aggressiveness of the algorithm to meet a lower glucose target during the second half of the night. For the percentage of time that the glucose level was less than 70 mg per deciliter, the daytime percentages were 1.6% in the closed-loop group and 2.2% the control group, and the nighttime percentages were 1.4% and 2.4%, respectively (Table S6).

The percentage of time that the blood glucose

Table 1. Characteristics of the Patients.*

Characteristic	Closed Loop (N=112)	Control (N=56)
Age — yr	33±16	33±17
Age group — no. (%)		
≥18 Yr	81 (72)	39 (70)
<18 Yr	31 (28)	17 (30)
Median duration of diabetes (IQR) — yr	17 (8–28)	15 (7–23)
Means of insulin administration — no. (%)		
Insulin pump	90 (80)	43 (77)†
Multiple daily injections	22 (20)	13 (23)
Use of continuous glucose monitor at enrollment — no. (%)	78 (70)	40 (71)
Median body-mass index (IQR)‡	25 (23–29)	25 (22–28)
Female sex — no. (%)	54 (48)	30 (54)
White race — no./total no. (%)§	94/109 (86)	53/56 (95)
Hispanic or Latino ethnic group — no. (%)§	13 (12)	5 (9)
Annual household income — no./total no. (%)		
<$50,000	10/89 (11)	2/50 (4)
$50,000 to <$100,000	24/89 (27)	18/50 (36)
≥$100,000	55/89 (62)	30/50 (60)
Highest education level — no./total no. (%)¶		
Less than bachelor's degree	16/111 (14)	13/56 (23)
Bachelor's degree	51/111 (46)	21/56 (38)
Advanced degree	44/111 (40)	22/56 (39)
Private medical insurance — no./total no. (%)	102/109 (94)	50/55 (91)
Glycated hemoglobin level — %		
Screening	7.6±1.1	7.6±1.0
Baseline	7.4±1.0	7.4±0.8
Glycated hemoglobin level at baseline — no. (%)		
<7.0%	38 (34)	19 (34)
7.0 to <7.5%	23 (21)	10 (18)
7.5 to <8.0%	22 (20)	12 (21)
8.0 to <9.0%	23 (21)	14 (25)
≥9.0%	6 (5)	1 (2)
Median blood glucose meter tests per day (IQR) — no.	3 (2–5)	3 (2–4)
Diabetic ketoacidosis in past 12 mo — no. (%)	4 (4)	1 (2)
Severe hypoglycemia in past 12 mo — no. (%)	6 (5)	1 (2)

* Plus–minus values are means ±SD. IQR denotes interquartile range.
† Among the 43 patients in the control group who were using a personal pump, the companies supplying the pumps were Medtronic (17 patients), Tandem (16), Insulet (6), and Animas (4).
‡ Body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Race and ethnic group were reported by the patients.
¶ Data are for the highest level of education completed by patient or, if patient was younger than 18 years of age, by the primary caregiver.

Table 2. Primary and Secondary Hierarchical Efficacy Outcomes.*

Outcome	2-Wk Baseline Period		26-Wk Trial Period†			
	Closed Loop (N=112)	Control (N=56)	Closed Loop (N=112)	Control (N=56)	Risk-Adjusted Difference, Closed Loop Minus Control (95% CI)‡	P Value‡
Median hours of sensor data (IQR)	307 (285–327)	306 (283–320)	4267 (4133–4348)	4141 (3922–4280)		
Primary outcome: percentage of time with glucose level in target range of 70 to 180 mg/dl	61±17	59±14	71±12	59±14	11 (9 to 14)	<0.001
Secondary hierarchical outcomes						
Percentage of time with glucose level >180 mg/dl	36±19	38±15	27±12	38±15	−10 (−13 to −8)	<0.001
Glucose level — mg/dl	166±32	169±25	156±19	170±25	−13 (−17 to −8)	<0.001
Glycated hemoglobin — %§	7.40±0.96	7.40±0.76	7.06±0.79	7.39±0.92	−0.33 (−0.53 to −0.13)	0.001
Percentage of time with glucose level <70 mg/dl¶	3.58±3.39	2.84±2.54	1.58±1.15	2.25±1.46	−0.88 (−1.19 to −0.57)	<0.001
Percentage of time with glucose level <54 mg/dl‖	0.90±1.36	0.56±0.79	0.29±0.29	0.35±0.32	−0.10 (−0.19 to −0.02)	0.02

* Plus–minus values are means ±SD. To convert the values for glucose to millimoles per liter, multiply by 0.05551.

