ORIGINAL ARTICLE

Closed-Loop Insulin Delivery for Glycemic Control in Noncritical Care

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ABSTRACT

BACKGROUND

In patients with diabetes, hospitalization can complicate the achievement of recommended glycemic targets. There is increasing evidence that a closed-loop delivery system (artificial pancreas) can improve glucose control in patients with type 1 diabetes. We wanted to investigate whether a closed-loop system could also improve glycemic control in patients with type 2 diabetes who were receiving noncritical care.

METHODS

In this randomized, open-label trial conducted on general wards in two tertiary hospitals located in the United Kingdom and Switzerland, we assigned 136 adults with type 2 diabetes who required subcutaneous insulin therapy to receive either closed-loop insulin delivery (70 patients) or conventional subcutaneous insulin therapy, according to local clinical practice (66 patients). The primary end point was the percentage of time that the sensor glucose measurement was within the target range of 100 to 180 mg per deciliter (5.6 to 10.0 mmol per liter) for up to 15 days or until hospital discharge.

RESULTS

The mean (±SD) percentage of time that the sensor glucose measurement was in the target range was 65.8±16.8% in the closed-loop group and 41.5±16.9% in the control group, a difference of 24.3±2.9 percentage points (95% confidence interval [CI], 18.6 to 30.0; P<0.001); values above the target range were found in 23.6±16.6% and 49.5±22.8% of the patients, respectively, a difference of 25.9±3.4 percentage points (95% CI, 19.2 to 32.7; P<0.001). The mean glucose level was 154 mg per deciliter (8.5 mmol per liter) in the closed-loop group and 188 mg per deciliter (10.4 mmol per liter) in the control group (P<0.001). There was no significant between-group difference in the duration of hypoglycemia (as defined by a sensor glucose measurement of <54 mg per deciliter; P=0.80) or in the amount of insulin that was delivered (median dose, 44.4 U and 40.2 U, respectively; P=0.50). No episode of severe hypoglycemia or clinically significant hyperglycemia with ketonemia occurred in either trial group.

CONCLUSIONS

Among inpatients with type 2 diabetes receiving noncritical care, the use of an automated, closed-loop insulin-delivery system resulted in significantly better glycemic control than conventional subcutaneous insulin therapy, without a higher risk of hypoglycemia. (Funded by Diabetes UK and others; ClinicalTrials.gov number, NCT01774565.)

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The burden of diabetes is increasing worldwide,[1] as is the proportion of patients with diabetes in hospitals. More than one quarter of hospitalized patients in the United States and other developed countries have diabetes.[2-4] In such patients, the achievement of recommended glycemic targets[5,6] is complicated by variable metabolic responses to acute illness, changes in the amounts and timing of dietary intake, nutritional support, and drug-induced temporally rapid alterations in insulin sensitivity from medications such as glucocorticoids.[7-9]

Strong associations have been reported between the rate of hyperglycemia among inpatients and an increased length of hospital stay and increased rates of complications and death.[10,11] Although the correction of hyperglycemia diminishes the risk of adverse clinical outcomes,[12] conventional insulin therapy increases the risk of hypoglycemia, which is associated with increased morbidity and length of hospital stay.[13] The implementation of current guidelines for inpatient glycemic management is hindered by the need for vigilant and constant blood glucose monitoring and the administration of insulin with meals, which increases the workload of hospital staff members and reduces staff adherence.[5,6] Consequently, glycemic control in hospitalized patients is often inadequate,[2,14] which has spurred the development of more effective and safe management strategies.[15]

An automated system that delivers insulin in response to glucose levels can address this need. Closed-loop glucose control (also known as the artificial pancreas) consists of a continuous glucose monitor and an insulin pump, coupled with a control algorithm that directs insulin delivery on the basis of real-time sensor glucose measurements.[16] Such autonomous glucose control obviates the need for the input of hospital staff members. There is increasing evidence that closed-loop technology improves glucose control in patients with type 1 diabetes.[17,18] In the critical care setting, closed-loop technology has been evaluated for intravenous insulin delivery.[19,20] However, for staffing and safety reasons, subcutaneous insulin delivery has been feasible and pragmatic in patients receiving noncritical care.[21] Here, we report the results of a two-center, randomized, open-label trial of closed-loop insulin delivery without meal-associated bolus administration in a diverse cohort of patients receiving noncritical care. We hypothesized that closed-loop insulin delivery would be safe and improve glycemic control without increasing the risk of hypoglycemia.

