

ORIGINAL ARTICLE

Closed-Loop Therapy and Preservation of C-Peptide Secretion in Type 1 Diabetes

Charlotte K. Boughton, Ph.D., Janet M. Allen, R.N., Julia Ware, M.D., Malgorzata E. Wilinska, Ph.D., Sara Hartnell, B.Sc., Ajay Thankamony, M.Phil., Tabitha Randell, M.D., Atrayee Ghatak, M.D., Rachel E.J. Besser, Ph.D., Daniela Elleri, Ph.D., Nicola Trevelyan, M.D., Fiona M. Campbell, M.D., Judy Sibayan, M.P.H., Peter Calhoun, Ph.D., Ryan Bailey, M.S., Gareth Dunseath, Ph.D., and Roman Hovorka, Ph.D., for the CLOuD Consortium*

ABSTRACT

BACKGROUND

Whether improved glucose control with hybrid closed-loop therapy can preserve C-peptide secretion as compared with standard insulin therapy in persons with new-onset type 1 diabetes is unclear.

METHODS

In a multicenter, open-label, parallel-group, randomized trial, we assigned youths 10.0 to 16.9 years of age within 21 days after a diagnosis of type 1 diabetes to receive hybrid closed-loop therapy or standard insulin therapy (control) for 24 months. The primary end point was the area under the curve (AUC) for the plasma C-peptide level (after a mixed-meal tolerance test) at 12 months after diagnosis. The analysis was performed on an intention-to-treat basis.

RESULTS

A total of 97 participants (mean [\pm SD] age, 12 \pm 2 years) underwent randomization: 51 were assigned to receive closed-loop therapy and 46 to receive control therapy. The AUC for the C-peptide level at 12 months (primary end point) did not differ significantly between the two groups (geometric mean, 0.35 pmol per milliliter [interquartile range, 0.16 to 0.49] with closed-loop therapy and 0.46 pmol per milliliter [interquartile range, 0.22 to 0.69] with control therapy; mean adjusted difference, -0.06 pmol per milliliter [95% confidence interval {CI}, -0.14 to 0.03]). There was not a substantial between-group difference in the AUC for the C-peptide level at 24 months (geometric mean, 0.18 pmol per milliliter [interquartile range, 0.06 to 0.22] with closed-loop therapy and 0.24 pmol per milliliter [interquartile range, 0.05 to 0.30] with control therapy; mean adjusted difference, -0.04 pmol per milliliter [95% CI, -0.14 to 0.06]). The arithmetic mean glycated hemoglobin level was lower in the closed-loop group than in the control group by 4 mmol per mole (0.4 percentage points; 95% CI, 0 to 8 mmol per mole [0.0 to 0.7 percentage points]) at 12 months and by 11 mmol per mole (1.0 percentage points; 95% CI, 7 to 15 mmol per mole [0.5 to 1.5 percentage points]) at 24 months. Five cases of severe hypoglycemia occurred in the closed-loop group (in 3 participants), and one occurred in the control group; one case of diabetic ketoacidosis occurred in the closed-loop group.

CONCLUSIONS

In youths with new-onset type 1 diabetes, intensive glucose control for 24 months did not appear to prevent the decline in residual C-peptide secretion. (Funded by the National Institute for Health and Care Research and others; CLOuD ClinicalTrials.gov number, NCT02871089.)

From the Wellcome–Medical Research Council Institute of Metabolic Science (C.K.B., J.M.A., J.W., M.E.W., R.H.) and the Department of Paediatrics (J.M.A., J.W., M.E.W., A.T., R.H.), University of Cambridge, and Wolfson Diabetes and Endocrine Clinic, Cambridge University Hospitals NHS Foundation Trust (C.K.B., S.H.), Cambridge, the Department of Paediatric Diabetes and Endocrinology, Nottingham Children's Hospital, Nottingham (T.R.), the Department of Diabetes, Alder Hey Children's NHS Foundation Trust, Liverpool (A.G.), the Department of Paediatrics, University of Oxford, and the National Institute for Health and Care Research Oxford Biomedical Research Centre, John Radcliffe Hospital, Oxford (R.E.J.B.), the Department of Diabetes, Royal Hospital for Sick Children, Edinburgh (D.E.), the Department of Paediatric Diabetes, Southampton Children's Hospital, Southampton (N.T.), the Department of Paediatric Diabetes, Leeds Children's Hospital, Leeds (F.M.C.), and the Diabetes Research Group, Swansea University, Swansea (G.D.) — all in the United Kingdom; and Jaeb Center for Health Research, Tampa, FL (J.S., P.C., R.B.). Dr. Hovorka can be contacted at rh347@cam.ac.uk or at the Wellcome–Medical Research Council Institute of Metabolic Science, Box 289, Addenbrooke's Hospital, Hills Rd., Cambridge CB2 0QQ, United Kingdom.