† Data are means or medians over the 26 weeks of the trial period with the exception of the glycated hemoglobin level, for which data are the mean at the 26-week follow-up visit.

‡ The differences were adjusted for the baseline value of the dependent variable plus age, previous use of a continuous glucose monitor, previous use of an insulin pump, and clinical center (random effects). To control the type I error, a hierarchical approach was used in which hypothesis testing was performed sequentially in the order listed in the table. If the result for an outcome metric had not reached significance (i.e., P>0.05), statistical testing would not have been conducted for the subsequent outcomes in the hierarchy. In this trial, the results for all six outcomes were significant, and therefore testing was not stopped. Differences in outcomes that were measured as percentages are given in percentage points.

§ These results were additionally adjusted for the 13-week values and the same-visit local values. One participant in the control group and one participant in the closed-loop group completed the 26-week visit outside the prespecified window, and these 26-week values were excluded from the analyses.

¶ The percentage of time that the glucose level was below 70 mg per deciliter (3.9 mmol per liter) had a skewed distribution; however, the residuals from the regression model were approximately normally distributed. The medians at baseline were 2.69% (IQR, 1.02 to 5.42) in the closed-loop group and 2.10% (IQR, 1.04 to 4.02) in the control group, and the medians after randomization were 1.40% (IQR, 0.67 to 2.29) in the closed-loop group and 1.93% (IQR, 1.15 to 3.06) in the control group.

‖ The percentage of time that the glucose level was below 54 mg per deciliter (3.0 mmol per liter) had a skewed distribution; however, the residuals from the regression model were approximately normally distributed. The medians at baseline were 0.32% (IQR, 0.05 to 1.23) in the closed-loop group and 0.31% (IQR, 0.07 to 0.54) in the control group, and the medians after randomization were 0.21% (IQR, 0.07 to 0.42) in the closed-loop group and 0.24% (IQR, 0.11 to 0.49) in the control group.

level was within the target range of 70 to 180 mg per deciliter or below 70 mg per deciliter consistently favored the closed-loop system across a broad range of baseline characteristics, including age, sex, body-mass index, income, educational level, insulin pump or injection use, previous use of a continuous glucose monitor, and glycated hemoglobin level, and the results were consistent across the seven clinical centers (Table S7).

Patients performed a median of 0.21 (interquartile range, 0.08 to 0.48) blood glucose measurements per day in the closed-loop group and 0.37 (interquartile range, 0.14 to 0.73) in the control group. There was no significant difference between the groups in the daily insulin amount (P=0.83) or in weight change (P=0.83) (Table S8).