Methods

Patients

From August 2, 2016, to December 11, 2017, we recruited patients on general wards at the University Hospital in Bern, Switzerland, and at Addenbrooke's Hospital in Cambridge, United Kingdom. Inclusion criteria included an age of 18 years or older and inpatient hyperglycemia requiring subcutaneous insulin therapy. Exclusion criteria were type 1 diabetes, pregnancy or breast-feeding, and any physical or psychological disease or the use of medication that was likely to interfere with the conduct of the trial or the interpretation of the results. Inpatients were identified through hospital electronic records. All the patients provided written informed consent before the initiation of trial procedures.

Trial Design

We randomly assigned the patients to receive insulin by means of a fully automated, closed-loop system (closed-loop group) or conventional subcutaneous therapy (control group). Patients were followed for a maximum of 15 days or until hospital discharge. Randomization was performed by means of the minimization method with the use of Minim randomization software,[22] which is a biased-coin approach with a probability of 0.7 to 0.8 for allocation of the "best fitting" treatment. Randomization was stratified according to glycated hemoglobin level, body-mass index (the weight in kilograms divided by the square of the height in meters), and pretrial total daily insulin dose to balance the two groups. Investigators who analyzed the trial data were aware of the trial-group assignments.

Trial Procedures

The body weight, height, and total daily insulin dose were recorded for each patient after enrollment. Throughout the trial, the patients chose standard hospital meals at usual mealtimes, according to local practice. The patients were free to consume other meals and snacks and were unrestricted in their usual activity on the general ward. In the two groups, glucose levels were

measured with the use of a continuous glucose monitor (Freestyle Navigator II, Abbott Diabetes Care). A glucose sensor was inserted subcutaneously into the abdomen or upper arm by the investigator and calibrated according to the manufacturer's instructions. Point-of-care capillary glucose measurements (StatStrip Glucose Hospital Meter System, Nova Biomedical, or Accu-Chek Inform II, Roche Diagnostics) were performed by nursing staff members according to local clinical practice in the two trial groups.

CLOSED-LOOP INSULIN DELIVERY

Investigators discontinued each patient's usual insulin therapy and sulfonylurea medication, if prescribed, on the day of closed-loop initiation. All other medications were continued. The investigator inserted a subcutaneous cannula into the abdomen for delivery of a rapid-acting insulin analogue (Humalog, Eli Lilly, or NovoRapid, Novo Nordisk) by means of a trial pump (Dana Diabecare R, Sooil). The investigator initialized the control algorithm by using the patient's weight and pretrial total daily insulin dose. When sensor readings became available, the investigator initiated automated closed-loop glucose control, which continued for up to 15 days. A low-glucose sensor alarm on the continuous glucose-monitoring receiver was initialized at a threshold of 63 mg per deciliter (3.5 mmol per liter).

The automated closed-loop system consisted of a model predictive control algorithm (version 0.3.70) residing on a control algorithm device (Dell Latitude 10 Tablet, Dell) linked by a USB cable to the continuous glucose-monitoring receiver (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The tablet device communicated with the pump by means of a Bluetooth wireless communication protocol. No prandial insulin boluses were delivered, and the timing or carbohydrate content of meals was not included in the control algorithm. (Additional details regarding the closed-loop system are provided in the Supplementary Appendix.)