*The members of the CLOuD Consortium are listed in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2022;387:882-93.

DOI: 10.1056/NEJMoa2203496

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TYPE 1 DIABETES IS CHARACTERIZED BY autoimmune destruction of pancreatic beta cells.¹ Loss of beta cells is gradual, with a substantial number remaining at clinical presentation and an ongoing decline after diagnosis.² Amelioration of hyperglycemia after diagnosis allows partial recovery of beta-cell insulin secretory function, which leads to a “honeymoon period” with relatively low exogenous insulin requirements.¹

The Diabetes Control and Complications Trial showed that in adults, persistence of residual functioning beta cells, measured by means of C-peptide secretion, is associated with improved glycemic control, a reduced risk of hypoglycemia, and a lower incidence of microvascular complications.^{3,4} Interventions that can preserve endogenous insulin secretion before and after clinical diagnosis of type 1 diabetes are clinically important.^{5,6}

Previous studies have investigated whether an early period of intensive glycemic control after diagnosis of type 1 diabetes can prevent the decline in endogenous insulin secretion, with conflicting results. An early exploratory study involving adolescents showed improved C-peptide secretion at 12 months after a period of intensive insulin treatment in the hospital for 2 weeks after diagnosis.⁷ A more recent study that applied a short period of hybrid closed-loop therapy within 7 days after diagnosis, followed by sensor-augmented pump therapy, did not alter C-peptide secretion at 12 months as compared with standard care, but there was no difference in glucose control between the two groups over the 12-month study period.⁸

It has yet to be determined whether sustained intensive glycemic control after diagnosis can ameliorate the decline in endogenous insulin secretion in youths with type 1 diabetes. Hybrid closed-loop systems have been shown to improve glucose control in youths⁹⁻¹² and accommodate variability in exogenous insulin requirements.^{13,14} We hypothesized that a sustained period of intensive glucose control with hybrid closed-loop therapy for 24 months after diagnosis of type 1 diabetes in children and adolescents could preserve C-peptide secretion as compared with standard insulin therapy.

METHODS

TRIAL DESIGN

The Closed Loop from Onset in Type 1 Diabetes (CLOuD) trial, a multicenter, open-label, parallel-group, randomized trial conducted by the CLOuD Consortium, compared hybrid closed-loop insulin delivery and standard insulin therapy (control) over a period of 24 months. The trial protocol has been published previously¹⁵ and is available with the full text of this article at NEJM.org. Participants were recruited from pediatric diabetes clinics in the United Kingdom (Cambridge, Edinburgh, Leeds, Liverpool, Nottingham, Oxford, and Southampton); trial sites are listed in the Supplementary Appendix, available at NEJM.org. Approval was received from the Cambridge East Research Ethics Committee (16/EE/0286) and the Medicines and Healthcare Products Regulatory Agency. Safety aspects were overseen by an independent data and safety monitoring board. The trial was co-coordinated by the Cambridge Clinical Trials Unit.

Author contributions to the trial are detailed in the Supplementary Appendix. The first and last authors wrote the manuscript. All the authors critically reviewed the manuscript and contributed to the interpretation of the results. The first, fourth, fourteenth, and last authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

Abbott Diabetes Care supplied glucose-monitoring devices at no cost, and Dexcom and Medtronic supplied discounted continuous glucose-monitoring devices. Medtronic also supplied discounted insulin pumps, telephone enclosures, and pump consumables. Representatives of Dexcom, Medtronic, and Abbott Diabetes Care read the manuscript before submission. None of the sponsors had any role in the trial design, data collection, data analysis, data interpretation, or the writing of the manuscript.

TRIAL PARTICIPANTS

The key inclusion criterion was a diagnosis of type 1 diabetes within the previous 21 days. Participants were 10.0 to 16.9 years of age. Among the key exclusion criteria was concomitant disease or treatment affecting metabolic



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control or interpretation of glycated hemoglobin levels. Complete inclusion and exclusion criteria are listed in Table S1 in the Supplementary Appendix. Eligible participants were identified by clinical teams at each center. Participants 16 years of age or older and parents or guardians of participants younger than 16 years of age provided written informed consent. Written assent was obtained from participants younger than 16 years of age.

