## Title

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# Trial of Hybrid Closed-Loop Control in Young Children with Type 1 Diabetes

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## Abstract

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*A full list of the Pediatric Artificial Pancreas (PEDAP) Trial Study Group members is provided in the Supplementary Appendix, available at NEJM.org.

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

**BACKGROUND—**Closed-loop control systems of insulin delivery may improve glycemic outcomes in young children with type 1 diabetes. The efficacy and safety of initiating a closed-loop system virtually are unclear.

**METHODS—**In this 13-week, multicenter trial, we randomly assigned, in a 2:1 ratio, children who were at least 2 years of age but younger than 6 years of age who had type 1 diabetes to receive treatment with a closed-loop system of insulin delivery or standard care that included either an insulin pump or multiple daily injections of insulin plus a continuous glucose monitor. The primary outcome was the percentage of time that the glucose level was in the target range of 70 to 180 mg per deciliter, as measured by continuous glucose monitoring. Secondary outcomes included the percentage of time that the glucose level was above 250 mg per deciliter or below 70 mg per deciliter, the mean glucose level, the glycated hemoglobin level, and safety outcomes.

**RESULTS—**A total of 102 children underwent randomization (68 to the closed-loop group and 34 to the standard-care group); the glycated hemoglobin levels at baseline ranged from 5.2 to 11.5%. Initiation of the closed-loop system was virtual in 55 patients (81%). The mean (±SD) percentage of time that the glucose level was within the target range increased from 56.7±18.0% at baseline to 69.3±11.1% during the 13-week follow-up period in the closed-loop group and from 54.9±14.7% to 55.9±12.6% in the standard-care group (mean adjusted difference, 12.4 percentage points [equivalent to approximately 3 hours per day]; 95% confidence interval, 9.5 to 15.3; P<0.001). We observed similar treatment effects (favoring the closed-loop system) on the percentage of time that the glucose level was above 250 mg per deciliter, on the mean glucose level, and on the glycated hemoglobin level, with no significant between-group difference in the percentage of time that the glucose level was below 70 mg per deciliter. There were two cases of severe hypoglycemia in the closed-loop group and one case in the standard-care group. One case of diabetic ketoacidosis occurred in the closed-loop group.

**CONCLUSIONS—**In this trial involving young children with type 1 diabetes, the glucose level was in the target range for a greater percentage of time with a closed-loop system than with standard care. (Funded by the National Institute of Diabetes and Digestive and Kidney Diseases; PEDAP ClinicalTrials.gov number, NCT04796779.)

THE TREATMENT OF TYPE 1 DIABETES IN children younger than 6 years of age is challenging because younger children receive small doses of insulin and have unpredictable food intake and unscheduled exercise activity. They also have less ability to articulate the need for treatment of hypoglycemia and more glycemic variability than older children. Consequently, most children in this age group do not meet glycemic targets.[1] Hybrid closed-loop therapy (also referred to as an artificial pancreas or automated insulin delivery) has been shown to improve glycemic control in youths and adults with type 1 diabetes. However, in the United States, only two hybrid closed-loop systems are approved for use in children with type 1 diabetes who are younger than 6 years of age.[2]

The t:slim X2 insulin pump with Control-IQ Technology system (Tandem Diabetes Care) is a hybrid closed-loop system that enables frequent (every 5 minutes) automated basal adjustments and bolus corrections delivered from an insulin pump. These adjustments are based on a software algorithm that uses data from a continuous glucose monitor. This system was approved in the United States for use in adults and youths 6 years of age or older on the

basis of results of randomized trials involving children 6 to 13 years of age and adolescents and adults 14 years of age or older.[3,4] However, little is known about the use of this system in children younger than 6 years of age. In a study involving 12 patients who were 2 to 5 years of age, the patients received treatment for 48 hours in a supervised outpatient setting, followed by treatment for 3 days at home. The study showed that the use of this system was feasible in this age group and was associated with improved glucose metrics.[5]

During the coronavirus disease 2019 (Covid-19) pandemic, access to in-person clinical care from pediatric endocrinologists and access to advanced diabetes technology has been challenging. Virtual visits have improved access to clinical care in the United States over the past 2 years.[6] Whether a hybrid closed-loop system of insulin delivery can be safely and effectively initiated remotely has been unclear in this age group. In this trial to assess the safety and efficacy of the closed-loop system described above in children who were 2 to younger than 6 years of age, we included the option of virtual training in the use of the device and virtual trial visits.

## METHODS

### TRIAL CONDUCT AND OVERSIGHT

The multicenter, unblinded, parallel-group, randomized, controlled Pediatric Artificial Pancreas (PEDAP) trial was conducted in pediatric diabetes centers at three universities 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. Electronic informed consent was obtained from a legally authorized representative (typically a parent) of each patient. An investigational device exemption was approved by the Food and Drug Administration. An independent data and safety monitoring board provided trial oversight.