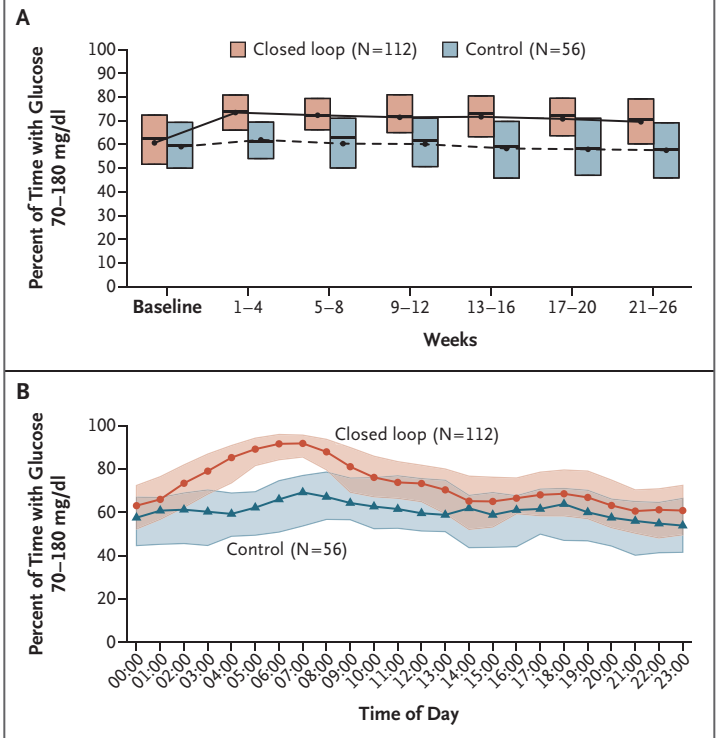

Figure 1. Percentage of Time with Glucose Level in Target Range.

Panel A shows a box plot of the percentage of time that the glucose level was within the range of 70 to 180 mg per deciliter (3.9 to 10.0 mmol per liter), as measured by continuous glucose monitoring, during 4-week periods over 6 months among patients who were assigned to receive treatment with either a closed-loop system (closed loop) or a sensor-augmented pump (control). Black dots indicate the mean values, horizontal bars in the boxes indicate the medians, and the bottom and top of each box represent the 25th and 75th percentiles, respectively. Panel B shows an envelope plot of the same outcome according to the time of day. Symbols denote the hourly median values, and the shaded regions are defined by the 25th and 75th percentiles.

SYSTEM USE

The median percentage use of continuous glucose monitoring over the 6 months of the trial was 97% (interquartile range, 96 to 98) in the closed-loop group and 96% (interquartile range, 90 to 97) in the control group. In the closed-loop group, the median percentage of time the system was in closed-loop mode was 90% (interquartile range, 86 to 94) and was consistent throughout the 6 months (92% when the 4 weeks of suspended use were excluded). There were 137 reported device problems, most commonly due to a connectivity problem during 20,286 days of system use (median number of device problems per patient, 1; interquartile range, 0 to 2). (Additional details of the system-use results are provided in Tables S9 and S10 and Figs. S4 and S5.)

ADVERSE EVENTS

A total of 17 adverse events were reported among 16 patients in the closed-loop group, and 2 adverse events were reported among 2 patients in the control group (P=0.05) (Table 3). Severe hypoglycemia did not occur in either group. Diabetic ketoacidosis occurred in 1 participant in the closed-loop group as a result of a pump infusion set failure; 13 hyperglycemia or ketosis events meeting the protocol reporting criteria but not meeting criteria for diabetic ketoacidosis occurred in 12 patients in the closed-loop group, and 2 events among 2 patients occurred in the control group; almost all these events were adjudicated by the investigators as having been caused by infusion set failures. There were 3 other serious adverse events in the closed-loop group (hospitalizations for concussion, otitis, and cardiac bypass surgery) and none in the control group. Blood ketone levels of greater than 1.0 mmol per liter were recorded in 11 patients (9.8%, on 14 days) in the closed-loop group and in 8 patients (14.3%, on 15 days) in the control group. Other safety-related events are listed in Table 3.

DISCUSSION

In our multicenter, randomized trial involving patients with type 1 diabetes, the percentage of time that glucose was in the target range of 70 to 180 mg per deciliter over the 6-month period, as measured by continuous glucose monitoring,