RANDOMIZATION

Eligible participants underwent randomization with the use of block randomization and central randomization software to receive hybrid closed-loop therapy or standard insulin therapy for 24 months. Randomization was stratified according to site and age (10 to 13 years or 14 to 16 years); the randomization ratio was 1:1 within each stratum.

CLOSED-LOOP SYSTEM

The Cambridge model predictive control algorithm (version 0.3.71) was run in two hardware configurations: the initial FlorenceM configuration, followed by the CamAPS FX configuration to improve usability and therapy adherence (Fig. S1). In both configurations, algorithm-driven insulin delivery was adjusted automatically every 8 to 12 minutes, with the app-based control algorithm communicating the insulin infusion rate to the insulin pump wirelessly. The control algorithm was initialized with the use of the total daily insulin dose and body weight and incorporated adaptive learning with respect to total daily insulin requirements, diurnal variations, meal patterns, and duration of insulin action.

TRIAL PROCEDURES

Participants and their families received structured diabetes education and training on the regimen of multiple daily insulin injections according to standard clinical practice in the United Kingdom.¹⁶ Within 21 days after diagnosis, participants underwent a baseline mixed-meal tolerance test.

Trial visit schedules are shown in Tables S2 and S3, and details of screening, randomization, and follow-up are shown in Figure S2. After randomization, participants assigned to the closed-loop group were trained to use the trial

insulin pump and glucose sensor before starting closed-loop insulin delivery within 6 weeks after diagnosis. Participants continued with closed-loop therapy for 24 months with no remote monitoring or trial-related restrictions. Participants assigned to standard insulin therapy received additional training to complement the core training and to match contact time with the closed-loop group. Participants continued with standard insulin therapy for 24 months but could switch to insulin-pump therapy or use flash or continuous glucose monitoring or approved closed-loop systems if clinically indicated, with application of National Institute for Health and Care Excellence criteria.¹⁶ The recommended glycemic target for both groups was a glycated hemoglobin level of less than 48 mmol per mole (<6.5%), according to the National Institute for Health and Care Excellence guidelines.¹⁶

Follow-up visits occurred at three monthly intervals. At each follow-up visit, glycated hemoglobin was measured, and participants wore a glucose sensor (FreeStyle Libre Pro, Abbott Diabetes Care) for 14 days. Both the participants and investigators were unaware of the glucose sensor results. Mixed-meal tolerance tests were conducted after an overnight fast at 6, 12, and 24 months after diagnosis. Participants were given a liquid meal (Boost, Nestle) according to body weight (6 ml per kilogram [maximum, 360 ml], including 17 g of carbohydrate, 4 g of protein, and 3 g of fat per 100 ml), and venous blood samples for measurement of C-peptide and glucose were obtained at -10, 0, 15, 30, 60, 90, and 120 minutes.

Participants, their parents or guardians, and the local diabetes clinical team were free to adjust insulin therapy, but no active treatment intensification was undertaken by the research team. Participants had access to a 24-hour telephone helpline to the local research team.

C-peptide, glucose, and glycated hemoglobin were measured centrally, and the lipid profile was measured locally. Details are provided in the Supplementary Appendix.

TRIAL END POINTS

The primary end point was the mean area under the curve (AUC) for the plasma C-peptide level (after a mixed-meal tolerance test) at 12 months after diagnosis. Key secondary end points included the percentage of time in the target glu-

glucose range of 70 to 180 mg per deciliter (3.9 to 10.0 mmol per liter), the glycated hemoglobin level, and the percentage of time with a glucose level of less than 70 mg per deciliter at 12 months tested with the use of a hierarchical gatekeeping procedure to control the type I error. Sensor glucose end points were based on data from a masked glucose sensor worn for 14 days.

Details of additional secondary end points based on C-peptide measurements, glycated hemoglobin level, sensor glucose data, insulin delivery data, body-mass index (BMI), blood pressure, and lipid profiles are listed in the Supplementary Appendix. All end points were compared between trial groups at 12 and 24 months of follow-up. Safety evaluation involved the frequency of severe hypoglycemia warranting assistance and of diabetic ketoacidosis, as well as other adverse events and serious adverse events.