Funding for the trial was provided by the National Institute of Diabetes and Digestive and Kidney Diseases. Tandem Diabetes Care provided the investigational closed-loop insulin pumps and infusion supplies, and Dexcom provided the continuous glucose monitoring system–related supplies. Tandem Diabetes Care assisted in training the legally authorized representatives of the patients in the use of the device and provided technical expertise with respect to device issues. Representatives of Tandem Diabetes Care and Dexcom reviewed the manuscript before submission for publication, but the companies were not otherwise involved in the design or conduct of the trial or in the analysis of the data. No agreements concerning confidentiality of the data were in place with respect to publication rights between the companies and the authors or their institutions.

The trial coordinating center, the Jaeb Center for Health Research, was responsible for the randomization scheme, database, data validation, analyses, monitoring, and trial management. The steering committee was responsible for the design of the trial and the decision to submit the manuscript for publication. The first, penultimate, and last authors wrote the first draft of the manuscript and vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. The statistical analysis plan is included with the protocol.

## TRIAL DESIGN AND PATIENTS

Patients were eligible for inclusion in the trial if they were at least 2 years of age but younger than 6 years of age and had received a diagnosis of type 1 diabetes at least 6 months before enrollment, had received treatment with insulin for at least 6 months, had a body weight of at least 9.1 kg (20 lb), and received a total daily insulin dose of at least 5 units. Patients who were currently using a hybrid closed-loop system were excluded (complete eligibility criteria are provided in Table S1 in the Supplementary Appendix, available at NEJM.org). All trial visits, including enrollment and training in the use of the system, could be conducted either virtually by means of video conference or in the clinic. After consent forms were obtained and eligibility was determined, the use of a continuous glucose monitor was initiated in patients who were not currently using a personal Dexcom continuous glucose monitor (Fig. S1).

Eligible patients were randomly assigned in a 2:1 ratio to the closed-loop control system of insulin delivery or to standard care with use of a continuous glucose monitor. Randomization was conducted with the use of a computer-generated sequence with a permuted block design, stratified according to trial site.

The legally authorized representatives of the patients who were assigned to the closed-loop group were trained in the use of the closed-loop system, which consisted of a t:slim X2 insulin pump with Control-IQ Technology (a software algorithm developed at the University of Virginia[7]) and a continuous glucose monitor (Dexcom G6, Dexcom) that transmitted glucose values to the pump. The algorithm was identical to the one in the commercial Control-IQ system, although unlike the commercial pump, a lower body weight and total daily insulin value could be entered for the trial insulin pump at system initialization. The legally authorized representatives of the patients who received multiple daily injections of insulin did not receive training in the use of the pump before randomization. Adjustments to pump settings (e.g., basal rates, the correction factor, and the insulin-to-carbohydrate ratio) could be made by clinical site personnel in accordance with the judgment of the investigator, as indicated.

Patients in the standard-care group continued to use the insulin-delivery method (personal pump or multiple daily injections of insulin) that they had used before the trial, and they received training in the use of a Dexcom G6 continuous glucose monitor. The patients in both groups received blood glucose meters and strips (Contour Next One, Ascensia Diabetes Care) and ketone meters and strips (Abbott Precision Xtra, Abbott Diabetes Care). In addition, at randomization the parents or guardians of the patients received education that included review of carbohydrate counting, bolus dosing for treatment of hyperglycemia, and management of hyperglycemia (including checking ketone levels and treatment of ketosis).

Both groups had virtual or in-person trial visits at 2, 6, and 13 weeks after randomization, with telephone contacts at 1 and 10 weeks. The legally authorized representatives of the patients were instructed to download data from the trial devices at each visit or telephone contact, or at least every 4 weeks. At randomization and at 13 weeks, a central laboratory at the University of Minnesota measured glycated hemoglobin levels in capillary blood

samples obtained with the use of a procedure that has been shown to have accuracy that is equivalent to that of a procedure for obtaining venous samples.[8]

### OUTCOMES

The primary outcome was the percentage of time that the glucose level was in the target range of 70 to 180 mg per deciliter (3.9 to 10.0 mmol per liter) over the 13-week trial period, as measured by continuous glucose monitoring. The key secondary outcomes, tested in a hierarchical fashion to maintain the type I error at 5%, included the percentage of time that the glucose level was above 250 mg per deciliter (13.9 mmol per liter), the mean glucose level, the percentage of time that the glucose level was below 70 mg per deciliter, and the percentage of time that the glucose level was below 54 mg per deciliter (3.0 mmol per liter), all assessed over the 13-week trial period, as well as the glycated hemoglobin level as measured at 13 weeks. Safety outcomes included the incidence of severe hypoglycemia, diabetic ketoacidosis, and other serious adverse events.

