ORIGINAL ARTICLE

A Randomized Trial of Automated Insulin Delivery in Type 2 Diabetes

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ABSTRACT

BACKGROUND

Automated insulin delivery (AID) systems have been shown to be beneficial for patients with type 1 diabetes, but data are needed from randomized, controlled trials regarding their role in the management of insulin-treated type 2 diabetes.

METHODS

In this 13-week, multicenter trial, adults with insulin-treated type 2 diabetes were randomly assigned in a 2:1 ratio to receive AID or to continue their pretrial insulin-delivery method (control group); both groups received continuous glucose monitoring (CGM). The primary outcome was the glycated hemoglobin level at 13 weeks.

RESULTS

A total of 319 patients underwent randomization. Glycated hemoglobin levels decreased by 0.9 percentage points (from 8.2±1.4% at baseline to 7.3±0.9% at week 13) in the AID group and by 0.3 percentage points (from 8.1±1.2% to 7.7±1.1%) in the control group (mean adjusted difference, −0.6 percentage points; 95% confidence interval [CI], −0.8 to −0.4; P<0.001). The mean percentage of time that patients were in the target glucose range of 70 to 180 mg per deciliter increased from 48±24% to 64±16% in the AID group and from 51±21% to 52±21% in the control group (mean difference, 14 percentage points; 95% CI, 11 to 17; P<0.001). All other multiplicity-controlled CGM outcomes reflective of hyperglycemia that were measured were significantly better in the AID group than in the control group. The frequency of CGM-measured hypoglycemia was low in both groups. A severe hypoglycemia event occurred in one patient in the AID group.

CONCLUSIONS

In this 13-week, randomized, controlled trial involving adults with insulin-treated type 2 diabetes, AID was associated with a greater reduction in glycated hemoglobin levels than CGM alone. (Funded by Tandem Diabetes Care; 2IQP ClinicalTrials.gov number, NCT05785832.)

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The benefits of automated insulin delivery (AID) systems are well established in patients with type 1 diabetes.[1-8] However, the efficacy and safety of this technology in those with type 2 diabetes has not been established. Although promising results of AID in type 2 diabetes have been reported, patients have been evaluated either in uncontrolled trials or in short crossover trials with small sample sizes.[9-17]

Treatment with medications such as glucagon-like peptide 1 (GLP-1) receptor agonists and sodium–glucose cotransporter 2 (SGLT2) inhibitors has enabled more patients with type 2 diabetes to have glycated hemoglobin levels below the American Diabetes Association target of 7%.[18] Even so, a substantial proportion of those with type 2 diabetes who have elevated glycated hemoglobin levels may benefit from using an AID system.

We conducted the Randomized Trial Evaluating the Efficacy and Safety of Control-IQ+ Technology in Adults with Type 2 Diabetes Using Basal-Bolus Insulin Therapy (2IQP) to evaluate the efficacy and safety of AID in adults with type 2 diabetes who were receiving multiple daily injections of insulin or using an insulin pump.

Methods

Trial Conduct and Oversight

This multicenter, randomized, controlled trial was conducted at 21 centers in the United States and Canada, including one U.S. Veterans Affairs hospital. The protocol (available with the full text of this article at NEJM.org) was approved by a central institutional review board. Written informed consent was obtained from each patient. An investigational-device exemption was approved by the Food and Drug Administration (FDA) and Health Canada. An independent data and safety monitoring board provided trial oversight.

The trial was designed by the authors in conjunction with Tandem Diabetes Care, which funded the trial and provided the automated insulin-delivery systems. Company representatives provided comments on the manuscript but did not have approval authority. The insulin aspart that was used in the trial was provided by Novo Nordisk. Continuous glucose monitor sensors and transmitters were purchased from Dexcom at a discounted price.

The Jaeb Center for Health Research was the trial coordinating center and was responsible for the trial monitoring and statistical analyses. The first and last authors wrote the first draft of the manuscript, made the decision to submit the manuscript for publication, and vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. There were no agreements concerning confidentiality of the data with respect to publication rights between the sponsor and the authors or their institutions.

Trial Design and Patients

Trial patients were at least 18 years old and had had type 2 diabetes for at least 6 months, according to clinical history and available laboratory data. All the patients were receiving multiple daily injections of insulin with at least one injection containing rapid-acting insulin per day or were using an insulin pump for at least 3 months before enrollment. Mixed insulin use with a rapid-acting component was allowed. Concurrent treatment with noninsulin glucose-lowering medications or weight-reduction medications was permitted, provided the dose had been stable for the previous 3 months; during the trial, these medications were continued in both treatment groups. Details regarding admission criteria, patient characteristics, and recruitment goals are provided in Tables S1 and S2 in the Supplementary Appendix, available at NEJM.org.