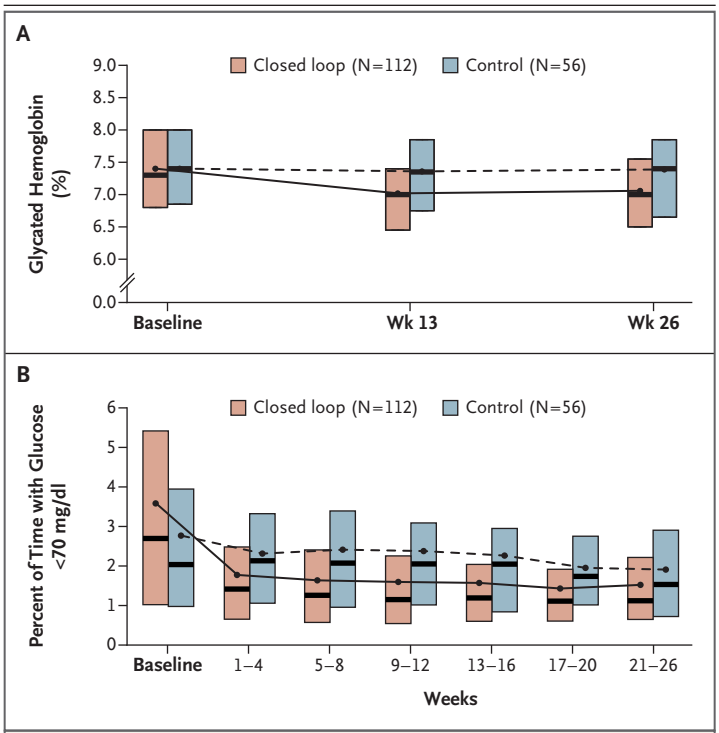

Figure 2. Glycated Hemoglobin Level and Percentage of Time with Glucose Level Less Than 70 mg per Deciliter.

Panel A shows a box plot of the glycated hemoglobin level at baseline, week 13, and week 26 among patients who were assigned to receive treatment with either a closed-loop system (closed loop) or a sensor-augmented pump (control). One patient in the control group and one patient in the closed-loop group completed the 26-week follow-up visit outside the prespecified window, and the corresponding values were excluded. Panel B shows a box plot of the percentage of time that the glucose level was less than 70 mg per deciliter, as measured by continuous glucose monitoring, during 4-week periods over 6 months in each treatment group. In both panels, black dots indicate the mean values, horizontal bars in the boxes indicate the medians, and the bottom and top of each box represent the 25th and 75th percentiles.

was 11 percentage points higher among patients with the closed-loop system than among those with a sensor-augmented pump, an advantage that amounted to 2.6 hours per day (10 percentage points [2.4 hours per day] less time in hyperglycemia and 0.88 percentage points [13 minutes per day] less time in hypoglycemia). Over the course of the trial, the glycated hemoglobin level improved among patients who used the closed-loop system and remained unchanged among those who used an insulin pump and a continuous glucose monitor alone. Beneficial glycemic effects associated with the closed-loop system were seen during both daytime and nighttime and were particularly prominent in the second half of the night. The glycemic benefits associated with closed-loop control were seen in the first month of the trial and were sustained over the entire 6 months. The trial population included both insulin-pump users and injection insulin users across a wide age range (14 to 71 years) and baseline range of glycated hemoglobin levels (5.4 to 10.6%), with consistent results across these and other baseline characteristics of the participants.

More adverse events were reported in the closed-loop group than in the control group, primarily as a result of hyperglycemia with ketosis from pump infusion set failure. We speculate that this may reflect differential requirements for adverse-event reporting between the groups, since the insulin pump used by the closed-loop group was part of an investigational device; this would be consistent with the fact that a comparison of the number of days in which patients had elevated blood ketone levels did not suggest that ketosis events occurred more often among patients receiving closed-loop treatment. No severe hypoglycemic events occurred in either group.

Few randomized trials have assessed a closed-loop system for 3 or more months. We previously reported the results of a 3-month trial of a closed-loop system using the same algorithm we used in the current trial. In that trial, the algorithm was implemented on a mobile phone, which resulted in a 4.8-percentage-point higher percentage of time that blood glucose was within the range of 70 to 180 mg per deciliter and a 1.7-percentage-point higher percentage of time that blood glucose was less than 70 mg per deciliter than with a sensor-augmented pump.[12] Other trials in which closed-loop systems that use a different algorithm have been compared with sensor-augmented pumps include a 12-week trial[13] that showed a percentage of time with the glucose level in the range of 70 to 180 mg per deciliter that was 10.8 percentage points higher with the closed-loop system, as well as a percentage of time with the glucose level lower than 70 mg per deciliter that was 0.8 percentage points lower with the closed-loop system. In another 12-week trial,[14] these measures were reported to be 9.2 percentage points higher and 2.4 percentage points lower, respectively, with the closed-loop system than with a sensor-aug-

