The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 20, 2022 VOL. 386 NO. 3

Randomized Trial of Closed-Loop Control in Very Young Children with Type 1 Diabetes

J. Ware, J.M. Allen, C.K. Boughton, M.E. Wilinska, S. Hartnell, A. Thankamony, C. de Beaufort, U. Schierloh, E. Fröhlich-Reiterer, J.K. Mader, T.M. Kapellen, B. Rami-Merhar, M. Tauschmann, K. Nagl, S.E. Hofer, F.M. Campbell, J. Yong, K.K. Hood, J. Lawton, S. Roze, J. Sibayan, L.E. Bocchino, C. Kollman, and R. Hovorka, for the KidsAP Consortium*

ABSTRACT

BACKGROUND

The possible advantage of hybrid closed-loop therapy (i.e., artificial pancreas) over sensor-augmented pump therapy in very young children with type 1 diabetes is unclear.

METHODS

In this multicenter, randomized, crossover trial, we recruited children 1 to 7 years of age with type 1 diabetes who were receiving insulin-pump therapy at seven centers across Austria, Germany, Luxembourg, and the United Kingdom. Participants received treatment in two 16-week periods, in random order, in which the closed-loop system was compared with sensor-augmented pump therapy (control). The primary end point was the between-treatment difference in the percentage of time that the sensor glucose measurement was in the target range (70 to 180 mg per deciliter) during each 16-week period. The analysis was conducted according to the intention-to-treat principle. Key secondary end points included the percentage of time spent in a hyperglycemic state (glucose level, >180 mg per deciliter), the glycated hemoglobin level, the mean sensor glucose level, and the percentage of time spent in a hypoglycemic state (glucose level, <70 mg per deciliter). Safety was assessed.

RESULTS

A total of 74 participants underwent randomization. The mean (±SD) age of the participants was 5.6±1.6 years, and the baseline glycated hemoglobin level was 7.3±0.7%. The percentage of time with the glucose level in the target range was 8.7 percentage points (95% confidence interval [CI], 7.4 to 9.9) higher during the closed-loop period than during the control period (P<0.001). The mean adjusted difference (closed-loop minus control) in the percentage of time spent in a hyperglycemic state was −8.5 percentage points (95% CI, −9.9 to −7.1), the difference in the glycated hemoglobin level was −0.4 percentage points (95% CI, −0.5 to −0.3), and the difference in the mean sensor glucose level was −12.3 mg per deciliter (95% CI, −14.8 to −9.8) (P<0.001 for all comparisons). The time spent in a hypoglycemic state was similar with the two treatments (P=0.74). The median time spent in the closed-loop mode was 95% (interquartile range, 92 to 97) over the 16-week closed-loop period. One serious adverse event of severe hypoglycemia occurred during the closed-loop period. One serious adverse event that was deemed to be unrelated to treatment occurred.

CONCLUSIONS

A hybrid closed-loop system significantly improved glycemic control in very young children with type 1 diabetes, without increasing the time spent in hypoglycemia. (Funded by the European Commission and others; ClinicalTrials.gov number, NCT03784027.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Hovorka can be contacted at rh347@cam.ac.uk or at the University of Cambridge Metabolic Research Laboratories and NIHR Cambridge Biomedical Research Centre, Wellcome Trust–MRC Institute of Metabolic Science, Box 289, Addenbrooke's Hospital, Hills Rd., Cambridge CB2 0QQ, United Kingdom.

*A list of the members of the KidsAP Consortium is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2022;386:209-19.
DOI: 10.1056/NEJMoa2111673

A Quick Take is available at NEJM.org

Management of type 1 diabetes is challenging in very young children, owing to high variability of insulin requirements,[1] marked insulin sensitivity, and unpredictable eating and activity patterns.[2] Caregiver fear of hypoglycemia, particularly overnight, is common[3] and, coupled with young children's unawareness that hypoglycemia is occurring,[4] contributes to children not meeting the recommended glycemic targets[5] or having difficulty maintaining recommended glycemic control unless caregivers can provide constant monitoring.[6] These issues often lead to a high management burden and reduced quality of life for the whole family.[6]

The use of continuous glucose-monitoring devices and insulin-pump therapy is increasing in very young children.[7] Although the use of continuous glucose monitoring has been associated with decreases in the incidence of severe hypoglycemia and episodes of diabetic ketoacidosis,[8] as well as with a reduction in the overall time spent in a hypoglycemic state,[9] it has not been shown to improve glycemic control in this age group.[9] The use of sensor-augmented pump therapy with low-glucose suspend features (in which the pump stops insulin delivery when an algorithm predicts that sensor glucose levels are likely to drop below the prespecified low-glucose threshold) is accompanied by modest improvements in glycemic control in children,[10] but the burden of management remains high.[2]

Hybrid closed-loop systems (also called an artificial pancreas), in which an algorithm automatically adjusts insulin delivery on the basis of real-time sensor glucose levels, may address ongoing challenges in this age group. Closed-loop systems have been shown to improve glycemic control and reduce the burden of management of type 1 diabetes in older children and adolescents.[11,12] However, evaluation studies involving very young children have been small and of short duration.[13,14] The efficacy and safety of longer-term use of a closed-loop system, as compared with standard therapy, is unclear. In the present trial, we hypothesized that use of the Cambridge closed-loop algorithm for 16 weeks in children 1 to 7 years of age with type 1 diabetes would improve glycemic control, as compared with sensor-augmented pump therapy, and have an acceptable safety profile.