STATISTICAL ANALYSIS

Primary analyses were performed on an intention-to-treat basis, with data for each participant analyzed according to the treatment assigned by randomization. All randomly assigned participants were included in the intention-to-treat population, and all enrolled participants were included in the safety cohort. Treatment interventions were compared with the use of a longitudinal mixed-effects linear model, with adjustment for baseline value, sex, the presence or absence of diabetic ketoacidosis at diagnosis, and age as fixed effects and clinical site as a random effect. Mixed-effects regression models addressed missing data with the use of maximum-likelihood estimation incorporating data from all randomly assigned participants, under the assumption that data were missing at random. To account for the skewed distribution of the AUCs for the C-peptide level, a log transformation was performed. A per-protocol analysis that was restricted to participants in the closed-loop group who used the system at least 60% of the time and those in the control group who did not start insulin-pump therapy was conducted.

The primary and key secondary end points comparing between-group differences at 12 months after diagnosis were tested in a hierarchical fashion to maintain a type I error rate of 5%. Secondary end points were adjusted for multiple comparisons to control the false discovery rate with the use of the two-stage adaptive

Benjamini–Hochberg method.¹⁷ Further details are provided in the Supplementary Appendix. Analyses were conducted with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PARTICIPANTS

Between February 6, 2017, and July 18, 2019, a total of 101 participants were enrolled. Four participants withdrew before randomization; thus, 97 participants underwent randomization: 51 were assigned to the closed-loop group, and 46 were assigned to the control group. The mean (\pm SD) age of the participants was 12 ± 2 years, 43 participants (44%) were female, the baseline glycated hemoglobin level was 93 ± 18 mmol per mole ($10.6\pm 1.7\%$), and 28 participants (29%) had diabetic ketoacidosis at the time of diagnosis (Table 1). The mean time from diagnosis to randomization was 9.5 ± 6.2 days. There were 12 withdrawals after randomization, 4 in the closed-loop group and 8 in the control group. Two participants (1 in each group) were withdrawn by the clinic owing to safety concerns, and the other 10 participant withdrawals were voluntary. The flow of participants is shown in Figure S3, and the reasons for withdrawal are shown in Table S4.

PRIMARY AND KEY SECONDARY END POINTS

The results for the primary and key secondary end points for all randomly assigned participants at 12 months are shown in Table 2. The AUC for the C-peptide level at 12 months (primary end point) did not differ significantly between the two groups (geometric mean, 0.35 pmol per milliliter [interquartile range, 0.16 to 0.49] with closed-loop therapy and 0.46 pmol per milliliter [interquartile range, 0.22 to 0.69] with control therapy; mean adjusted difference, -0.06 pmol per milliliter [95% confidence interval {CI}, -0.14 to 0.03]).

The percentage of time in the target glucose range of 70 to 180 mg per deciliter on the basis of sensor glucose data at 12 months was higher by 10 percentage points (95% CI, 2 to 17) in the closed-loop group ($64\pm 14\%$) than in the control group ($54\pm 23\%$). Because the P value for this end point did not reach the threshold of 0.01 in the hierarchical analysis, other key secondary end points were not tested for statistical significance.

Characteristic	Overall (N=97)	Closed-Loop Group (N=51)	Control Group (N=46)
Age			
Mean — yr	12±2	12±2	12±2
Distribution — no. (%)			
10 to 13 yr	79 (81)	41 (80)	38 (83)
14 to <17 yr	18 (19)	10 (20)	8 (17)
Sex — no. (%)			
Female	43 (44)	25 (49)	18 (39)
Male	54 (56)	26 (51)	28 (61)
BMI percentile†	52±31	53±29	51±34
Race — no. (%)‡			
White	79 (81)	44 (86)	35 (76)
Black	3 (3)	1 (2)	2 (4)
Asian	6 (6)	2 (4)	4 (9)
More than one race	5 (5)	4 (8)	1 (2)
Unknown or not reported	4 (4)	0	4 (9)
Glycated hemoglobin level			
In millimoles per mole	93±18	94±20	91±17
As a percentage	10.6±1.7	10.7±1.8	10.5±1.6
Diabetic ketoacidosis at diagnosis — no. (%)	28 (29)	17 (33)	11 (24)

* Plus-minus values are means ±SD. Percentages may not total 100 because of rounding.

† The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

‡ Race was reported by the participants or their parents or guardians.

The arithmetic mean glycated hemoglobin level was lower in the closed-loop group than in the control group by 4 mmol per mole (0.4 percentage points; 95% CI, 0 to 8 mmol per mole [0.0 to 0.7 percentage points]) at 12 months. The mean between-group difference in the percentage of time with a glucose level of less than 70 mg per deciliter was 0.9 percentage points (95% CI, -1.0 to 2.8).