Patients were randomly assigned in a 2:1 ratio to receive AID or to continue their pretrial insulin-delivery method (control group); both groups received continuous glucose monitoring (CGM). Before randomization, baseline CGM data were collected while the patients continued to receive their pretrial insulin-delivery regimen.

The patients who were assigned to the AID group were provided with and trained on use of the AID system, which consisted of the t:slim X2 insulin pump with Control-IQ+ technology (Tandem) that was used in conjunction with a Dexcom G6 sensor, which together had been cleared by the FDA for use in type 1 diabetes. The patients who were assigned to the control group continued to receive their pretrial insulin-delivery regimen and used a trial-provided real-time unblinded Dexcom G6 monitor.

The patients in the AID group were contacted 2 to 4 days after they had started using the AID system to address questions and provide further training. Otherwise, the schedule of visits and contacts was the same for the two groups: virtual

visits after 7 days and 8 weeks and in-clinic visits after 4 weeks and 13 weeks. Adjustments in pump settings or in noninsulin glucose-lowering drugs were prohibited unless required for safety. Levels of glycated hemoglobin, lipids, and creatinine were measured at a central laboratory at randomization and at 13 weeks. C-peptide and glutamic acid decarboxylase (GAD) antibody levels were measured at randomization. At 13 weeks, patients in the AID group were transitioned back to their pretrial insulin-delivery method and had a follow-up contact 2 to 4 days later. Patient-reported outcome surveys were completed at screening and at 13 weeks (Table S3).

The numerate ability of the patients was assessed at baseline with a numeracy survey consisting of four items that measure patients' beliefs about their skill in performing various mathematical operations and four items that measure their preferences regarding the presentation of numerical information.[19] The scores on this survey range from 1 to 6, with higher scores indicating a better perceived numerate ability.

OUTCOMES

The primary efficacy outcome was the glycated hemoglobin level at 13 weeks. The following key secondary outcomes, measured by means of CGM over the 13 weeks of the trial, were tested with the use of a hierarchical-testing procedure to preserve the overall type 1 error: the percentage of time that patients' glucose levels were in the range of 70 to 180 mg per deciliter (3.9 to 10 mmol per liter); the percentage of time with a mean sensor glucose value of more than 180 mg per deciliter and more than 250 mg per deciliter (13.9 mmol per liter); a prolonged hyperglycemia event, which was defined as 90 cumulative minutes or more with a CGM glucose level of more than 300 mg per deciliter (16.7 mmol per liter) within a 120-minute period; the percentage of time with a mean sensor glucose value of less than 70 mg per deciliter or less than 54 mg per deciliter (3 mmol per liter); a hypoglycemia event, which was defined as 15 consecutive minutes or more with a CGM glucose value of less than 54 mg per deciliter; and the coefficient of variation of glucose levels. Additional exploratory outcomes are listed in Table S4.

Safety outcomes included the frequency of severe hypoglycemia, diabetic ketoacidosis, hyperosmolar hyperglycemic syndrome, other serious adverse events, and device malfunctions, including infusion-set failures and unanticipated problems with the device.

STATISTICAL ANALYSIS

We determined that an overall sample size of 300 patients who completed the trial would provide the trial with 90% power to detect a between-group difference in the glycated hemoglobin level of 0.38 percentage points at 13 weeks. In making this determination, we assumed a standard deviation of 1.0 for the mean glycated hemoglobin level at 13 weeks, a correlation of 0.3 for the comparison between baseline and 13-week glycated hemoglobin levels, and a type I error of 5%.

Statistical analyses were performed on an intention-to-treat basis. The primary and other analyses of continuous variables compared the AID and control groups with the use of a linear mixed-effects regression model after adjustment for the baseline value of the outcome variable and site (random factor). Missing data were handled with the use of the direct-likelihood method. For binary outcomes, risk-adjusted percentages were computed according to treatment group at 13 weeks from a logistic-regression model, with adjustment for the baseline level of the outcome and site with the use of generalized estimating equations.

For outcomes that were not part of the hierarchy to control for the type I error rate, P values are not reported; confidence intervals around point estimates in each treatment group were adjusted by means of the adaptive Benjamini–Hochberg procedure but do not represent hypothesis testing. All analyses were performed with the use of SAS software, version 9.4. Additional statistical methods are listed in Table S4 and are detailed in the statistical analysis plan in the protocol.