Methods

Trial Design

In this trial, we used an open-label, multicenter, randomized, crossover design to compare the use of hybrid closed-loop insulin delivery for 16 weeks, followed by the use of sensor-augmented pump therapy for 16 weeks, or vice versa (in random order). Participants were recruited from outpatient clinics at diabetes centers in Austria (Graz, Innsbruck, and Vienna), Germany (Leipzig), Luxembourg (Luxembourg), and the United Kingdom (Cambridge and Leeds) (see the Supplementary Appendix, available with the full text of this article at NEJM.org).[15]

Approval of the trial protocol (available at NEJM.org) was received from relevant ethics committees and national regulatory bodies (see the Supplementary Appendix). Safety aspects were overseen by an independent data and safety monitoring board.

The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. Dexcom supplied continuous glucose-monitoring devices at a discount, and Dexcom representatives read the manuscript before submission, but Dexcom had no other role in the trial.

Trial Participants

Key inclusion criteria were a diagnosis of type 1 diabetes at least 6 months before enrollment, receipt of insulin-pump therapy for at least 3 months before enrollment, and a glycated hemoglobin level of no more than 11.0% (97 mmol per mole) at the screening (baseline) visit. Participants were 1 to 7 years of age. Key exclusion criteria were current use of closed-loop therapy and concomitant disease affecting metabolic control or interpretation of the glycated hemoglobin level (Table S1 in the Supplementary Appendix).

Eligible participants were identified by clinical teams at each trial center. All the parents or guardians (caregivers) of the participants provided written informed consent. When possible, written assent was obtained from participants.

Closed-Loop System

The hybrid closed-loop system comprised an unlocked smartphone (Galaxy S8, Samsung) hosting the proprietary CamAPS FX application

(CamDiab), which ran the Cambridge proprietary model predictive control algorithm (version 0.3.71). The smartphone communicated wirelessly with both the Dana Diabecare RS insulin pump (Sooil) and the Dexcom G6 transmitter (Dexcom) (Fig. S1). This algorithm automatically adjusts insulin delivery by the insulin pump on the basis of real-time sensor glucose readings and provides alarms if the glucose level is below or above user-specified thresholds.

The CamAPS FX application was used during each trial period. During the sensor-augmented pump therapy period, closed-loop functionality was disabled.

PROCEDURES

Screening and Run-In Period

Participants were screened for eligibility, including measurement of glycated hemoglobin. After enrollment, caregivers were trained in the use of the trial glucose sensor, the trial insulin pump, and the CamAPS FX application. The application was used in open-loop mode for 2 to 4 weeks during the run-in period. Investigators were free to adjust insulin therapy according to clinical judgment before randomization. Children were eligible to undergo randomization if sensor data for at least an 8-day period and safe use of the trial devices had been demonstrated.

Randomization

Eligible participants underwent randomization with the use of central randomization software. Randomization was conducted in a 1:1 ratio with a permuted block design (random block sizes of two and four), with stratification according to trial site.

Intervention Period

The trial flowchart and visit schedules are provided in Figure S2 and Tables S2 and S3. After randomization, the caregivers of the participants who had been assigned to initial use of closed-loop insulin delivery were trained in the use of the closed-loop system; the caregivers of participants who had been assigned to initial use of sensor-augmented pump therapy received refresher training. Participants received their assigned initial treatment for 16 weeks and then crossed over to the second trial treatment after a washout period of 1 to 4 weeks, during which the application was in the open-loop mode, with training as described above.

Contact and Monitoring during the Trial

After two initial contacts by telephone or email in the first week of each treatment period, caregivers were contacted monthly to allow staff to record adverse events, device deficiencies, and other relevant information. Caregivers and members of the clinical team were free to adjust insulin therapy according to usual clinical practice throughout the trial, but no active treatment optimization was undertaken by the research team. All the participants and caregivers had access to a 24-hour telephone helpline to the local research team. Glycated hemoglobin was measured locally at baseline and at the end of each trial period with the use of an International Federation of Clinical Chemistry and Laboratory Medicine–aligned method and following the guidelines of the National Glycohemoglobin Standardization Program.

END POINTS

There were three types of end points in this trial. The primary end point was the between-treatment difference in the percentage of time spent in the target glucose range (70 to 180 mg per deciliter [3.9 to 10.0 mmol per liter]) during each 16-week period. Key secondary end points included the percentage of time spent in a hyperglycemic state (defined as a glucose level of >180 mg per deciliter), the glycated hemoglobin level, the mean glucose level according to the device sensor, and the percentage of time spent in a hypoglycemic state (defined as a glucose level of <70 mg per deciliter); these end points were tested with the use of a hierarchical gatekeeping procedure to control the type I error. Additional secondary end points included the coefficient of variation and standard deviation of the glucose level; the percentages of time spent with glucose levels of less than 54 mg per deciliter (3.0 mmol per liter), of less than 63 mg per deciliter (3.5 mmol per liter), and of more than 300 mg per deciliter (16.7 mmol per liter); and insulin metrics. All the glycemic end points were based on sensor glucose data.

All the end points were calculated over the whole trial period. For a subset of end points, calculations were made separately for daytime

(8:00 a.m. to 11:59 p.m.) and nighttime (midnight to 7:59 a.m.). Device use was assessed in both trial periods. The safety evaluation comprised the frequency of severe hypoglycemia and diabetic ketoacidosis events and other adverse events.