### STATISTICAL ANALYSIS

We calculated that a sample of 90 patients would provide the trial with 90% power to reject the null hypothesis that there would be no between-group difference with respect to the primary outcome (the percentage of time that the glucose level was in the target range of 70 to 180 mg per deciliter). We assumed that the randomization ratio would be 2:1 between the closed-loop group and the standard-care group, and we assumed that the mean percentage of time with the glucose level 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 10% and a two-sided, type I error rate of 5%. The total sample was increased to 102 patients to account for dropouts.

Statistical analyses were performed on an intention-to-treat basis, and all the patients were included in the primary 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 the use of a linear mixed-effects regression model. Analyses of the secondary continuous outcomes (glycated hemoglobin level, total daily insulin dose, body weight, and body-mass index percentile) were conducted with the same method that was used in the primary analysis. Binary outcomes were analyzed with the use of a logistic-regression model. Additional details about the statistical methods are provided in the Supplementary Appendix. All P values are two-tailed. Analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

## RESULTS

### PATIENTS

Between April 28, 2021, and January 13, 2022, a total of 102 patients (34 per trial site) in the United States were randomly assigned to the closed-loop group (68 patients) or the standard-care group (34 patients). The enrolled patients were from 27 different states; 40 patients were concurrently patients at one of the three trial clinics, and 62 were recruited from outside the clinics. At baseline, the youngest patient had turned 2 years of age, the

oldest patients were younger than 6 years of age, and 46% of the patients were younger than 4 years of age. The time since the diagnosis of diabetes ranged from 6 months to 5 years, and the glycated hemoglobin level ranged from 5.2 to 11.5%. A total of 75 patients (74%) were both White and non-Hispanic. Before the trial, 66 patients (65%) had been using insulin pumps and 36 (35%) had been receiving multiple daily injections; 100 patients (98%) had been using a continuous glucose monitor (Table 1 and Table S2). The relevance and representativeness of the trial population are noted and described in Table S3.

The 13-week trial was completed by all but 1 patient in the closed-loop group and by all the patients in the standard-care group. Among the 101 patients who completed the trial, 98.3% of the trial visits and 97.5% of the telephone contacts were completed. Training in the use of the closed-loop system was virtual for 55 of the 68 patients (81%) in the closed-loop group. A total of 372 of the 407 trial visits (91%) in the closed-loop group and 195 of the 204 trial visits (96%) in the standard-care group were virtual (Table S4). The number of unscheduled contacts was greater in the closed-loop group than in the standard-care group (Table S5).

## EFFICACY OUTCOMES

In the primary analysis, the mean (±SD) percentage of time that the glucose level was in the target range of 70 to 180 mg per deciliter increased from 56.7±18.0% at baseline to 69.3±11.1% during the 13-week follow-up period in the closed-loop group and from 54.9±14.7% to 55.9±12.6% in the standard-care group, with a mean adjusted difference (the value in the closed-loop group minus the value in the standard-care group) of 12.4 percentage points (95% confidence interval [CI], 9.5 to 15.3; P<0.001) (Table 2 and Figs. S2 and S3). The results of the sensitivity analyses were similar to those of the primary analysis (Table S6). The treatment effect was evident in the first week and appeared to be consistent over the 13-week period (Fig. 1A). During follow-up, the mean percentage of time that the glucose level was in the target range during the daytime (6 a.m. to 9:59 p.m.) was 67% in the closed-loop group and 56% in the standard-care group, and the corresponding values during the nighttime (10 p.m. to 5:59 a.m.) were 74% and 56%, with the maximum between-group difference observed at approximately 5 a.m. (Fig. 1B and Table S7).

Similar treatment effects favoring the closed-loop group were observed in the percentage of time that the glucose level was above 250 mg per deciliter (mean difference between the closed-loop group and the standard-care group, −5.4 percentage points; 95% CI, −7.3 to −3.6; P<0.001), in the mean glucose level (mean difference, −17.7 mg per deciliter; 95% CI, −23.2 to −12.2; P<0.001), and in the glycated hemoglobin level (mean difference, −0.42 percentage points; 95% CI, −0.62 to −0.22; P<0.001) (Table 2). The percentage of time that the glucose level was below 70 mg per deciliter did not differ significantly between the two groups (P = 0.57).