OTHER SECONDARY END POINTS

The AUC for the C-peptide level declined after diagnosis in both trial groups (Table 2, Fig. 1A, and Fig. S4). There was not a substantial between-group difference in the AUC for the C-peptide level at 24 months (mean adjusted difference, -0.04 pmol per milliliter; 95% CI, -0.14 to 0.06). The AUC for the plasma glucose level was similar in the two groups at 12 months but was lower in the closed-loop group at 24 months (mean difference, -35 mg per deciliter [-1.9 mmol per liter]; 95% CI, -69 to -2 mg per deci-

liter [-3.8 to -0.1 mmol per liter]). There was not a substantial between-group difference in the fasting C-peptide level (measured in femtomoles per milliliter) divided by the fasting glucose level (measured in milligrams per deciliter) at 12 or 24 months. The percentage of participants with negative C-peptide stimulation in response to a mixed-meal tolerance test was similar in the two groups (Table S5).

The percentage of time in the target glucose range of 70 to 180 mg per deciliter on the basis of sensor data was higher by 14 percentage points (95% CI, 6 to 21) in the closed-loop group than in the control group at 24 months (Table 2). The mean glucose level was lower by 31 mg per deciliter (1.7 mmol per liter; 95% CI, 11 to 50 mg per deciliter [0.6 to 2.8 mmol per liter]) in the closed-loop group than in the control group at 24 months. The time spent in a hyperglycemic state with a glucose level of more than 180 mg per deciliter was lower by 19 percentage points (95% CI, 13 to 26) in the closed-loop group than

in the control group at 24 months. The mean difference in the percentage of time with a glucose level of less than 70 mg per deciliter was 2.8 percentage points (95% CI, -0.6 to 6.2) at 24 months. Glucose variability as measured by the standard deviation and coefficient of variation of the glucose level was similar in the closed-loop and control groups. The mean glycated hemoglobin level was lower by 11 mmol per mole (1.0 percentage points; 95% CI, 7 to 15 mmol per mole [0.5 to 1.5 percentage points]) in the closed-loop group than in the control group at 24 months.

Results for end points according to trial group at 6 months are shown in Table S6. Day and night glucose control is shown in Table S7. Data on longitudinal sensor glucose end points are shown in Table S8 and Figure S5. The AUC for the C-peptide level according to glycated hemoglobin level, the coefficient of variation of the glucose level, and the time in the target glucose range of 70 to 180 mg per deciliter are shown in Table S9 and Figure S6.

The total, basal, and bolus insulin doses were similar in the two trial groups at 12 and 24 months (Table 2). In addition, results for the clinical end points of blood pressure, lipid profile, and BMI percentile were similar in the two groups at 12 and 24 months.

TECHNOLOGY USAGE

In the closed-loop group, the median percentage of time using continuous glucose monitoring was 81% (interquartile range, 66 to 91) and the median percentage of time using the closed-loop system was 76% (interquartile range, 60 to 85) over the 24-month period for the two closed-loop platforms (Table S10). At 12 months, 4 of 39 participants (10%) in the control group were using insulin-pump therapy and 21 of 37 participants (57%) were using a flash or real-time continuous glucose sensor. By 24 months, 16 of 37 participants (43%) in the control group were using insulin-pump therapy and 25 of 37 participants (68%) were using a glucose sensor (Table S11).

PER-PROTOCOL ANALYSIS

The findings of the primary analysis were similar to those of a per-protocol analysis of data from randomly assigned participants in the closed-loop group who used the system at least

60% of the time and those in the control group who did not start insulin-pump therapy (Table S12). The results of the per-protocol analysis at 24 months are provided in Table S13.

ADVERSE EVENTS

Safety-related events are summarized in Table 3. A total of 5 cases of severe hypoglycemia occurred in 3 participants assigned to the closed-loop group, and 1 case of severe hypoglycemia occurred in 1 participant assigned to the control group. There was 1 case of diabetic ketoacidosis in the closed-loop group and none in the control group. Details of the events are provided in Table S14. A total of 6 non-treatment-related serious adverse events occurred in the closed-loop group, and 4 occurred in the control group. A total of 123 other adverse events (62 in the closed-loop group and 61 in the control group) were reported.