At the end of the closed-loop period, patients completed a brief questionnaire to evaluate their satisfaction and trust of automated glucose control with the closed-loop system, their acceptance of wearing trial devices, and their views as to whether they would recommend the technology to other patients. Conventional insulin therapy and sulfonylurea medication were resumed at the end of closed-loop use as appropriate.

CONVENTIONAL INSULIN THERAPY

For each patient, the usual insulin and other antihyperglycemic therapies were continued throughout the trial period. To reflect usual care, the continuous glucose monitor was masked to the patient, investigators, and hospital staff members. Each patient's glucose control was managed by the clinical team, according to local clinical practice on the basis of capillary glucose measurements. The clinical team was allowed to modify and adjust each patient's insulin and other antihyperglycemic therapies and to initiate additional point-of-care capillary glucose measurements as appropriate.

TRIAL OVERSIGHT

The protocol (available at NEJM.org) was approved by the local research ethics committee at each center and by regulatory authorities in Switzerland (Swissmedic) and in the United Kingdom (Medicines and Healthcare Products Regulatory Agency). The safety aspects of the trial were overseen by an independent data and safety monitoring board. The trial was performed in accordance with the principles of the Declaration of Helsinki.

Abbott Diabetes Care supplied discounted continuous glucose-monitoring devices, sensors, and details regarding the communication protocol to facilitate real-time connectivity; company representatives reviewed the manuscript before submission but otherwise had no role in the trial conduct. All the authors participated in the design of the trial or provided patient care and obtained samples. The first, second, and last author wrote the first draft of the manuscript. The last author designed and implemented the control algorithm, and all the authors critically reviewed the manuscript. The first and last authors vouch for the completeness and accuracy of the data and analyses and for the adherence of the trial to the protocol. All the authors made the decision to submit the manuscript for publication.

PRIMARY AND SECONDARY OUTCOMES

The primary outcome was the percentage of time that the sensor glucose measurement was in the target glucose range of 100 to 180 mg per deciliter (5.6 to 10.0 mmol per liter) for up to 15 days or until hospital discharge. Secondary outcomes

were the percentage of time that the sensor glucose measurement was either above or below the target range; the percentage of time spent above 360 mg per deciliter (20.0 mmol per liter), below 70 mg per deciliter (3.9 mmol per liter), below 54 mg per deciliter (3.0 mmol per liter), and below 50 mg per deciliter (2.8 mmol per liter); the area under the curve below 63 mg per deciliter (3.5 mmol per liter) and below 54 mg per deciliter; the mean daily sensor glucose measurement; and the total daily insulin dose. We used data collected throughout the trial period to evaluate glucose variability according to the standard deviation and the coefficient of variation in the sensor glucose measurement. We calculated the between-day coefficient of variation in the sensor glucose measurement from daily mean glucose values (midnight to midnight). Additional secondary outcomes and exploratory analyses are described in the Supplementary Appendix.

Safety end points included clinically significant hyperglycemia (>360 mg per deciliter) with ketonemia and severe hypoglycemia (<40 mg per deciliter), as determined by point-of-care capillary measurements, along with other adverse events and serious adverse events.

STATISTICAL ANALYSIS

The trial was designed to have a power of 80% to detect a clinically significant between-group difference in the primary outcome of 20 percentage points with the use of a two-sided t-test and an alpha level of 0.05. To reflect heterogeneity among the patients, a standard deviation of ±39 for the primary outcome was used for the power calculations. We planned that 150 patients would undergo randomization in order to permit the analysis of at least 48 hours of data from 120 patients.