The percentage of time that the glucose level was within the target range consistently favored the closed-loop system across a broad range of baseline characteristics, including age, sex, body-mass index, household income, parental education level, use of an insulin pump or receipt of multiple daily injections of insulin before the trial, and glycated hemoglobin level (Table S8). A greater increase in the percentage of time that the glucose

level was in the target range and a greater decrease in the glycated hemoglobin level were observed with higher baseline glycated hemoglobin levels (Fig. 2 and Table S12).

The target of a glycated hemoglobin level of less than 7% (as recommended by the American Diabetes Association) was met at 13 weeks in 30 of 62 patients (48%) in the closed-loop group and in 10 of 33 patients (30%) in the standard-care group (Table S9). The percentage of time with the glucose level in target range (70 to 180 mg per deciliter) of more than 70% plus a percentage of time with the glucose level below 70 mg per deciliter of less than 4% [9] was attained in 21 of 68 patients (31%) in the closed-loop group and in 2 of 34 patients (6%) in the standard-care group (Table S10). The results of the other secondary and exploratory outcome analyses are provided in Tables S11 through S13 and Figures S4 and S5. The total daily insulin dose (Tables S14 and S15) and change in body weight (Table S16) were similar in the closed-loop and standard-care groups.

### USE OF THE CLOSED-LOOP SYSTEM

In the closed-loop group, two patients never used the closed-loop system and three others started to use it but then stopped (Table S17). All the other patients used the closed-loop system until trial week 13. In the closed-loop group, the median percentage of time that the system was in the closed-loop mode over the 13-week trial was 94% (interquartile range, 90 to 95) (Table S18). Reported issues with the closed-loop system are summarized in Table S19. In the standard-care group, the median percentage of continuous glucose monitor use over the 13-week trial was 96% (interquartile range, 89 to 98) (Table S20).

### ADVERSE EVENTS

A total of 71 adverse events were reported in 41 patients (60%) in the closed-loop group, and 14 adverse events were reported in 11 patients (32%) in the standard-care group (P = 0.001) (Table 3). There were two cases of severe hypoglycemia in the closed-loop group and one case in the standard-care group. One case of diabetic ketoacidosis related to infusion-set failure occurred in the closed-loop group, and none occurred in the standard-care group. A total of 51 cases of hyperglycemia with or without ketosis — most of which were related to infusion-set failures — were reported in the closed-loop group, and 8 cases (not related to a trial device) were reported in the standard-care group. Other safety outcomes are listed in Table 3.

## DISCUSSION

In this randomized, controlled trial, the duration of time that the glucose level was in the target range of 70 to 180 mg per deciliter was significantly longer — by approximately 3 hours per day — in patients who used the closed-loop system than in those in the standard-care group who used a continuous glucose monitor in conjunction with their usual insulin-delivery method. The benefit with respect to increased time in the target range was observed across various patient characteristics, including age, race or ethnic group, parental education, family income, baseline glycated hemoglobin level, and the insulin-delivery method used before the trial (insulin pump or insulin injections). We infer that the finding that patients with higher baseline glycated hemoglobin levels had the greatest improvement

in the percentage of time that the glucose level was in the target range may be of public health importance for the prevention of long-term complications of type 1 diabetes. An increase in the mean time in range was observed within 1 day after the initiation of the closed-loop system, regardless of pretrial use of a pump or injections for insulin delivery, and this increase was observed during both daytime and nighttime.

A beneficial effect of the closed-loop system was also seen in decreases in the percentage of time that the glucose level was above 250 mg per deciliter and in improved mean glucose and glycated hemoglobin levels. These findings are similar to those observed in older children, adolescents, and adults using the same software algorithm in a very similar hybrid closed-loop system.[3,4] The incidence of hypoglycemia (as measured by continuous glucose monitoring) was low at baseline and did not differ between the trial groups during follow-up.

In another randomized crossover trial involving 74 children who were 2.3 to 7.9 years of age (mean, 5.6 years), Ware et al.[11] found that the percentage of time that the glucose level was in the target range was 8.7 percentage points higher among children who used the CamAPS FX closed-loop system than among those who used a sensor-augmented pump (without automation). Our trial results showed a greater improvement in the percentage of the time in the target range, even though our cohort had a lower mean age and a substantially greater proportion of the cohort was younger than 4 years of age. Managing type 1 diabetes in very young children is particularly difficult because of the challenges associated with normal childhood development, including less predictable food intake and activity levels than those of older children. In addition, 36 of the 102 patients in our cohort (35%) were receiving injections of insulin before the trial, whereas the trial conducted by Ware et al.[11] was limited to children who were already using insulin pumps at the beginning of the trial. In a pair of 13-week, single-group trials, Forlenza et al.[12] reported an 8.1-percentage-point increase in the time that the glucose level was in the target range in 46 children who were at least 2 years of age but younger than 7 years of age and who were using the MiniMed 670G hybrid closed-loop system, and Sherr et al.[2] reported an 11-percentage-point increase in the time that the glucose level was in the target range in 80 children between 2.0 and 5.9 years of age who were using the Omnipod 5 system.