STATISTICAL ANALYSIS

We determined that a sample of 65 participants who had undergone randomization would provide the trial with 90% power to detect a between-treatment difference in the percentage of time spent in the target glucose range, assuming a treatment effect of 5 percentage points, a standard deviation of 10.3 percentage points for individual measurements, and a correlation of 0.3 between the periods. The sample size was increased to 72 to account for withdrawals.

Analyses were performed on an intention-to-treat basis. All the participants who underwent randomization and had at least 168 hours of continuous glucose-monitoring data in at least one trial period were included in the primary analysis. The treatment interventions were compared with the use of a repeated-measures linear mixed model with adjustment for period as a fixed effect and site as a random effect and with accounting for the baseline value as a separate period. A 95% confidence interval was reported for the difference between interventions on the basis of the linear mixed model. For highly skewed data, a ranked normal score transformation was used. Missing data were not imputed for the primary analysis.

All the P values are two-sided at an alpha level of 0.05. For the primary end point and other key secondary end points, the familywise type I error rate (the probability of making at least one type I error) was controlled with the use of a gatekeeping strategy (see the Supplementary Appendix). Analyses were conducted with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PARTICIPANTS

Between May 17, 2019, and June 16, 2020, a total of 81 children were enrolled. Seven participants withdrew during the run-in period, so 74 children underwent randomization (Fig. S3). The mean (±SD) age of the participants was 5.6±1.6 years, and the baseline glycated hemoglobin level was 7.3±0.7% (56.6±7.2 mmol per mole) (Table 1). After randomization and the initiation of sensor-augmented pump therapy in the first period, one participant withdrew because of difficulties accessing trial consumables (e.g., infusion sets, batteries, and insulin reservoirs) at the local clinic; therefore, no data are available for the closed-loop period for this participant.

PRIMARY AND KEY END POINTS

The results of the primary, key secondary, and secondary end-point analyses, which included all the participants who underwent randomization, are shown in Table 2. The percentage of time in the target glucose range (70 to 180 mg per deciliter) was higher by 8.7 percentage points (95% confidence interval [CI], 7.4 to 9.9) during the 16-week closed-loop period than during the 16-week sensor-augmented pump period (P<0.001) (Fig. S4). The result was similar in a per-protocol analysis that used data from all the participants who had undergone randomization and had at least 60% of continuous glucose-monitoring data available for the sensor-augmented pump period and had used the closed-loop system for at least 60% of the time during closed-loop period (Table S4).

The mean adjusted difference (closed-loop minus control) in the percentage of time spent in a hyperglycemic state (>180 mg per deciliter) was −8.5 percentage points (95% CI, −9.9 to −7.1) (P<0.001). The mean adjusted between-treatment difference in the glycated hemoglobin level was −0.4 percentage points (−3.9 mmol per mole; 95% CI, −0.5 to −0.3 percentage points [−4.9 to −2.9 mmol per mole]), with a significantly lower glycated hemoglobin level at the end of the closed-loop period than at the end of the sensor-augmented pump period (P<0.001). The mean sensor glucose level was significantly lower during the closed-loop period than during the sensor-augmented pump period (mean adjusted difference, −12.3 mg per deciliter [−0.7 mmol per liter]; 95% CI, −14.8 to −9.8 mg per deciliter [−0.8 to −0.5 mmol per liter]; P<0.001). Figure 1 shows the 24-hour glucose profiles. The final key secondary end point that was tested in the hierarchy was the percentage of time spent in a hypoglycemic state (<70 mg per deciliter), which did not differ significantly between the interventions (P=0.74).

SECONDARY END POINTS

The percentages of time with glucose levels of less than 63 mg per deciliter and of less than 54 mg per deciliter did not differ significantly between the two interventions (Table 2). The percentage of time spent in a hyperglycemic state (>300 mg per deciliter) was 1.0 percentage point (95% CI, 0.6 to 1.6) lower during the closed-loop period than during the sensor-augmented pump period. The median glucose variability as measured by the standard deviation of the glucose level was lower during the closed-loop period (58.6 mg per deciliter [3.3 mmol per liter]) than during the sensor-augmented pump period (64.2 mg per deciliter [3.6 mmol per liter]) (difference, −6.2 mg per deciliter [−0.3 mmol per liter]; 95% CI, −7.6 to −4.8 [−0.4 to −0.3 mmol per liter]). However, there was no meaningful difference in the coefficient of variation of the glucose level between the closed-loop period and the sensor-augmented pump period.

Although the total daily insulin dose was similar in the two treatment periods, the basal insulin dose (i.e., the amount of insulin delivered by preset pump basal rates during sensor-augmented pump therapy or the amount of insulin delivered automatically by the closed-loop algorithm during closed-loop therapy) was higher, and the bolus insulin dose lower, during the closed-loop period than during the sensor-augmented pump period (Table 2). Tight glucose control was more prominent with the closed-loop system during nighttime than during daytime, with a percentage of time in the target glucose range of 82%, a mean sensor glucose level of 136.2 mg per deciliter (7.6 mmol per liter), a median standard deviation of the glucose level of 46.6mg per deciliter (2.6 mmol per liter), and a median percentage of time spent in a hypoglycemic state of 2.8%. The total amount of insulin used overnight was low, with predominantly basal insulin delivered during the closed-loop period, as compared with a roughly even split between the basal and bolus insulin doses during the sensor-augmented pump period (Tables 3 and S5).

USE OF THE CLOSED-LOOP SYSTEM

Glucose sensor use was high during both treatment periods. The median use was more than 99% (interquartile range, 99 to >99) during the closed-loop period and 96% (interquartile range, 94 to 97) during the sensor-augmented pump period. During the closed-loop period, the system was in the closed-loop mode for 95% (interquartile range, 92 to 97) of the time (Table S6).