Table 3. Adverse Events.*

Event	Closed Loop (N=112)	Control (N=56)	P Value†
Any adverse event			
No. of events	17	2	
No. of patients (%)	16 (14)	2 (4)	0.05
No. of events per 100 person-yr	30.2	7.1	
Specific events — no. of patients (%) [no. of events]			
Severe hypoglycemia	0	0	
Diabetic ketoacidosis	1 (1) [1]‡	0	
Serious adverse events related to trial device	1 (1) [1]‡	0	
Other serious adverse events	3 (3) [3]§	0	
Hyperglycemia or ketosis without diabetic ketoacidosis	12 (11) [13]	2 (4) [2]	
Glycated hemoglobin level worsening by >0.5% — no. of patients (%)¶	8 (7)	5 (9)	0.60
Median hypoglycemic events per wk (IQR)‖	0.4 (0.1–0.9)	0.5 (0.2–0.9)	0.06
Median hyperglycemic events per wk (IQR)**	1.2 (0.4–2.6)	2.7 (1.1–4.6)	<0.001
Days with at least one blood glucose measurement <54 mg/dl — no./total person-days of follow-up (%)	129/20,571 (0.63)	72/10,285 (0.70)	
Days with at least one blood glucose measurement >350 mg/dl — no./total person-days of follow-up (%)	243/20,571 (1.18)	181/10,285 (1.76)	
Days with ≥1 ketone measurement >1.0 mmol/liter — no./total person-days of follow-up (%)	14/20,571 (0.07)	15/10,285 (0.15)	

* To convert the values for glucose to millimoles per liter, multiply by 0.05551.
† P values were calculated only for the outcomes that had been prespecified in the statistical analysis plan.
‡ The event was diabetic ketoacidosis due to a pump infusion set failure.
§ The 3 serious adverse events were hospitalizations for concussion, otitis, and cardiac bypass surgery.
¶ One patient in each treatment group completed the 26-week visit outside the prespecified window, and these 26-week values were excluded from the analyses.
‖ A hypoglycemic event was defined as a period of at least 15 consecutive minutes during which the glucose level was less than 54 mg per deciliter (<3.0 mmol per liter).
** A hyperglycemic event was defined as a period of at least 15 consecutive minutes during which the glucose level was higher than 300 mg per deciliter (>16.6 mmol per liter).

mented pump, but with five severe hypoglycemic episodes occurring in the group that received closed-loop treatment.[14]

Interpretation of the present results must be viewed in the context of the characteristics of the participants and the setting of university-based diabetes centers. In our trial, 70% of the patients were using a continuous glucose monitor and 79% were using an insulin pump at the time of enrollment, percentages that are substantially higher than the reported usage in the general population of patients with type 1 diabetes.[2] These data may reflect an interest in and willingness to use a closed-loop system among patients who were already using devices as part of diabetes management. However, our results appeared to be similar in patients who were not using a pump or a continuous glucose monitor before the trial.

Strengths of the present trial include the inclusion of patients across a wide range of baseline characteristics, 100% patient retention, and a high level of adherence to the use of the assigned devices in both treatment groups. Continuous glucose monitoring was used by both groups, with minimal reliance on blood glucose measurements. The trial was conducted without remote monitoring, to reflect real-world use.

Our trial also had certain limitations. There were more unscheduled contacts in the closed-loop group, which was attributed to the use of an investigational device, and the insulin pumps

used by the control group did not have a feature to suspend insulin for predicted hypoglycemia, which is now available for some pumps and has been shown to reduce the amount of continuous glucose monitor–measured hypoglycemia.[15-17]

In conclusion, over a 6-month period, the closed-loop system used in our trial led to a greater percentage of time that the glucose level was in a target range, less hyperglycemia and hypoglycemia, and better glycated hemoglobin levels than a sensor-augmented pump.

Presented in part at the 79th Scientific Sessions of the American Diabetes Association, San Francisco, June 9, 2019.

Supported by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health (UC4 108483). The University of Virginia Strategic Investment Fund Project #88 provided institutional and regulatory support.