The patients in our trial appeared to have no unanticipated safety problems with the use of the closed-loop system. The incidences of clinical severe hypoglycemia and hypoglycemia (as measured by continuous glucose monitoring) were low and similar in the two groups. More occurrences of pump infusion-set failure leading to hyperglycemia with or without ketosis, a common occurrence in patients who use an insulin pump,[13] were reported in the closed-loop group than in the standard-care group. However, we speculate that this difference probably reflects differential reporting between the groups, as has been noted in other studies.[3,4,14] This presumption is supported by the finding of a lower incidence of prolonged hyperglycemia in the closed-loop group than in the standard-care group.

The current trial was conducted in the United States during the public health emergency due to the Covid-19 pandemic, which necessitated the creation of processes to train the legally authorized representatives of the patients in the use of the closed-loop system virtually rather than with conventional in-person visits. Consequently, more than 80% of the training

in the use of the closed-loop system and more than 90% of all the visits were conducted virtually. Successful use of the closed-loop system under these conditions is an important finding that could affect the approach to initiating and monitoring the use of the closed-loop system and expand the use of such systems, particularly in patients living in areas without an endocrinologist but with reliable Internet access. Insurance coverage and licensing issues related to conducting a trial or providing care across multiple states need to be considered.

The strengths of the current trial include its parallel-group, randomized, controlled design and a protocol that allowed for the conduct of the trial with virtual visits without the usual requirement for in-person visits. As a consequence, recruitment of a broad group of patients from all over the United States, beyond the usual catchment area of each clinical site, was possible. However, even with this approach to recruitment, overrepresentation of families with higher socioeconomic status in the trial cohort may affect the generalizability of the results. An additional limitation was the trial period of only 13 weeks; it is unknown whether the observed treatment effect would be sustained over a longer period of time, as has been seen in older patients,[4] but an extension trial is ongoing. There were more contacts with the patients in the closed-loop group than with those in the standard-care group; this is an inherent issue in trials in which one group is using an investigational device and the other group is receiving standard care.

In this 13-week trial involving children 2 to younger than 6 years of age who had type 1 diabetes, the glucose level was in the target range for a greater percentage of time with a hybrid closed-loop system than with standard-care insulin delivery involving a continuous glucose monitor.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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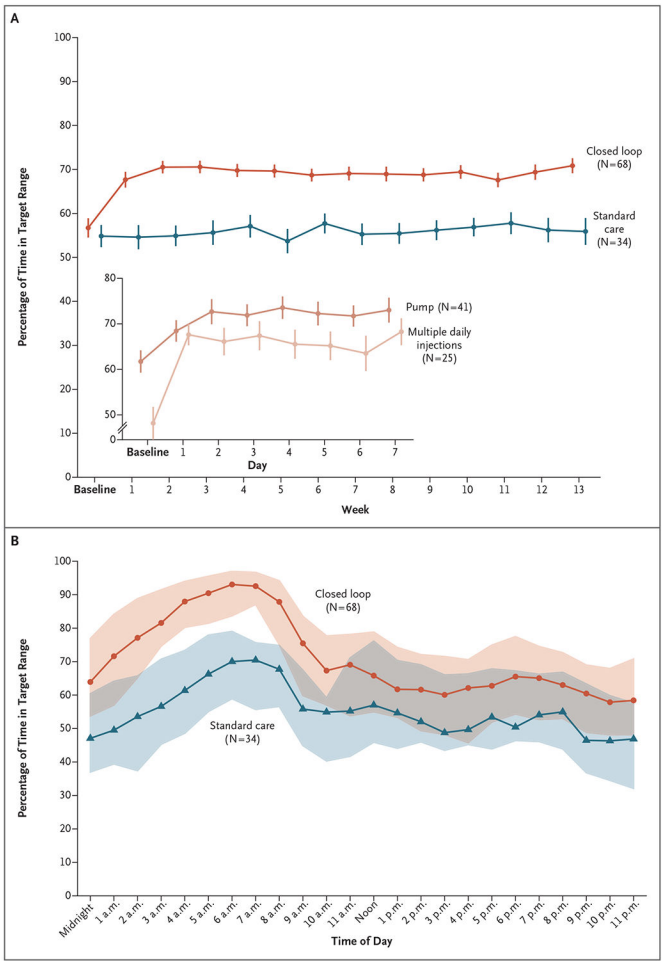