ADVERSE EVENTS

One serious adverse event of severe hypoglycemia occurred in the closed-loop period; details of the event are provided in Table 4. There were no episodes of diabetic ketoacidosis. One serious adverse event that was considered by the investigators and the data and safety monitoring board to be unrelated to the treatment (hospital admission for gastroenteritis) occurred during the sensor-augmented pump period. A total of 75 other adverse events (27 during the closed-loop period, 27 during the sensor-augmented pump period, 18 during the run-in period, and 3 during the washout period) were reported. Safety-related events are summarized in Table 4.

UNSCHEDULED PARTICIPANT CONTACTS

There were 380 unscheduled contacts (178 during the closed-loop period, 119 during the sensor-augmented pump period, 69 during the run-in period, and 14 during the washout period) (Table S7). The reasons for such contacts were related mostly to device issues (63 during the closed-loop period and 47 during the sensor-augmented pump period), which encompassed any sensor-, pump-, or application-related issues; and to diabetes-management queries (76 during the closed-loop period and 52 during the sensor-augmented pump period) (Table S8).

DISCUSSION

In the present trial, we found that the Cambridge hybrid closed-loop algorithm significantly improved glycemic control over a period of 16 weeks, as compared with sensor-augmented pump therapy, in very young children with type 1 diabetes. The closed-loop system appeared to have an acceptable safety profile. The reduction in the glycated hemoglobin level of 0.4 percentage points (3.9 mmol per mole) is important in a population of patients who had tight glycemic control at baseline. This result was observed without an increase in the time spent in a hypoglycemic state.

Our result of 71.6±5.9% of the time being spent in the target glucose range (70 to 180 mg

Table 1. Characteristics of the Participants at Baseline, According to Group.*

Characteristic	Total (N=74)	Closed-Loop Period–First Group (N=39)	Sensor-Augmented Pump Period–First Group (N=35)
Age			
Mean — yr	5.6±1.6	5.6±1.4	5.6±1.7
Range — yr	2.3–7.9	2.5–7.9	2.3–7.9
Distribution — no. (%)			
2 to <5 yr	27 (36)	14 (36)	13 (37)
5 to <7 yr	29 (39)	17 (44)	12 (34)
7 yr	18 (24)	8 (21)	10 (29)
Sex — no. (%)			
Female	31 (42)	21 (54)	10 (29)
Male	43 (58)	18 (46)	25 (71)
Race — no. (%)†			
White	66 (89)	34 (87)	32 (91)
Black	2 (3)	2 (5)	0
Asian	2 (3)	1 (3)	1 (3)
Multiple	4 (5)	2 (5)	2 (6)
Duration of diabetes — yr			
Mean	2.6±1.8	2.5±1.7	2.7±1.9
Range	0–6	0–6	0–6
Glycated hemoglobin level at screening			
Percent	7.3±0.7	7.3±0.7	7.4±0.6
Millimoles per mole	56.6±7.2	56.3±7.4	57.0±7.1
Median total daily insulin dose (IQR) — U/kg/day	0.76 (0.67–0.85)	0.76 (0.67–0.83)	0.77 (0.69–0.86)
Age- and sex-adjusted BMI percentile	69.1±23.8	67.3±23.2	71.1±24.6
Continuous glucose monitor use — no. (%)			
Current	67 (91)	35 (90)	32 (91)
In past but not current	1 (1)	0	1 (3)
Never	6 (8)	4 (10)	2 (6)
Continuous glucose-monitoring metrics at baseline			
Percent of time in glucose range of 70–180 mg/dl	61.2±10.1	61.5±9.5	60.8±10.9
Mean sensor glucose level — mg/dl	161.8±21.4	161.7±20.7	161.9±22.3
Median glucose SD (IQR) — mg/dl‡	66.1 (57.9–74.2)	66.8 (59.6–73.7)	66.0 (56.6–77.5)
Median coefficient of variation in sensor glucose measurement (IQR) — %‡	41.6 (36.7–44.5)	42.4 (36.9–45.0)	41.1 (36.6–43.9)
Median percent of time with sensor glucose at specified level (IQR) — %			
>180 mg per deciliter	34.4 (24.0–42.2)	32.2 (24.0–42.7)	36.7 (21.6–41.8)
>300 mg per deciliter	3.7 (1.8–7.9)	3.4 (2.0–7.9)	3.8 (1.2–8.5)
<70 mg per deciliter	4.4 (2.3–7.0)	4.5 (2.4–6.7)	3.9 (2.0–7.4)
<54 mg per deciliter	0.7 (0.3–1.6)	0.8 (0.2–1.8)	0.6 (0.3–1.4)

Table 1. (Continued.)

* Plus–minus values are means ±SD. The characteristics of the participants at baseline are shown here according to the trial group to which the participants were assigned for the first 16-week trial period (closed-loop therapy first or sensor-augmented pump therapy first). Percentages may not total 100 because of rounding. To convert values for glucose to millimoles per liter, multiply by 0.05551. The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. IQR denotes interquartile range.
† Race was reported by the participant's caregiver.
‡ The glucose SD and coefficient of variation values indicate within-participant variability of sensor glucose measurements.

per deciliter) in the closed-loop group is similar to findings in other studies involving very young children[13,14] and was sustained over a 16-week period of at-home use. The difference of 8.7 percentage points in the percentage of time spent in the target glucose range translates to a clinically meaningful 125 minutes per day. A previous study that compared diluted insulin with standard insulin in the Cambridge hybrid closed-loop system for a 3-week period in the same pediatric age group showed that the percentages of time spent in the target range were 72±8% with diluted insulin and 70±7% with standard-strength insulin,[13] with similar glycated hemoglobin levels at baseline.