Dr. Brown reports receiving grant support and supplies, paid to her institution, from Tandem Diabetes Care, and supplies, provided to her institution, from Dexcom and Roche Diagnostics; Dr. Kovatchev, receiving lecture fees and equipment, provided to the University of Virginia, from Dexcom, equipment, provided to the University of Virginia, from Roche Diagnostics, grant support, paid to University of Virginia, advisory board fees, and consulting fees from Sanofi, consulting fees, and equipment, provided to the University of Virginia, from Tandem Diabetes Care, previously holding shares in TypeZero Technologies, holding patents 8,562,587 and 9,750,438 B2 on continuous glucose monitor (CGM)–based prevention of hypoglycemia via hypoglycemia risk assessment and smooth reduction of insulin delivery, licensed to Dexcom, for which royalties are received, and holding patent 9,430,022 B2 on method and apparatus for modular power management and protection of critical services in ambulatory medical devices, licensed to Dexcom, for which royalties are received; Mr. Raghinaru, receiving grant support and supplies, paid to his institution, from Tandem Diabetes Care; Mr. Lum, receiving consulting fees, paid to his institution, from Animas Corporation, Bigfoot Biomedical, Tandem Diabetes Care, and Eli Lilly and Company; Dr. Buckingham, receiving grant support and advisory board fees from Medtronic Diabetes and ConvaTec, grant support and presentation fees from Insulet, advisory board fees from Novo Nordisk and Profusa, grant support from Eli Lilly, grant support and equipment from Dexcom, and holding patent 61197230 on a hypoglycemia prediction algorithm; Dr. Kudva, receiving supplies from Dexcom, Roche Diabetes, Tandem Diabetes Care, grant support from Medtronic Diabetes, consulting fees from Novo Nordisk, and holding patent US9486172B2 on estimation of insulin sensitivity from CGM and subcutaneous insulin delivery in type 1 diabetes; Dr. Laffel, receiving consulting fees from Dexcom, Sanofi, Eli Lilly, Novo Nordisk, Roche, Boehringer Ingelheim, Johnson & Johnson, Insulet, Insulogic, ConvaTec, and Merck; Dr. Levy, receiving advisory board fees from Sanofi, and grant support, paid to her institution, from Dexcom, Abbott Diabetes, Senseonics, and Lexicon Pharmaceuticals; Dr. Pinsker, receiving grant support, consulting fees, and fees for serving on a speakers bureau from Tandem Diabetes Care, grant support from Medtronic, grant support and consulting fees from Eli Lilly, grant support and supplies, provided to his institution, from Insulet, and supplies, provided to his institution, from Dexcom; Dr. Wadwa, receiving grant support, consulting fees, and supplies, provided to his institution, from Dexcom, advisory board fees from Medtronic, and grant support, provided to his institution, from Tandem Diabetes Care and Bigfoot Biomedical, grant support, paid to his institution, advisory board fees, and supplies, provided to his institution, from Eli Lilly, and grant support, paid to his institution, and supplies, provided to his institution, from MannKind and Novo Nordisk; Dr. Dassau, receiving equipment and supplies from Tandem Diabetes Care, LifeScan, and Dexcom, consulting fees, royalties, and equipment and supplies from Insulet, fees for serving on a speakers bureau and equipment and supplies from Roche, consulting fees from Eli Lilly, grant support and drugs from Xeris, consulting fees and royalties from Mode AGC, holding patents 9,984,773 and 2,957,432 on moving-horizon state-initializer for control applications, for which royalties are received, holding patent 9,907,515 on a health monitoring system, for which royalties are received, holding patent 2,897,189 on a model-based personalization scheme of an artificial pancreas for type 1 diabetes applications, for which royalties are received, holding patents 9,700,708, 6,062,859, and 2,816,388 on maintaining multiple defined physiological zones using model predictive control, for which royalties are received, holding patents 2,897,925 and 2014800152784 on daily periodic target-zone modulation in the model predictive control problem for artificial pancreas for type 1 diabetes applications, for which royalties are received, holding patent 2,789,630 on systems, devices and methods to deliver biological factors or drugs to a subject, for which royalties are received, holding patent 2,521,483 B1 on a system to deliver insulin to a subject, for which royalties are received, holding patent 8,762,070 on systems, devices and methods to deliver biological factors or drugs to a subject, for which royalties are received, holding pending patent 14/734,994 on systems and method of variable dose glucagon delivery, holding patents 10,327,681 and 2014349078 on glucose rate increase detector: a meal detection module for the health monitoring system, for which royalties are received, holding pending patent 61/751,942 on daily periodic target-zone modulation in the model predictive control problem for artificial pancreas for type 1 diabetes applications, for which royalties are received, and holding pending patent 61/751,941 on model-based personalization scheme of an artificial pancreas for type 1 diabetes applications, for which royalties are received; Dr. Doyle, receiving equity, holding licensed intellectual property, and serving on an advisory board for Mode AGC, holding patents 9,984,773 and 2,957,432 on moving-horizon state-initializer for control applications, for which royalties are received, holding patent 9,907,515 on health monitoring system, for which royalties are received, holding patent 2,897,189 on model-based personalization scheme of an artificial pancreas for type 1 diabetes applications, for which royalties are received, holding patent 2,957,432 on moving-horizon state-initializer for control applications, for which royalties are received, holding patents 9,700,708, 6,062,859, and 2,816,388 on maintaining multiple defined physiological zones using model predictive control, for which royalties are received, holding patents 2,897,925 and 2014800152784 on daily periodic target-zone modulation in the model predictive control problem for artificial pancreas for type 1 diabetes applications, for which royalties are received, holding patent 2,789,630 on systems, devices, and methods to deliver biologic factors or drugs to a subject, for while royalties are received, holding patent 2,521,483 B1 on system to deliver insulin to a subject, for which royalties are received, holding patent 8,762,070 on systems, devices, and methods to deliver biologic factors or drugs to a subject, for which royalties are received, holding pending patent 14/734,994 on systems and method of variable dose glucagon delivery, holding patents 10,327,68 and 2014349078 on glucose rate increase detector: a meal detection module for the health monitoring system, for which royalties are received, holding pending patent 61/751,942 on daily periodic target-zone modulation in the model predictive control problem for artificial pancreas for type 1 diabetes application, for which royalties are received, and holding pending patent