The intention-to-treat analysis was performed on data collected during subcutaneous insulin delivery. Data from patients who participated in a separate feasibility study[21] were not included in the present analysis. Outcomes were calculated with the use of GStat software, version 2.2 (University of Cambridge), and statistical analyses were performed with the use of SPSS software, version 21.0 (IBM). We used the unpaired t-test to compare normally distributed variables and the Mann–Whitney U test for highly skewed variables. The numbers of events that were related to a capillary glucose measurement of less than 63 mg per deciliter and 40 mg per deciliter and more than 360 mg per deciliter were tabulated in each trial group and compared with the use of Fisher's exact test. Values are reported as means (±SD) or medians (interquartile range), unless stated otherwise. All P values are two-tailed, and P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

PATIENTS

Of the 165 patients who were invited to enroll in the trial, 138 consented to participate (Fig. S2 in the Supplementary Appendix). One patient was withdrawn before randomization because of imminent hospital discharge. Of the remaining 137 patients, 70 were assigned to the closed-loop group and 67 to the control group. One patient in the control group was excluded from the analysis because the transition from intravenous insulin to subcutaneous insulin did not occur as originally planned.

The demographic and clinical characteristics of the patients were similar with respect to sex, age, body-mass index, glycated hemoglobin level, duration of diabetes, receipt of insulin, and insulin requirements (Table 1). Sepsis was the predominant reason for admission (in 43% of the patients); approximately two thirds of the patients were being treated with basal bolus insulin therapy. Additional data regarding the patients, including reasons for admission and antidiabetic treatment before randomization, are provided in Tables S1 and S2 in the Supplementary Appendix. The burden of coexisting illnesses was significantly higher in the closed-loop group than in the control group, according to the mean score on the Charlson Comorbidity Index (9.4±3.4 vs. 7.0±2.8, P<0.001). Scores on this index range from 0 to 33, with a score of ≥5 indicating a severe burden of illness. Additional details are provided in Table S3 and Fig. S3 in the Supplementary Appendix.

OVERALL GLUCOSE CONTROL

The mean (±SD) percentage of time that the sensor glucose measurement was in the target glucose range (primary outcome) was 65.8±16.8% in the closed-loop group and 41.5±16.9% in the control group, for a difference of 24.3±2.9 percentage points (95% confidence interval [CI], 18.6 to 30.0;

P<0.001) (Table 2). The mean sensor glucose measurement was significantly lower in the closed-loop group than in the control group (154±29 mg per deciliter vs. 188±43 mg per deciliter; difference, 35±6 mg per deciliter; 95% CI, 23 to 47; P<0.001). Values above the target range (>180 mg per deciliter) were found in 23.6±16.6% of the patients in the closed-loop group and in 49.5±22.8% of those in the control group, a difference of 25.9±3.4 percentage points (95% CI, 19.2 to 32.7; P<0.001); there was no significant between-group difference in the time spent at levels lower than the target range (<100 mg per deciliter, P=0.37) or lower than 70 mg per deciliter (P=0.13). The burden of hypoglycemia was similar in the two groups, as measured by the area under the curve of values below 63 mg per deciliter and below 54 mg per deciliter (Table 2). There was no significant between-group difference in the median total daily insulin dose that was delivered (44.4 U in the closed-loop group and 40.2 in the control group, P=0.50). The mean glucose variability in individual patients, as measured by the standard deviation of the sensor glucose value, was significantly lower in the closed-loop group than in the control group (46 vs. 59, P<0.001) (Table 2). The mean coefficient of variation in the sensor glucose measurement between 24-hour periods was significantly lower in the closed-loop group than in the control group (15.6±8.0% vs. 21.7±12.2%, P=0.001). The 24-hour sensor glucose measurements and insulin-delivery profiles are shown in Figure 1. End points for the first 48 hours and for the period thereafter until the end of the trial are provided in Table S4 in the Supplementary Appendix.