**Figure 1. Mean Percentage of Time with the Glucose Level in the Target Range.**

Panel A shows the mean percentage of time that the glucose level was in the target range of 70 to 180 mg per deciliter (3.9 to 10.0 mmol per liter) each week over the 13 weeks of the trial among patients who were assigned to receive treatment with either a closed-loop system or standard care. The inset shows the mean percentage of time that the glucose level was in the target range each day for the first 7 days in the closed-loop group, according to whether the patient had been using an insulin pump or receiving multiple daily injections of insulin before the trial. The circles denote the mean values, and the vertical lines extend to ±1 SE of the mean. Panel B shows an envelope plot of the same outcome, as measured by continuous glucose monitoring, according to the time of day over the 13-week period. The circles denote the hourly median values, and the lower and upper boundary of each shaded region the 25th and 75th percentiles, respectively.

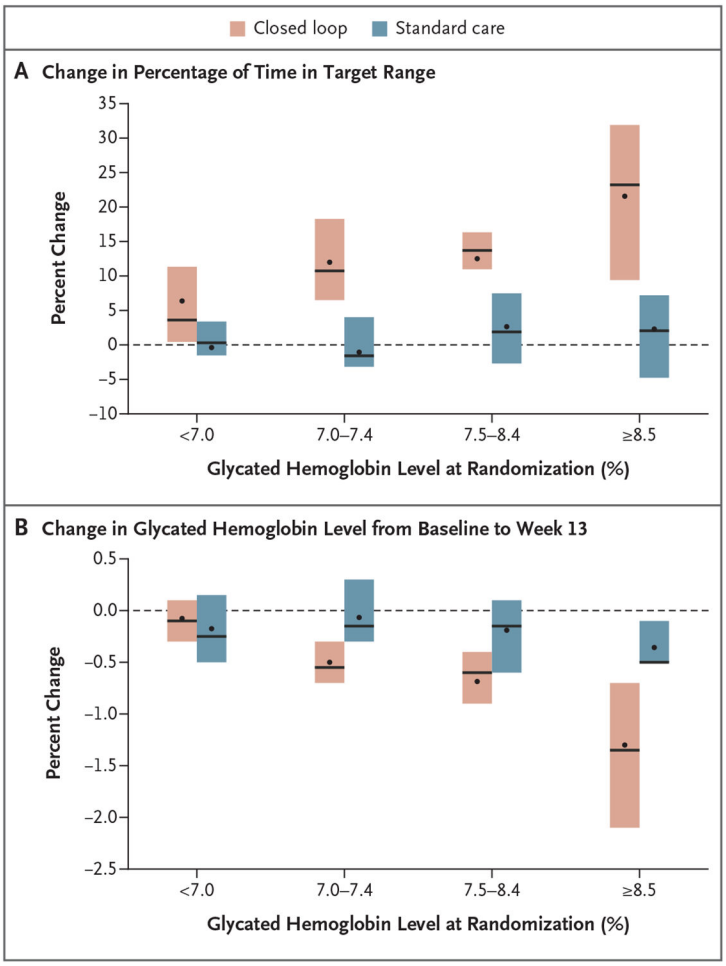


**Figure 2. Changes from Baseline in Time within the Target Glucose Range and the Glycated Hemoglobin Level.**

Panel A shows the change from baseline (randomization) to 13 weeks in the percentage of time with the glucose level in the target range of 70 to 180 mg per deciliter, according to the baseline glycated hemoglobin level. The numbers of patients in each baseline group were the following: glycated hemoglobin level less than 7.0%, 22 patients in the closed-loop group and 8 patients in the standard-care group; glycated hemoglobin level 7.0 to 7.4%, 11 and 6 patients, respectively; glycated hemoglobin level 7.5 to 8.4%, 15 and 11 patients, respectively; and glycated hemoglobin level 8.5% or higher, 15 and 7 patients, respectively. Panel B shows the change from baseline to 13 weeks in glycated hemoglobin levels, according to the baseline glycated hemoglobin level. The numbers of patients in each baseline group were the following: glycated hemoglobin level less than 7.0%, 21 patients in the closed-loop group and 8 patients in the standard-care group; glycated hemoglobin level 7.0 to 7.4%, 10 and 6 patients, respectively; glycated hemoglobin level 7.5 to 8.4%, 14 and 10 patients, respectively; and glycated hemoglobin level 8.5% or higher, 14 and 7 patients, respectively. In both panels, the black dots denote the mean values, the horizontal bars in the boxes the median values, and the lower and upper boundaries of each box the 25th and 75th percentiles, respectively.