UNSCHEDULED PARTICIPANT CONTACTS

More unscheduled contacts were recorded in the closed-loop group than in the control group. The majority of such contacts were related to device issues, but reporting of unscheduled contacts was inconsistent between sites and within sites longitudinally.

DISCUSSION

The present trial showed that closed-loop glucose control over a period of up to 24 months did not slow the decline in C-peptide secretion in children and adolescents with new-onset type 1 diabetes. Stimulated C-peptide levels declined in both the closed-loop group and the control group by 12 months, with further decline by 24 months. The percentage of participants with negative C-peptide stimulation in response to a mixed-meal tolerance test also increased over time and was similar in the two groups. The stimulated C-peptide levels at 12 months in the present trial (0.35 pmol per milliliter in the closed-loop group and 0.46 pmol per milliliter in the control group) are in keeping with those in the trial by Buckingham et al., in which there was also no meaningful difference between a 3-day period of early intensive closed-loop glucose control, initiated within the first 7 days after diagnosis, and usual care (0.43 pmol per milliliter in the intensive group and 0.52 pmol

Table 2. Primary, Key Secondary, and Other Secondary End Points at 12 and 24 Months.*

End Point	Baseline		12 Months		24 Months		Mean Adjusted Between-Group Difference (95% CI) [†]
	Closed-Loop Group	Control Group	Closed-Loop Group	Control Group	Closed-Loop Group	Control Group	
Primary end point at 12 mo							
AUC for C-peptide level							
No. of participants evaluated	49	45	46	37	43	32	
Geometric mean (IQR) — pmol/ml [‡]	0.56 (0.41 to 0.74)	0.64 (0.43 to 0.81)	0.35 (0.16 to 0.49)	0.46 (0.22 to 0.69)	0.18 (0.06 to 0.22)	0.24 (0.05 to 0.30)	-0.04 (-0.14 to 0.06)
Key secondary end points at 12 mo							
Time in the target glucose range of 70–180 mg/dL [§]							
No. of participants evaluated	50	43	44	33	42	30	
Mean — %	74±14	72±13	64±14	54±23	64±15	49±18	14 (6 to 21)
Glycated hemoglobin level							
No. of participants evaluated	51	46	46	39	47	36	
Mean — mmol/mole	94±20	91±17	52±8	56±12	52±11	63±16	-11 (-15 to -7)
Mean — %	10.7±1.8	10.5±1.6	6.9±0.7	7.3±1.1	6.9±1.0	8.0±1.4	-1.0 (-1.5 to -0.5)
Time with a glucose level of <70 mg/dL ^{¶¶}							
No. of participants evaluated	50	43	44	33	42	30	
Mean — %	9.1±6.3	10.7±7.1	6.2±3.8	5.4±4.7	11.2±7.3	7.5±6.7	2.8 (-0.6 to 6.2)
Other secondary end points							
Sensor glucose end points [§]							
No. of participants evaluated	50	43	44	33	42	30	
Glucose level — mg/dl	130±29	125±29	152±29	176±59	142±34	176±47	-31 (-50 to -11)
Standard deviation of the glucose level — mg/dl	49±13	49±15	64±16	67±25	66±24	72±24	-8 (-18 to 3)
Coefficient of variation of the glucose level — %	38±7	39±7	42±7	39±8	46±9	41±8	4 (0 to 8)

Table 2. (Continued.)

End Point	Baseline		12 Months		24 Months (all end points secondary)		Mean Adjusted Between-Group Difference (95% CI) [†]
	Closed-Loop Group	Control Group	Closed-Loop Group	Control Group	Closed-Loop Group	Control Group	
Lipid profile [¶]							
No. of participants evaluated	46	44	42	38	44	33	
Total cholesterol — mg/dl	172±28	172±29	149±19	153±26	148±21	149±27	1 (-10 to 12)
Triglycerides — mg/dl	74±23	73±26	64±19	68±30	63±19	66±28	-6 (-29 to 16)
HDL cholesterol — mg/dl	60±10	59±9	55±9	57±12	55±10	55±11	0 (-6 to 7)
LDL cholesterol — mg/dl ^{††}	96±24	97±25	80±12	82±23	81±19	81±19	3 (-18 to 24)

* Plus-minus values are means ±SD. To convert the values for glucose, cholesterol, and triglycerides to millimoles per liter, multiply by 0.05551, 0.02586, and 0.01129, respectively. AUC denotes area under the curve, CI confidence interval, HDL high-density lipoprotein, IQR interquartile range, and LDL low-density lipoprotein.