Capillary glucose measurements that were obtained before meals and before bedtime were significantly lower in the closed-loop group than in the control group (P<0.01 for all comparisons) (Table 2). Hypoglycemic episodes with a capillary glucose measurement of less than 63 mg per deciliter, as confirmed by point-of-care measurements, occurred three times in the closed-loop group (in 3 patients) and nine times in the control group (in 8 patients). Hospital staff members treated these episodes with oral carbohydrates according to local guidelines, without the need for intravenous dextrose. As per protocol, two patients in the closed-loop group received supplemental insulin when their sensor glucose measurements were greater than 434 mg per deciliter for more than 1 hour. Supplemental insulin was not administered in the control group, since the sensor glucose measurement was masked in those patients.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Closed-Loop Group (N=70)	Control Group (N=66)
Male sex — no. (%)	50 (71)	43 (65)
Age — yr	67.7±10.1	67.1±13.0
Body-mass index†	32.7±8.2	32.3±8.1
Glycated hemoglobin		
Percentage	8.1±1.9	8.0±1.9
Mean value — mmol/mol	65±21	64±21
Duration of diabetes — yr	17.1±11.2	15.5±11.2
Duration of insulin therapy — yr	10.0±9.1	8.0±9.1
Total daily insulin dose — U	64.2±59.4	50.6±38.9

* Plus–minus values are means ±SD. There was no significant difference between the groups in the listed categories.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.

OVERNIGHT AND DAYTIME GLUCOSE CONTROL

The mean percentage of time that sensor glucose measurements were in the target range was higher in the closed-loop group than in the control group, both overnight (midnight to 8 a.m.) and during the daytime (8 a.m. to midnight). Overnight, the percentage of time was 74.0±19.3% in the closed-loop group and 54.2±25.1% in the control group, for a difference of 19.8±3.8 percentage points (95% CI, 12.2 to 27.4; P<0.001); during the daytime, the percentage of time was 61.9±18.9% and 34.9±18.6%, respectively, for a difference of 26.9±3.2 percentage points (95% CI, 20.6 to 33.3; P<0.001) (Table 3). The sensor glucose measurements were significantly lower in the closed-loop group than in the control group, both overnight and during the daytime (P<0.001 for both comparisons), as were the standard deviations of sensor glucose measurements during overnight periods (P<0.001) and daytime periods (P=0.001). In addition, the between-night and between-day coefficients of variation in the sensor glucose measurement were significantly lower in the closed-loop group than in the control group (P=0.004 for both comparisons). There was no significant between-group difference in the nocturnal and daytime burden of hypoglycemia, as measured by the area

Table 2. Primary and Secondary Outcomes.*

Outcome	Closed-Loop Group (N=70)	Control Group (N=66)	P Value
Time spent in sensor glucose measurement — %			
Within target range of 100 to 180 mg/dl: primary end point	65.8±16.8	41.5±16.9	<0.001
Mean >180 mg/dl	23.6±16.6	49.5±22.8	<0.001
Mean >360 mg/dl	1.2±4.8	2.6±7.0	0.18
Mean <100 mg/dl	10.6±6.7	9.0±13.2	0.37
Median <70 mg/dl (IQR)	0.5 (0.0–1.1)	0.0 (0.0–1.8)	0.13
Median <54 mg/dl (IQR)	0.0 (0.0–0.1)	0.0 (0.0–0.0)	0.80
Median <50 mg/dl (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.79
Glucose — mg/dl	154±29	188±43	<0.001
SD of glucose — mg/dl†	46±19	59±19	<0.001
Coefficient of variation in glucose level — %	29.4±6.4	31.5±9.3	0.13
Between-day coefficient of variation in glucose level — %	15.6±8.0	21.7±12.2	0.001
Median AUC per day for glucose level (IQR)‡			
<63 mg/dl	7.0 (0.0–298.7)	0.0 (0.0–305.7)	0.28
<54 mg/dl	0.0 (0.0–17.1)	0.0 (0.0–0.0)	0.63
Median total daily insulin dose (IQR) — U	44.4 (27.2–70.6)	40.2 (26.5–65.5)	0.50
Capillary glucose values — mg/dl§			
Before breakfast (5 to 8 a.m.)	134±32	156±58	0.009
Before lunch (11 a.m. to 1 p.m.)	175±49	227±63	<0.001
Before dinner (4 to 7 p.m.)	161±66	195±59	0.002
Before bedtime (9 p.m. to midnight)	170±54	218±81	<0.001
No. of events with capillary glucose <63 mg/dl¶	3	9	0.09