**Table 1.**

Characteristics of the Patients at Baseline.*

| Characteristic | Closed-Loop Group (N = 68) | Standard-Care Group (N = 34) |
|---|---|---|
| Age | | |
| Mean — yr | 3.84±1.23 | 4.06±1.25 |
| Range — yr | 2.00–5.98 | 2.02–5.90 |
| Distribution — no. (%) | | |
| 2 to <4 yr | 31 (46) | 16 (47) |
| 4 to <6 yr | 37 (54) | 18 (53) |
| Glycated hemoglobin level† | | |
| Mean — % | 7.5±1.2 | 7.7±0.9 |
| Range — % | 5.2–11.5 | 6.0–9.7 |
| Distribution — no./total no. (%) | | |
| <7% | 23/64 (36) | 8/32 (25) |
| 7% to <8% | 20/64 (31) | 8/32 (25) |
| 8% to <9% | 15/64 (23) | 15/32 (47) |
| ≥9% | 6/64 (9) | 1/32 (3) |
| Female sex — no. (%) | 33 (49) | 19 (56) |
| Race or ethnic group — no. (%)‡ | | |
| White, non-Hispanic | 50 (74) | 25 (74) |
| Black, non-Hispanic | 4 (6) | 2 (6) |
| Hispanic or Latinx | 11 (16) | 5 (15) |
| Asian | 1 (1) | 1 (3) |
| Multiple, non-Hispanic | 2 (3) | 1 (3) |
| Annual household income — no./total no. (%) | | |
| <$50,000 | 8/64 (12) | 6/32 (19) |
| $50,000 to <$100,000 | 19/64 (30) | 12/32 (38) |
| ≥$100,000 | 37/64 (58) | 14/32 (44) |
| Highest education level of parent — no. (%) | | |
| Less than bachelor's degree | 14 (21) | 9 (26) |
| Bachelor's degree | 22 (32) | 13 (38) |

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| Characteristic | Closed-Loop Group (N = 68) | Standard-Care Group (N = 34) |
|---|---|---|
| More than bachelor's degree | 32 (47) | 12 (35) |
| Insulin-delivery method — no. (%) | | |
| Pump[§] | 42 (62) | 24 (71) |
| Multiple daily injections | 26 (38) | 10 (29) |
| Current use of continuous glucose monitoring system — no. (%)[¶] | 66 (97) | 34 (100) |

[*] Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. A more extensive listing of baseline characteristics is provided in Table S2.

[†] Data on the glycated hemoglobin level were missing for 4 patients in the closed-loop group and 2 patients in the standard-care group.

[‡] Race and ethnic group were reported by the legally authorized representatives (typically parents) of the patients.

[§] Among pump users, 21 of 42 patients in the closed-loop group and 11 of 24 patients in the standard-care group used a pump with a predictive low-glucose suspend feature (t:slim X2 insulin pump with Basal-IQ Technology), 1 patient in each group used the 670G closed-loop system in open-loop mode, and 20 patients in the closed-loop group and 12 patients in the standard-care group used the Insulet OmniPod pump.

[¶] All the patients who used continuous glucose monitoring used a Dexcom continuous glucose monitor except for 1 patient in the standard-care group who used a FreeStyle Libre (Abbott) continuous glucose monitor.

**Table 2.**

Key Outcomes According to Treatment Group.*

| Outcome | Baseline | | 13-Wk Trial Period | | Difference (95% CI)† | P Value |
|---|---|---|---|---|---|---|
| | Closed-Loop Group (N = 67) | Standard-Care Group (N = 34) | Closed-Loop Group (N = 68) | Standard-Care Group (N = 34) | | |
| Hours of continuous glucose monitoring data | 311±26 | 305±35 | 2067±236 | 1941±289 | — | |
| Primary outcome: glucose level in range of 70–180 mg/dl — % of time | 56.7±18.0 | 54.9±14.7 | 69.3±11.1 | 55.9±12.6 | 12.4 (9.5 to 15.3) | <0.001 |
| Secondary hierarchical outcomes in prespecified order‡ | | | | | | |
| Glucose level >250 mg/dl — % of time§ | 14.8±15.5 | 16.0±13.9 | 8.4±7.2 | 15.0±10.9 | −5.4 (−7.3 to −3.6) | <0.001 |
| Mean glucose level — mg/dl | 173±36 | 176±26 | 155±20 | 174±22 | −17.7 (−23.2 to −12.2) | <0.001 |
| Glycated hemoglobin level — % ¶ | 7.5±1.2 | 7.7±0.9 | 7.0±0.8 | 7.5±0.9 | −0.42 (−0.62 to −0.22) | <0.001 |
| Glucose level <70 mg/dl — % of time§ | 3.0±2.2 | 2.7±2.0 | 3.0±1.8 | 3.0±2.2 | −0.2 (−0.7 to 0.4) | 0.57 |
| Glucose level <54 mg/dl — % of time§ | 0.6±0.7 | 0.5±0.6 | 0.6±0.5 | 0.5±0.5 | 0.01 (−0.1 to 0.1) | — |

*Plus–minus values are means ±SD. One patient in the closed-loop group was missing baseline continuous glucose monitoring data. To convert the values for glucose to millimoles per liter, multiply by 0.05551.