† Mean adjusted between-group differences were based on a linear model that was adjusted for baseline value, sex, the presence or absence of diabetic ketoacidosis at diagnosis, and age as fixed effects and clinical site as a random effect. Confidence intervals for primary and key secondary end points were not adjusted for multiple comparisons and may not be used in place of hypothesis testing. Confidence intervals for other secondary end points were adjusted for multiple comparisons.

‡ Analysis of geometric means was performed with the use of log-transformed values. All randomly assigned participants had the AUC for the C-peptide level measured at either baseline or follow-up and were included in the primary analysis.

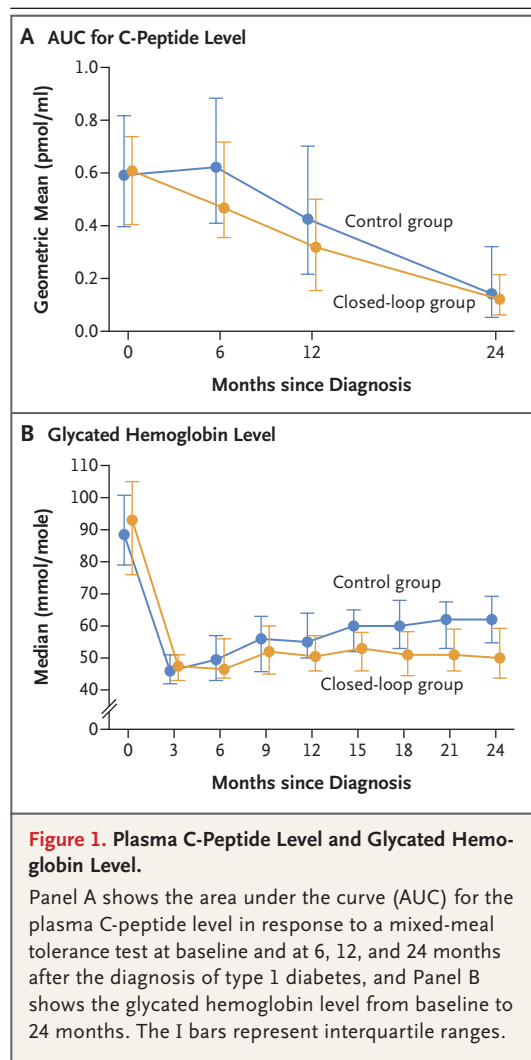
§ Values are based on blinded sensor glucose data provided by FreeStyle Libre Pro over a period of up to 14 days. Three participants who underwent randomization (one in the closed-loop group and two in the control group) did not have any sensor glucose readings and were excluded from sensor glucose analyses.

¶ The variable was Winsorized at the 10th and 90th percentiles.

|| The variable was calculated from samples collected during a mixed-meal tolerance test.

** The fasting C-peptide level was measured in femtomoles per milliliter, and the fasting glucose level was measured in milligrams per deciliter.

†† For LDL cholesterol, the number of participants evaluated at 12 months was 41 in the closed-loop group and 36 in the control group, and the number evaluated at 24 months was 42 and 33, respectively.



per milliliter in the control group).⁸ However, because glycemic control in the trial by Buckingham et al. was similar in the two groups after the initial intensive period, the trial investigators were not able to determine the effect of a sustained period of intensive glucose control on C-peptide secretion.⁸

In our trial, total daily exogenous insulin requirements, a surrogate marker of residual insulin secretion, were similar in the two groups at all time points after diagnosis. However, this comparison may be hampered by any between-group differences in glycemic control.

The mean time in the target glucose range was 10 percentage points higher and the mean glycated hemoglobin level was 0.4 percentage points (4 mmol per mole) lower in the closed-

loop group than in the control group at 12 months, but these results did not reach the pre-specified significance thresholds, and it is possible that a greater improvement in glucose control with attainment of normoglycemia could prevent the decline in C-peptide secretion.¹⁸ Further research is needed to definitively rule out a role of glycemic burden in the decline of C-peptide secretion. In addition, the greater mean time below the target glucose range and greater mean glycemic coefficient of variation observed in the closed-loop group may have reduced beta-cell viability.¹⁹

It is likely that factors other than glycemic control, such as autoimmune response, affect the rate of C-peptide decline after diagnosis of type 1 diabetes and that closed-loop glucose control for 24 months after diagnosis is unable to preserve endogenous insulin secretion. It is possible that other factors act in concert with dysglycemia on C-peptide secretion.