* Plus–minus values are means ±SD. To convert the values for glucose to millimoles per liter, multiply by 0.05551. IQR denotes interquartile range.
† This category of SD is an average of the variability of sensor glucose measurements for each patient, rather than the variation in the mean glucose values among patients in the trial. The category is included because an increased variability in glucose measurements has been linked to adverse medical outcomes in individual patients.
‡ The area under the curve (AUC) was calculated as the area below the respective threshold throughout the follow-up period, with normalization to a 24-hour period.
§ Capillary glucose values were recorded in 68 patients in the closed-loop group and 65 patients in the control group.
¶ The listed events occurred in 3 patients in the closed-loop group and in 8 patients in the control group.

under the curve for values below 63 mg per deciliter (P=0.86 and P=0.24, respectively).

FOLLOW-UP PERIOD AND PATIENT FEEDBACK

The mean trial follow-up period, which was defined as the period from the first sensor reading until the last sensor reading, was 7.9±3.9 days in the closed-loop group and 6.4±4.0 days in the control group (P=0.03). This time frame included suspension of the trial period in 8 patients in the closed-loop group and 3 patients in the control group because of surgery or other procedures that required transient removal of trial devices. Sensor glucose measurements were available during 96% of the follow-up period in the closed-loop group and 92% of the follow-up period in the control group (P=0.01). The closed-loop system was operational during 99% of the time when sensor glucose measurements were available.

Overall, 54 of 62 patients (87%) in the closed-loop group reported that they were happy with their glucose levels during the trial, and 61 of 62 (98%) reported that they were happy to have their glucose levels controlled automatically by the closed-loop system (Fig. S4 in the Supplementary Appendix). All 62 patients reported that they would

recommend the system to a friend or family member during hospitalization.

ADVERSE EVENTS AND DEVICE DEFICIENCIES

No episodes of severe hypoglycemia or clinically significant hyperglycemia with ketonemia occurred in either group. Adverse events that were related to trial devices occurred in three patients in the closed-loop group and three patients in the control group. These events included skin irritation from sensor adhesive and bruising at cannula insertion sites. In the closed-loop group, device deficiencies included sensor failures in two patients and a pump-check error in one patient. The results for the safety end points are summarized in Table 4.

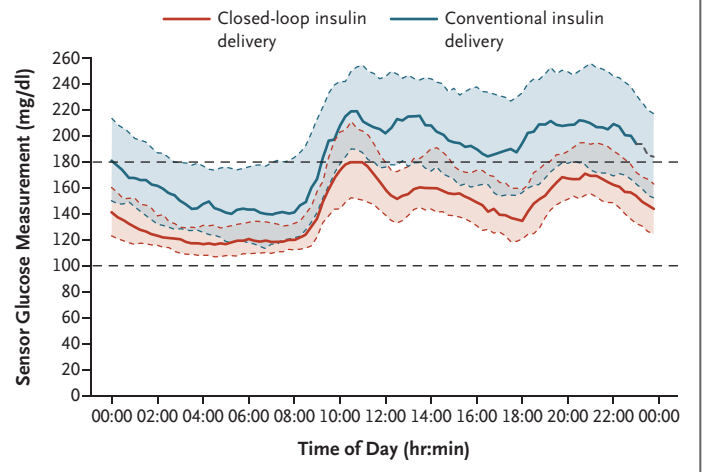
DISCUSSION

In this trial involving hospitalized patients with type 2 diabetes, those who received insulin with a fully automated, closed-loop system had significantly better glucose control than those who received standard subcutaneous insulin therapy. The percentage of time that the sensor glucose measurement was in the target range was significantly higher in the closed-loop group than in the control group, whereas the duration of hyperglycemia, the mean glucose level, and glucose variability were significantly lower. These values were achieved without changing the total daily insulin dose and without increasing the risk of hypoglycemia.