We observed a higher incidence of hypoglycemia in this trial than was observed in a trial involving older children.[11] This finding may reflect the stringent treatment targets in European centers, as evidenced by the lower mean glycated hemoglobin levels observed in the Diabetes Patienten Verlaufdokumentation registry for this age group,[5] as well as the higher incidence of hypoglycemia at baseline and during the sensor-augmented pump therapy period in our trial.

The present trial was of sufficient duration to report glycated hemoglobin outcomes in very young participants who used the hybrid closed-loop therapy, and the results were similar to those that have been reported in studies of commercially available closed-loop systems in older children and adolescents.[11,12,16] Given the low glycated hemoglobin levels at baseline, the improved levels in our trial are noteworthy, because higher baseline glycated hemoglobin levels are associated with a greater reduction in the level when hybrid closed-loop therapy is used.[17] The time that the system was in the closed-loop mode in this trial was consistently high (median, 95% of the time), a finding that supports longer-term usability in this age group. This observation compares well with the use of the closed-loop system over a 26-week period in older children (median, 93% of the time).[11] Consistently high time with the system in the closed-loop mode has been associated with lower glycated hemoglobin levels in older children.[17]

Children who receive a diagnosis of type 1 diabetes at a young age may be at greatest risk for neurocognitive deficits.[18] A longitudinal study that compared brain growth and cognitive function in young children with type 1 diabetes with those in age-matched controls over a period of 6 years showed that children with type 1 diabetes had lower IQ scores and slower brain growth than the controls.[19] These changes were negatively correlated with measures of hyperglycemia.[19] Our findings showed reductions in the amount of time in a hyperglycemic state with hybrid closed-loop insulin delivery, without an increase in the time spent in a hypoglycemic state, which leads us to speculate that closed-loop therapy may be particularly beneficial for young children during this vulnerable stage of brain development.

Poor sleep quality is a major challenge for families of young children with type 1 diabetes, because variability in insulin requirements and parental fear of hypoglycemia are highest overnight.[1,4] In the present trial, we observed that more than 80% of the overnight sensor readings were within the target range, with less than 3% of the time spent in a hypoglycemic state (<70 mg per deciliter). Accordingly, we hypothesize that hybrid closed-loop therapy may address the nighttime problem more effectively than sensor-augmented pump therapy, which would confer associated quality-of-life benefits.[20]

The strengths of our trial include its international, randomized, crossover design, as well as

Table 2. Glycemic Outcomes during Hybrid Closed-Loop Insulin Delivery and Sensor-Augmented Pump Therapy over a 16-Week Period.*

End Point	Closed-Loop Period (N=73)	Sensor-Augmented Pump Period (N=74)	Mean Adjusted Difference (95% CI)	P Value
Primary end point				
Percent of time spent at glucose level 70–180 mg/dl	71.6±5.9	62.9±9.0	8.7 (7.4 to 9.9)	<0.001
Key end points				
Median percent of time spent at glucose level >180 mg/dl (IQR)	22.9 (19.3 to 27.3)	31.7 (23.4 to 40.1)	−8.5 (−9.9 to −7.1)	<0.001
Glycated hemoglobin				
Percent	6.6±0.6	7.0±0.7	−0.4 (−0.5 to −0.3)	<0.001
Millimoles per mole	49.0±5.9	52.8±7.2	−3.9 (−4.9 to −2.9)	
Sensor glucose level — mg/dl	145.8±11.8	158.1±18.5	−12.3 (−14.8 to −9.8)	<0.001
Median percent of time spent at glucose level <70 mg/dl (IQR)†	4.9 (3.3 to 6.7)	4.5 (2.9 to 7.3)	0.1 (−0.4 to 0.5)	0.74
Secondary end points				
Median percent of time spent at glucose level (IQR)†				
>300 mg/dl	2.0 (1.2 to 3.1)	3.1 (1.3 to 5.7)	−1.0 (−1.6 to −0.6)	—
<63 mg/dl	2.6 (1.8 to 3.7)	2.4 (1.4 to 4.2)	0.04 (−0.3 to 0.3)	—
<54 mg/dl	1.0 (0.6 to 1.4)	0.9 (0.4 to 1.6)	0.02 (−0.1 to 0.1)	—
Median glucose AUC (IQR)†				
<63 mg/dl	0.1 (0.0 to 0.1)	0.1 (0.0 to 0.1)	0.002 (−0.006 to 0.009)	—
<54 mg/dl	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.001 (−0.001 to 0.003)	—
Median glucose SD (IQR) — mg/dl†	58.6 (53.7 to 64.4)	64.2 (58.1 to 71.9)	−6.2 (−7.6 to −4.8)	—
Median coefficient of variation of glucose (IQR) — %†	41 (39 to 43)	41 (38 to 44)	−0.7 (−1.5 to 0.05)	—
Insulin metrics†				
Median total daily insulin use (IQR) — U/day	16.9 (13.2 to 21.5)	17.6 (13.6 to 20.3)	0.3 (−0.1 to 0.8)	—
Median total daily basal insulin use (IQR) — U/day	8.0 (5.8 to 10.9)	5.7 (4.0 to 6.9)	2.5 (2.1 to 2.9)	—
Median total daily bolus insulin use (IQR) — U/day	8.6 (6.9 to 10.6)	11.0 (9.1 to 13.5)	−2.3 (−2.7 to −1.9)	—