61/751,941 on model-based personalization scheme of an artificial pancreas for type 1 diabetes applications, for which royalties are received; Dr. Anderson, receiving grant support from Medtronic; Dr. Forlenza, receiving grant support and lecture fees from Medtronic, MiniMed, Insulet, and Tandem, grant support from Abbott, and grant support and consulting fees from Eli Lilly; Dr. Kollman, receiving consulting fees, paid to his institution, from Bigfoot Biomedical and grant support and supplies, provided to his institution, from Tandem and Dexcom; Dr. Beck, receiving consulting fees, paid to his institution, from Insulet, Bigfoot Biomedical, and Eli Lilly, grant support and supplies, provided to his institution, from Tandem and Dexcom, and supplies from Ascensia and Roche. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

The authors' full names and academic degrees are as follows: Sue A. Brown, M.D., Boris P. Kovatchev, Ph.D., Dan Raghinaru, M.S., John W. Lum, M.S., Bruce A. Buckingham, M.D., Yogish C. Kudva, M.D., Lori M. Laffel, M.D., M.P.H., Carol J. Levy, M.D., Jordan E. Pinsker, M.D., R. Paul Wadwa, M.D., Eyal Dassau, Ph.D., Francis J. Doyle III, Ph.D., Stacey M. Anderson, M.D., Mei Mei Church, N.P., M.S., Vikash Dadlani, M.B., B.S., Laya Ekhlaspour, M.D., Gregory P. Forlenza, M.D., Elvira Isganaitis, M.D., M.P.H., David W. Lam, M.D., Craig Kollman, Ph.D., and Roy W. Beck, M.D., Ph.D.