The advantage of a closed-loop system is the finely tuned, instantaneous glucose-responsive modulation of insulin delivery, with its continual adaptation to changing insulin needs during the day and between days. In contrast, conventional treatment approaches are less responsive to glucose changes and insulin needs; with tighter glycemic control, such treatments are associated with an increased risk of hypoglycemia[12,23] and adverse medical outcomes.[13] The latter is a primary concern for many health care professionals and, we speculate, may explain why many practitioners are reluctant to encourage tight glucose control.

Other techniques that address inpatient glycemic control include remote monitoring and consultation by a dedicated specialist team,[24] as well as algorithm-driven, computerized, tablet-based insulin-dosing support systems for hospital staff members.[25] Although glycemic benefits have been shown with the use of such systems, input by staff members is still required, thereby decreasing usability, given the time constraints of daily practice.

Our findings expand the results of a single-center, randomized feasibility trial that evaluated a fully automated, closed-loop system during a 72-hour period.[21] Our trial was conducted at two centers in two countries, had a longer follow-up



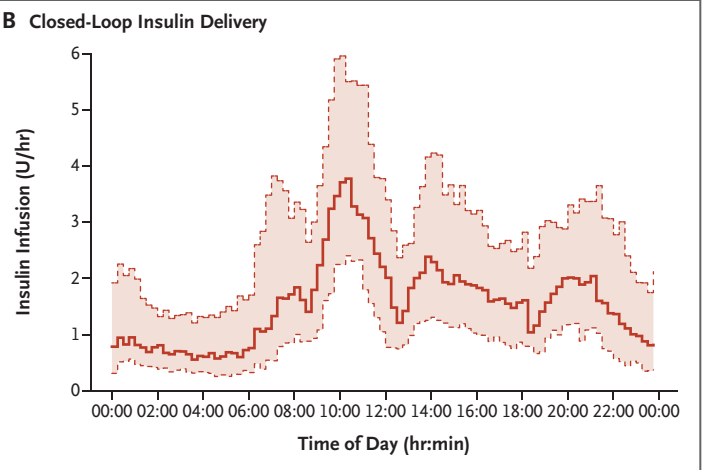


Figure 1. Sensor Glucose Measurements and Insulin Delivery.

Panel A shows median sensor glucose measurements during closed-loop insulin delivery (solid red line) and conventional subcutaneous insulin therapy (solid blue line), with the red and blue shaded areas indicating the interquartile range for each treatment. The values were measured during a 24-hour period from midnight to midnight. The lower and upper limits of the glucose target range of 100 to 180 mg per deciliter (5.6 to 10.0 mmol per liter) are indicated by black horizontal dashed lines. To convert the values for glucose to millimoles per liter, multiply by 0.05551. Panel B shows the median amount of algorithm-directed insulin delivered during the closed-loop intervention, with the shaded area indicating the interquartile range.

Table 3. Daytime and Overnight Secondary Outcomes.*

Outcome	Closed-Loop Group (N=70)	Control Group (N=66)	P Value
Overnight period from midnight to 8 a.m.			
Time spent with sensor glucose value within target range of 100 to 180 mg/dl — %	74.0±19.3	54.2±25.1	<0.001
Mean glucose — mg/dl	129±24	160±49	<0.001
SD of glucose — mg/dl	27±15	38±18	<0.001
Coefficient of variation in glucose level — %	20.7±8.4	24.4±9.6	0.02
Between-night coefficient of variation in glucose level — %	16.9±9.0	22.9±13.7	0.004
Median AUC per day below 63 mg/dl (IQR)	0.0 (0.0–39.3)	0.0 (0.0–129.3)	0.86
Median insulin dose (IQR) — U	8.0 (4.5–14.5)	ND	ND
Daytime period from 8 a.m. to midnight			
Time spent with sensor glucose value within target range of 100 to 180 mg/dl — %	61.9±18.9	34.9±18.6	<0.001
Mean glucose — mg/dl	165±36	204±46	<0.001
SD of glucose — mg/dl	46±16	57±21	0.001
Coefficient of variation in glucose level — %	27.6±5. 5	28.6±10.4	0.48
Between-day coefficient of variation in glucose level — %	14.9±8.0	20.7±14.2	0.004
Median AUC per day below 63 mg/dl	0.0 (0.0–71.7)	0.0 (0.0–0.5)	0.24
Median insulin dose (IQR) — U	36.2 (23.0–52.9)	ND	ND