* Plus–minus values are means ±SD. End points were calculated with the use of data from all participants who underwent randomization and had at least 168 hours of continuous glucose-monitoring data in at least one trial period. Data in the closed-loop period exclude one participant who had been randomly assigned to initial use of sensor-augmented pump therapy and who withdrew before crossing over to closed-loop insulin delivery. The mean adjusted differences are based on a linear mixed model with adjustment for repeated participant measures, with period as a fixed effect and trial site as a random effect; the model also accounted for the baseline values. Differences in percents are shown in percentage points. Outcomes not following a normal distribution were summarized with medians instead of means. Treatment differences from the regression model therefore do not reflect the difference of the medians since the median of the differences is not the same as the difference of the medians. The primary and key secondary end points were tested in the hierarchy as listed to control the type 1 error with the use of the fixed-sequence method. Confidence intervals for the secondary end points were adjusted for multiple comparisons with the use of the Benjamini–Hochberg procedure to control the false discovery rate. Details are provided in the Statistical Analysis section in the Supplementary Appendix. AUC denotes area under the curve.

† This end point is provided as a ranked normal score transformation owing to a skewed distribution.

a longer trial duration than previous trials of closed-loop systems in this age group,[13,14] with no restriction on the enrollment of participants on the basis of previous severe hypoglycemia or diabetic ketoacidosis. There was near-100% retention of the participants who had undergone

Table 3. Daytime and Nighttime Glucose Control during 16-Week Periods of Hybrid Closed-Loop Insulin Delivery and Sensor-Augmented Pump Therapy.*

Variable	Daytime		Nighttime	
	Closed-Loop Period (N=73)	Sensor-Augmented Pump Period (N=74)	Closed-Loop Period (N=73)	Sensor-Augmented Pump Period (N=74)
Percent of time spent at glucose level				
70–180 mg/dl — mean	66.2±7.1	61.1±9.2	82.2±5.8	66.3±10.7
<70 mg/dl — median (IQR)†	5.7 (4.0–7.8)	4.3 (2.9–6.9)	2.8 (1.7–3.7)	4.6 (2.7–7.3)
Sensor glucose level — mg/dl	150.6±14.6	161.3±20.0	136.2±9.5	151.8±18.3
Median glucose SD (IQR) — mg/dl†	63.6 (57.7–68.1)	66.4 (60.1–74.6)	46.6 (41.8–53.7)	59.4 (52.6–66.9)

* Plus–minus values are means ±SD. Daytime was defined as 8:00 a.m. to 11:59 p.m., and nighttime as midnight to 7:59 a.m. End points were calculated with the use of data from all participants who underwent randomization and had at least 168 hours of continuous glucose-monitoring data in at least one trial period. Data in the closed-loop period exclude one participant who had been randomly assigned to initial use of sensor-augmented pump therapy and who withdrew before crossing over to closed-loop insulin delivery.
† This end point is provided as a ranked normal score transformation owing to a skewed distribution.

randomization and consistently high use of the closed-loop system, findings that suggest high acceptability of the hybrid closed-loop therapy in this vulnerable population.

Our trial had certain limitations. Although the eligibility criteria were broad, the trial population may not have been representative of the general population (Table S9). Insulin-pump use was a prerequisite for trial participation, because it represents the standard of care in this age group in the countries of enrollment.[7] However, access to insulin-pump therapy is not ubiquitous worldwide. Sensor use at enrollment was higher than average.[7,21,22] In addition, children from ethnic minorities were underrepresented.[21,22] A glycated hemoglobin level of less than 11.0% (97 mmol per mole) was required for trial participation, which potentially limited access to enrollment. The observed low baseline glycated hemoglobin level was consonant with reported epidemiologic data in this age group in Europe,[21,23] although the mean glycated hemoglobin level is higher in other regions of the world.[23] Investigators were free to adjust insulin therapy according to clinical judgment before randomization, which may have affected baseline characteristics.

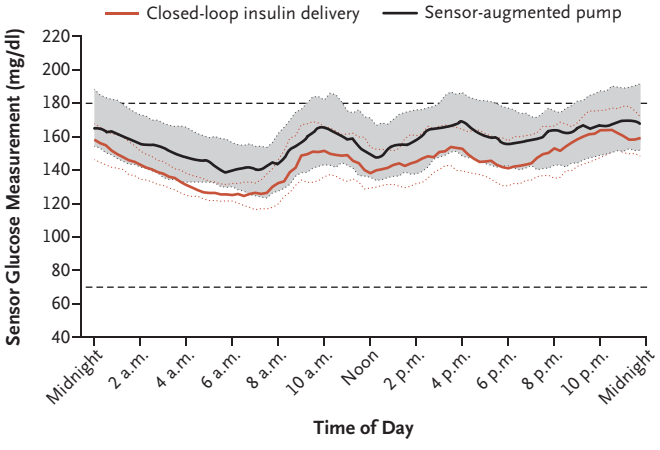

Figure 1. Sensor Glucose Levels.
Shown are the median sensor glucose levels during closed-loop insulin delivery (red line; data from 73 participants) and sensor-augmented pump therapy (black line; data from 74 participants). The red dotted lines (closed-loop insulin delivery) and the gray shaded area (sensor-augmented pump therapy) indicate interquartile ranges. Dashed horizontal lines indicate the target glucose range of 70 to 180 mg per deciliter (3.9 to 10.0 mmol per liter). To convert values for glucose to millimoles per liter, multiply by 0.05551.