The present trial showed that hybrid closed-loop therapy was effective in new-onset type 1 diabetes in youths and can safely accommodate the variability in exogenous insulin requirements that occur with beta-cell recovery after diagnosis. Intensive glycemic control was sustained over a period of 2 years in the closed-loop group, whereas glycemic control started to deteriorate in the control group 6 to 9 months after diagnosis (Fig. 1). At 12 months after diagnosis, only 56% of youths in the control group (78% in the closed-loop group) had a glycated hemoglobin level of less than 58 mmol per mole (<7.5%), which is above the current national and international glycemic targets.^{16,20} This declined further to 39% of the control group at 24 months (74% in the closed-loop group) despite high uptake of pump therapy (43%) and glucose sensor devices (68%) in the control group. Analysis of data from the Epidemiology of Diabetes Interventions and Complications study suggests a reduced risk of renal and cardiovascular complications with earlier implementation of intensive therapy as compared with later implementation, despite similar overall glycemic control.²¹ These findings highlight the need for improved therapies to allow youths to reach recommended glycemic targets from the onset of type 1 diabetes, irrespective of the lack of effect on residual C-peptide secretion.

Strengths of our trial include the multicenter,

Table 3. Safety Outcomes during the 24-Month Intervention Period.*

Event	Closed-Loop Group (N=51)	Control Group (N=46)	P Value†
Severe hypoglycemia			
Total no. of events	5	1	
No. of events per participant	0.10±0.41	0.02±0.15	0.17
Incidence rate per 100 person-yr	5.4	1.2	0.18
No. of participants with ≥1 event (%)	3 (6)	1 (2)	0.62
Diabetic ketoacidosis			
Total no. of events	1	0	
No. of events per participant	0.02±0.14	0.00±0.00	0.98
Incidence rate per 100 person-yr	1.1	0.0	0.98
No. of participants with ≥1 event (%)	1 (2)	0	>0.99
Serious adverse events			
Total no. of events	6	4	
No. of events per participant	0.12±0.38	0.09±0.28	0.64
Other adverse events			
Total no. of events	62	61	
No. of events per participant	1.22±1.84	1.33±2.09	0.63

* Plus–minus values are means ±SD. The safety cohort included all enrolled participants. However, comparisons of safety outcomes occurring on or after randomization are restricted to participants who had undergone randomization. No adverse events were reported in the four participants who were enrolled but did not undergo randomization.

† For binary outcomes, P values are based on Fisher's exact test. For count variables and incidence rates, P values are based on a repeated-measures Poisson regression model.

parallel-group, randomized design and the 2-year trial duration. We applied no exclusions at enrollment such as proficiency in the use of technology or health care professional considerations about suitability, which minimized selection bias. The trial population was representative of the general population of youths with newly diagnosed type 1 diabetes (Table S15). There were no limitations to diabetes therapies used in the control group, which supports the generalizability of the findings.

Our trial has limitations. There was no central measurement of autoantibodies at diagnosis. There was an imbalance in the incidence of diabetic ketoacidosis at diagnosis, and diabetic ketoacidosis is associated with a more rapid decline in C-peptide secretion.²² The incidence of diabetic ketoacidosis was higher in the closed-loop group (33%) than in the control group (24%), but we adjusted for this difference in the analyses. Retention of participants was lower in the control group, which may reflect a lower level of motivation, than in the closed-loop group, but this was within the anticipated with-

drawal rate for the analysis of the primary end point. There were missing data points related to national restrictions caused by the coronavirus disease 2019 pandemic. We recorded a higher number of unscheduled contacts in the closed-loop group than in the control group. Recording of these contacts was inconsistent longitudinally within and among clinical sites, which prevents coherent interpretation.

In this trial, a sustained period of hybrid closed-loop glucose control after diagnosis of type 1 diabetes in children and adolescents did not appear to prevent the decline in residual C-peptide secretion.

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

Supported by the National Institute for Health and Care Research (NIHR) Efficacy and Mechanism Evaluation Programme (14/23/09), the Helmsley Charitable Trust (2016PG-T1D045 and 2016PG-T1D046), and JDRF (22-2013-266 and 2-RSC-2019-828-M-N). Additional support for the artificial pancreas work was provided by the NIHR Cambridge Biomedical Research Centre and the NIHR Oxford Biomedical Research Centre.

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 participants for their involvement in the trial, the staff at the Cambridge Clinical Research Centre for their assistance, and the members of the data and safety monitoring board and trial steering committee for their oversight of the trial.

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