* Plus–minus values are means ±SD. ND denotes that the analysis was not done, because the use of long-acting insulin in the control group did not allow for the quantification of overnight and daytime insulin doses.

period, and had a larger sample size in a considerably more diverse and complex inpatient population (including 19 patients who were receiving hemodialysis). In addition, patients in the closed-loop group in our trial did not receive long-acting basal insulin, as was the case in the feasibility study. In spite of enrolling a more challenging and more diverse inpatient population, we found that patients in the closed-loop group spent a higher percentage of time within the glycemic target range than those in the control group (a between-group difference of 24 percentage points in our trial vs. 21 percentage points in the feasibility trial) and a lower percentage of time above the glycemic target range (a between-group difference of 26 percentage points vs. 19 percentage points). The observed differences may be attributable to enhanced adaptive aspects of the control algorithm that we used and the longer trial duration, a hypothesis that is supported by the greater benefit accrued beyond 48 hours of closed-loop operation (Fig. S5 in the Supplementary Appendix).

A strength of our trial is that it addressed the unmet need for better glycemic control among hospitalized patients with diabetes, an issue that affects nearly all areas of in-hospital care, patient outcomes, and health care costs. The two-country design and sample size allowed for the evaluation of the safety and efficacy of closed-loop glycemic control over a wide range of disease conditions, demographic characteristics, and different health care systems.

Our trial also has some limitations. Sensor glucose measurements were more available and the trial duration was longer in the closed-loop group than in the control group. The observed imbalance may be attributable to between-group differences in the burden of coexisting illnesses (which was higher in the closed-loop group than in the control group), since the presence of such illnesses often increases the need for acute hospital care and may prolong hospitalization.[26,27] In addition, because the sensor glucose measurements were clinically unavailable in the control

Table 4. Adverse Events and Safety Analyses.*

Adverse Event	Closed-Loop Group (N=70)	Control Group (N=66)	P Value
No. of severe hypoglycemic events or other serious adverse events†	0	0	NA
No. of clinically significant hyperglycemic events‡	18	41	0.03
No. of adverse events			
Adverse trial-related device effects	3	3	ND
Other§	4	0	ND
No. of device deficiencies¶	3	0	ND

* NA denotes not applicable, and ND not done.
† Severe hypoglycemia was defined as a capillary glucose level of less than 40 mg per deciliter or an episode that required the assistance of another person.
‡ Clinically significant hyperglycemia was defined as a capillary glucose level of more than 360 mg per deciliter.
§ Other adverse events that were not related to trial interventions included gastrointestinal bleeding in three patients and hepatic encephalopathy in one patient.
¶ Device deficiencies included sensor failures in two patients and a pump-check error in one patient.

group, any loss of connectivity between the sensor and the receiver device was not detected and may have contributed to the collection of fewer sensor glucose data in the control group.

As part of the translation of research regarding the closed-loop system into clinical practice, further work is required to determine practical considerations, facilitate ease of use, and assess costs. Standardized procedures will be needed to ensure the most effective transition from acute care to outpatient care.[28,29] Before closed-loop systems can have widespread use, they may need to be integrated with electronic-record systems in hospitals and with training for health care professionals.

In conclusion, in patients with type 2 diabetes who were receiving noncritical care, we found that the use of a fully automated, closed-loop insulin-delivery system resulted in better glycemic control than standard insulin therapy. In addition, the improved glucose control was achieved without increasing the risk of hypoglycemia in these patients.

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