Research participants in closed-loop studies tend to be highly motivated, which may also limit generalizability. The consistently high use of the closed-loop system (>90%) in a population that was not previously familiar with closed-loop therapy signifies high treatment adherence, but further research is warranted to confirm our findings. Finally, the crossover design may limit the generalizability of our findings, because growth and development are rapid in very young children and may have affected trial results. Additional exclusion criteria that were unrelated to

Table 4. Summary of Postrandomization Adverse Events during 16-Week Periods of Closed-Loop Insulin Delivery and Sensor-Augmented Pump Therapy.*

Event	Closed-Loop Period (N=73)	Sensor-Augmented Pump Period (N=74)
Any reportable adverse event — no. of participants (%)†		
No events	53 (73)	56 (76)
1 event	15 (21)	12 (16)
≥2 events	5 (7)	6 (8)
No. of events per participant	0.4±0.7	0.4±0.8
Prespecified events of interest		
Severe hypoglycemia‡		
No. of events	1	0
Incidence rate per 100 person-yr	4.1	0.0
Diabetic ketoacidosis — no. of events	0	0
Other serious adverse event — no. of events§	0	1

* Plus–minus values are means ±SD. Data in the closed-loop period exclude one participant who had been randomly assigned to initial use of sensor-augmented pump therapy who withdrew before crossing over to closed-loop insulin delivery.
† A total of 75 adverse events were recorded during the trial.
‡ The severe hypoglycemia event occurred in a participant who had 15% of the time with a glucose level below 70 mg per deciliter (3.9 mmol per liter); the parents had chosen to set the nocturnal personal glucose target to 80 mg per deciliter (4.4 mmol per liter) without consulting with their clinical team before implementation. Before the severe hypoglycemia event, an audio alarm for hypoglycemia was issued overnight every 5 minutes for 3 hours. Alarms were acknowledged by the parents, but no treatment for hypoglycemia was administered, and the participant had a hypoglycemic seizure. The closed-loop system functioned as intended; the event occurred as a result of the very low nocturnal glucose target and parents not responding to hypoglycemia alarms over the 3-hour period before the event.
§ One participant was admitted to the hospital owing to gastroenteritis.

diabetes applied to participants at sites in Germany, which potentially affected the reported treatment effect. We recorded a higher number of unscheduled contacts than has been observed in closed-loop studies[11,12] in other age groups, but these were reasonably balanced across the treatment periods and are reflective of a population that requires higher input from health care professionals than older children or adults. Furthermore, other studies have had more frequent prespecified trial contacts, such as a similar trial involving children 6 to 13 years of age in which planned contacts occurred every 2 weeks,[11] rather than monthly, as was done in our trial.

In this trial, hybrid closed-loop insulin delivery with the use of a proprietary Cambridge algorithm led to significant improvements in glycemic control, as compared with sensor-augmented pump therapy, in very young children with type 1 diabetes over a period of 16 weeks.

The views expressed in this article are those of the authors and not necessarily those of the funders.

Supported by the European Commission within the Horizon 2020 Framework Program (grant agreement number, 731560). The NIHR Cambridge Biomedical Research Centre (grant number, BRC-1215-20014) and JDRF (grant numbers, 22-2013-266 and 2-RSC-2019-828-M-N) provided additional support for work with the hybrid closed-loop therapy system (artificial pancreas) and all resulting analyses.

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.

We thank the trial participants and the staff at the Addenbrooke's Wellcome Trust Clinical Research Facility for their assistance.

APPENDIX

The authors' full names and academic degrees are as follows: Julia Ware, M.D., Janet M. Allen, R.N., Charlotte K. Boughton, Ph.D., Malgorzata E. Wilinska, Ph.D., Sara Hartnell, B.Sc., Ajay Thankamony, M.Phil., Carine de Beaufort, Ph.D., Ulrike Schierloh, M.D., Elke Fröhlich-Reiterer, M.D., Julia K. Mader, M.D., Thomas M. Kapellen, Ph.D., Birgit Rami-Merhar, M.D., Martin Tauschmann, Ph.D., Katrin Nagl, M.D., Sabine E. Hofer, M.D., Fiona M. Campbell, M.D., James Yong, M.D., Korey K. Hood, Ph.D., Julia Lawton, Ph.D., Stephane Roze, M.Sc., Judy Sibayan, M.P.H., Laura E. Bocchino, M.P.H., Craig Kollman, Ph.D., and Roman Hovorka, Ph.D.

The authors' affiliations are as follows: the Wellcome Trust–Medical Research Council (MRC) Institute of Metabolic Science (J.W., J.M.A., C.K.B., M.E.W., R.H.) and the Department of Paediatrics (J.W., M.E.W., A.T., R.H.), University of Cambridge, and the Wolfson Diabetes and Endocrine Clinic, Cambridge University Hospitals NHS Foundation Trust (S.H.), Cambridge, the Department of Paediatric Diabetes, Leeds Children's Hospital, Leeds (F.M.C., J.Y.), and Usher Institute, University of Edinburgh, Edinburgh (J.L.) — all in the United Kingdom; Diabetes and Endocrine Care Clinique Pédiatrique, Clinique Pédiatrique, Centre Hospitalier de Luxembourg, Luxembourg (C.B., U.S.); the Department of Pediatric Endocrinology, Universitair Ziekenhuis Brussel–Vrije Universiteit Brussel, Brussels (C.B.); the Department of Pediatric and Adolescent Medicine (E.F.-R.), and the Division of Endocrinology and Diabetology, Department of Internal Medicine (J.K.M.), Medical University of Graz, Graz, the Department of Pediatrics and Adolescent Medicine, Medical University of Vienna, Vienna (B.R.-M., M.T., K.N.), and the Department of Pediatrics I, Medical University of Innsbruck, Innsbruck (S.E.H.) — all in Austria; the Hospital for Children and Adolescents, University of Leipzig, Leipzig, and the Hospital for Children and Adolescents "am Nicolausholz," Bad Kösen — both in Germany (T.M.K.); the Division of Pediatric Endocrinology, Stanford University, Stanford, CA (K.K.H.); Vyoo Agency, Lyon, France (S.R.); and the Jaeb Center for Health Research, Tampa, FL (J.S., L.E.B., C.K.).