†Differences were calculated as percentage points (the value in the closed-loop group minus the value in the standard-care group). A direct likelihood model was used for outcomes for which the mean and standard deviation are reported. This model adjusted for the baseline value of the metric, age, previous use of a continuous glucose monitor and pump, and trial site as a random effect.

‡To preserve the overall type I error for the multiple outcomes listed in this table, a hierarchical gatekeeping approach was used. Since the percentage of time with the glucose level below 70 mg per deciliter, as measured by continuous glucose monitoring, was not significant, the remaining outcome on the list (the percentage of time with the glucose level <54 mg per deciliter, as measured by continuous glucose monitoring) was not formally tested.

§For outcomes with a skewed distribution, the mean, standard deviation, difference, and P value were calculated by means of robust regression with the use of an M-estimator.

¶Data on the glycated hemoglobin level at baseline were available for 64 patients in the closed-loop group and for 32 patients in the standard-care group, and data on the glycated hemoglobin level at 13 weeks were available for 62 patients in the closed-loop group and for 33 patients in the standard-care group.

**Table 3.**

Safety Outcomes during the 13-Week Trial Period.[*]

| Event | Closed-Loop Group (N = 68) | Standard-Care Group (N = 34) | P Value[†] |
|---|---|---|---|
| All adverse events | | | |
| No. of patients with an event (%) | 41 (60) | 11 (32) | 0.001 |
| No. of events | 71 | 14 | |
| No. of events per 100 person-yr | 413 | 163 | |
| Serious adverse events — no. of patients | | | |
| Severe hypoglycemia | 2 | 1 | |
| Diabetic ketoacidosis | 1[‡] | 0 | |
| Other serious adverse events[§] | 0 | 1 | |
| Nonserious adverse events | | | |
| Hyperglycemia with or without ketosis, related to trial device[¶] | | | |
| No. of patients with an event (%) | 26 (38) | NA | |
| No. of events | 39 | | |
| Hyperglycemia with or without ketosis, not related to trial device | | | |
| No. of patients with an event (%) | 9 (13) | 7 (21) | |
| No. of events | 12 | 8 | |
| Other reportable adverse events[‖] | | | |
| No. of patients with an event (%) | 15 (22) | 3 (9) | |
| No. of events | 17 | 4 | |
| Other safety outcomes | | | |
| Increase in glycated hemoglobin level by >0.5 percentage points from baseline to 13 wk — no. of patients (%)[**] | 1 (2) | 0 | |
| Days with ≥1 blood ketone meter measurement >1.0 mmol/liter — no./total person-days of follow-up (%) | 27/6350 (0.43) | 7/3165 (0.22) | 0.14 |

[*] Reportable adverse events included serious adverse events, adverse events that occurred in association with a trial device or procedure, severe hypoglycemia with altered consciousness that required the assistance of a third party for treatment, diabetic ketoacidosis as defined in the Diabetes Control and Complications Trial,[10] acute cases of hyperglycemia or ketosis for which a health care provider was contacted, and a blood ketone level of at least 1.0 mmol per liter, even if there was no communication with a health care provider at the time of the event. NA denotes not applicable.

[†] P values were calculated only for the outcomes that were prespecified in the statistical analysis plan.

[‡] This case of diabetic ketoacidosis was related to an infusion-set failure.

[§] One patient in the standard-care group was hospitalized for an asthma flare.

[¶] The trial device included the insulin pump, infusion set, and continuous glucose monitor. Most cases of hyperglycemia that were considered by the medical monitor to be related to the trial device were due to infusion-set failures.

[‖] In the closed-loop group, other reportable adverse events (in 17 patients) were the following: bleeding at the pump infusion site (in 1 patient), burn (in 1 patient), coronavirus disease 2019 (in 3 patients), gastroenteritis (in 2 patients), hematuria (in 1 patient), hypoglycemia (in 2 patients), infection at the pump infusion site (in 2 patients), infection at the sensor infusion site (in 1 patient), injury from a fall (in 2 patients), streptococcus pharyngitis (in 1 patient), and upper respiratory infection (in 1 patient); in the standard-care group, an adverse event in this category was gastroenteritis (in 4 patients).

[**] Data regarding an increase in the glycated hemoglobin level were available for 59 patients in the closed-loop group and for 31 patients in the standard-care group.