The authors' affiliations are as follows: the University of Virginia Center for Diabetes Technology, Charlottesville (S.A.B., B.P.K., S.M.A.); the Jaeb Center for Health Research, Tampa, FL (D.R., J.W.L., C.K., R.W.B.); the Department of Pediatrics, Division of Pediatric Endocrinology and Diabetes, Stanford University School of Medicine, Stanford (B.A.B., L.E.), and the Sansum Diabetes Research Institute, Santa Barbara (J.E.P., M.C.) — both in California; the Division of Endocrinology, Diabetes, Metabolism and Nutrition, Department of Internal Medicine, Mayo Clinic, Rochester, MN (Y.C.K., V.D.); the Research Division, Joslin Diabetes Center and Department of Pediatrics, Harvard Medical School, Boston (L.M.L., E.I.), and the Harvard John A. Paulson School of Engineering and Applied Sciences, Harvard University, Cambridge (E.D., F.J.D.) — both in Massachusetts; the Division of Endocrinology, Icahn School of Medicine at Mount Sinai, New York (C.J.L., D.W.L.); and the Barbara Davis Center for Diabetes, University of Colorado, Anschutz Medical Campus, Aurora (R.P.W., G.P.F.).

REFERENCES

1. American Diabetes Association. Glycemic targets: *Standards of Medical Care in Diabetes — 2019*. Diabetes Care 2019;42:Suppl 1:S61-S70.
2. Foster NC, Beck RW, Miller KM, et al. State of type 1 diabetes management and outcomes from the T1D Exchange in 2016-2018. Diabetes Technol Ther 2019;21:66-72.
3. Kovatchev B. The artificial pancreas in 2017: the year of transition from research to clinical practice. Nat Rev Endocrinol 2018;14:74-6.
4. Kovatchev B. A century of diabetes technology: signals, models, and artificial pancreas control.Trends Endocrinol Metab 2019;30:432-44.
5. Bekiari E, Kitsios K, Thabit H, et al. Artificial pancreas treatment for outpatients with type 1 diabetes: systematic review and meta-analysis. BMJ 2018;361:k1310.
6. Karageorgiou V, Papaioannou TG, Bellos I, et al. Effectiveness of artificial pancreas in the non-adult population: a systematic review and network meta-analysis. Metabolism 2019;90:20-30.
7. Weisman A, Bai JW, Cardinez M, Kramer CK, Perkins BA. Effect of artificial pancreas systems on glycaemic control in patients with type 1 diabetes: a systematic review and meta-analysis of outpatient randomised controlled trials. Lancet Diabetes Endocrinol 2017;5:501-12.
8. Bergenstal RM, Garg S, Weinzimer SA, et al. Safety of a hybrid closed-loop insulin delivery system in patients with type 1 diabetes. JAMA 2016;316:1407-8.
9. Brown S, Raghinaru D, Emory E, Kovatchev B. First look at Control-IQ: a new-generation automated insulin delivery system. Diabetes Care 2018;41:2634-6.
10. Keith-Hynes P, Guerlain S, Mize B, et al. DiAs user interface: a patient-centric interface for mobile artificial pancreas systems. J Diabetes Sci Technol 2013;7:1416-26.
11. Nathan DM, Genuth S, Lachin J, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977-86.
12. Anderson SM. The International Diabetes Closed Loop Trial. Presented at the 18th Annual Diabetes Technology Meeting, Bethseda, MD, November 8–10, 2018.
13. Tauschmann M, Thabit H, Bally L, et al. Closed-loop insulin delivery in suboptimally controlled type 1 diabetes: a multicentre, 12-week randomised trial. Lancet 2018;392:1321-9.
14. Benhamou P-Y, Franc S, Reznik Y, et al. Closed-loop insulin delivery in adults with type 1 diabetes in real-life conditions: a 12-week multicentre, open-label randomised controlled crossover trial. Lancet Digital Health 2019;1(1):e17-e25.
15. Battelino T, Nimri R, Dovc K, Phillip M, Bratina N. Prevention of hypoglycemia with predictive low glucose insulin suspension in children with type 1 diabetes: a randomized controlled trial. Diabetes Care 2017;40:764-70.
16. Abraham MB, Nicholas JA, Smith GJ, et al. Reduction in hypoglycemia with the predictive low-glucose management system: a long-term randomized controlled trial in adolescents with type 1 diabetes. Diabetes Care 2018;41:303-10.
17. Forlenza GP, Li Z, Buckingham BA, et al. Predictive low-glucose suspend reduces hypoglycemia in adults, adolescents, and children with type 1 diabetes in an at-home randomized crossover study: results of the PROLOG Trial. Diabetes Care 2018;41:2155-61.