REFERENCES

1. Dovc K, Boughton C, Tauschmann M, et al. Young children have higher variability of insulin requirements: observations during hybrid closed-loop insulin delivery. Diabetes Care 2019;42:1344-7.
2. Sherr JL. Closing the loop on managing youth with type 1 diabetes: children are not just small adults. Diabetes Care 2018;41:1572-8.
3. Van Name MA, Hilliard ME, Boyle CT, et al. Nighttime is the worst time: parental fear of hypoglycemia in young children with type 1 diabetes. Pediatr Diabetes 2018;19:114-20.
4. Sundberg F, Forsander G. Detection and treatment efficacy of hypoglycemic events in the everyday life of children younger than 7 yr. Pediatr Diabetes 2014; 15:34-40.
5. Anderzén J, Hermann JM, Samuelsson U, et al. International benchmarking in type 1 diabetes: large difference in childhood HbA1c between eight high-income countries but similar rise during adolescence — a quality registry study. Pediatr Diabetes 2020;21:621-7.
6. Kimbell B, Lawton J, Boughton C, Hovorka R, Rankin D. Parents' experiences of caring for a young child with type 1 diabetes: a systematic review and synthesis of qualitative evidence. BMC Pediatr 2021;21:160.
7. van den Boom L, Karges B, Auzanneau M, et al. Temporal trends and contemporary use of insulin pump therapy and glucose monitoring among children, adolescents, and adults with type 1 diabetes between 1995 and 2017. Diabetes Care 2019;42:2050-6.
8. Tauschmann M, Hermann JM, Freiberg C, et al. Reduction in diabetic ketoacidosis and severe hypoglycemia in pediatric type 1 diabetes during the first year of continuous glucose monitoring: a multicenter analysis of 3,553 subjects from the DPV Registry. Diabetes Care 2020;43(3): e40-e42.
9. Strategies to Enhance New CGM Use in Early Childhood (SENCE) Study Group. A randomized clinical trial assessing continuous glucose monitoring (CGM) use with standardized education with or without a family behavioral intervention compared with fingerstick blood glucose monitoring in very young children with type 1 diabetes. Diabetes Care 2021;44:464-72.
10. 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.
11. Breton MD, Kanapka LG, Beck RW, et al. A randomized trial of closed-loop control in children with type 1 diabetes. N Engl J Med 2020;383:836-45.
12. Bergenstal RM, Nimri R, Beck RW, et al. A comparison of two hybrid closed-loop systems in adolescents and young adults with type 1 diabetes (FLAIR): a multicentre, randomised, crossover trial. Lancet 2021;397:208-19.
13. Tauschmann M, Allen JM, Nagl K, et al. Home use of day-and-night hybrid closed-loop insulin delivery in very young children: a multi-center, 3-week, randomized trial. Diabetes Care 2019;42:594-600.
14. Ekhlaspour L, Schoelwer MJ, Forlenza GP, et al. Safety and performance of the Tandem t:slim X2 with Control-IQ automated insulin delivery system in toddlers and preschoolers. Diabetes Technol Ther 2021;23:384-91.
15. Fuchs J, Allen JM, Boughton CK, et al. Assessing the efficacy, safety and utility of closed-loop insulin delivery compared with sensor-augmented pump therapy in very young children with type 1 diabetes (KidsAP02 study): an open-label, multicentre, multinational, randomised crossover study protocol. BMJ Open 2021;11(2): e042790.
16. 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.
17. Berget C, Messer LH, Vigers T, et al. Six months of hybrid closed loop in the real-world: an evaluation of children and young adults using the 670G system. Pediatr Diabetes 2020;21:310-8.
18. Northam EA, Rankins D, Lin A, et al. Central nervous system function in youth with type 1 diabetes 12 years after disease onset. Diabetes Care 2009;32:445-50.
19. Mauras N, Buckingham B, White NH, et al. Impact of type 1 diabetes in the developing brain in children: a longitudinal study. Diabetes Care 2021;44:983-92.
20. Musolino G, Dovc K, Boughton CK, et al. Reduced burden of diabetes and improved quality of life: experiences from unrestricted day-and-night hybrid closed-loop use in very young children with type 1 diabetes. Pediatr Diabetes 2019;20: 794-9.
21. National Paediatric Diabetes Audit. Annual report 2019-20: care processes and outcomes. London: Royal College of Paediatrics and Child Health, 2021.
22. 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.
23. Hermann JM, Miller KM, Hofer SE, et al. The Transatlantic HbA_{1c} gap: differences in glycaemic control across the lifespan between people included in the US T1D Exchange Registry and those included in the German/Austrian DPV Registry. Diabet Med 2020;37:848-55.