RESULTS

PATIENTS AND FOLLOW-UP

From June 1, 2023, to June 21, 2024, a total of 319 patients were randomly assigned to the AID group (215 patients) or the control group (104 patients). The age range was 19 to 87 years, the interval since the diabetes diagnosis was 1 to 59 years, and the glycated hemoglobin level at baseline ranged from 5.2 to 14.1% (mean [±SD] value, 8.2±1.3%). A total of 39% of the patients reported being a member of a racial or ethnic minority group.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	AID Group (N=215)	Control Group (N=104)
Age — yr		
Mean	59±12	57±12
Range	19–87	23–80
Female sex — no. (%)	105 (49)	49 (47)
Race or ethnic group — no. (%)†		
White	148 (69)	74 (71)
Black	45 (21)	24 (23)
Asian	10 (5)	3 (3)
Native Hawaiian or other Pacific Islander	2 (1)	0
American Indian or Alaska Native	1 (<1)	1 (1)
More than one race or ethnic group	6 (3)	2 (2)
Unknown or not reported	3 (1)	0
Hispanic or Latino — no. (%)†		
Yes	23 (11)	11 (11)
No	190 (88)	93 (89)
Unknown or not reported	2 (1)	0
Education level — no. (%)		
Less than bachelor's degree	123 (57)	52 (50)
Bachelor's degree	49 (23)	32 (31)
More than bachelor's degree	33 (15)	16 (15)
Unknown or did not wish to provide	10 (5)	4 (4)
Annual household income in U.S. dollars — no. (%)		
<$50,000	60 (28)	26 (25)
$50,000 to $100,000	52 (24)	21 (20)
>$100,000	53 (25)	36 (35)
Unknown or did not wish to provide	50 (23)	21 (20)
Health insurance — no. (%)		
Private	116 (54)	65 (62)
Medicare	57 (27)	15 (14)
Medicaid	10 (5)	13 (12)
Other government insurance	23 (11)	8 (8)
No coverage	2 (1)	2 (2)
Unknown	7 (3)	1 (1)
Diabetes duration — yr		
Median (IQR)	18 (11–26)	18 (11–24)
Range	1–59	2–45
Body-mass index‡		
Median (IQR)	33 (29–40)	35 (29–40)
Range	19–56	20–57

Table 1. (Continued.)

Characteristic	AID Group (N=215)	Control Group (N=104)
Glycated hemoglobin level§		
Distribution — no. (%)		
<7.0%	28 (13)	15 (14)
7.0 to <8.0%	73 (34)	40 (38)
8.0 to <9.0%	66 (31)	24 (23)
≥9.0%	47 (22)	25 (24)
Mean value — %	8.2±1.4	8.1±1.2
Range in values — %	5.7–14.1	5.2–12.4
Insulin delivery method — no. (%)		
Multiple daily injections	206 (96)	100 (96)
Insulin pump	9 (4)	4 (4)
Noninsulin glucose-lowering medication — no. (%)¶		
Metformin	109 (51)	61 (59)
SGLT2 inhibitor	76 (35)	41 (39)
GLP-1 receptor agonist	87 (40)	54 (52)
SGLT2 inhibitor and GLP-1 receptor agonist	44 (20)	24 (23)
Other	9 (4)	10 (10)
Use of CGM — no. (%)		
Current	147 (68)	78 (75)
In past, but not current	40 (19)	16 (15)
Never	28 (13)	10 (10)

* Plus–minus values are means ±SD. AID denotes automated insulin delivery, CGM continuous glucose monitoring, GLP-1 glucagon-like peptide 1, IQR interquartile range, and SGLT2 sodium–glucose cotransporter 2.
† Race or ethnic group was reported by the patients.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The glycated hemoglobin level was missing for one patient in the AID group.
¶ Patients can be included in multiple categories, so percentages may not total 100%.

Multiple daily injections of insulin were used by 96% of the patients and an insulin pump by 4%; 75% were receiving fixed-dose insulin injections at mealtime (without carbohydrate counting), and 71% were using CGM. A GLP-1 receptor agonist (or dual gastric inhibitory polypeptide and GLP-1 receptor agonist) was being used by 44%, an SGLT2 inhibitor by 37%, and medications in both classes by 21%. The AID and control groups appeared to be well balanced with respect to baseline characteristics (Table 1 and Table S5). The relevance and representativeness of the trial population is discussed in the Supplementary Appendix, as noted in Table S6.

The 13-week trial was completed by 211 of 215 patients (98%) in the AID group and by 102 of 104 patients (98%) in the control group (Fig. S1 and Table S7). Among the patients who completed the trial, completion rates of trial visits and contacts were 99% in each group. There were 717 unscheduled visits or contacts related to diabetes management, device use, or an adverse event by 174 patients (81%) in the AID group and 167 unscheduled visits or contacts by 74 patients (71%) in the control group.

DEVICE USE

In the AID group, 15 patients (7%) discontinued the AID system before 13 weeks but remained in the trial through the 13-week visit (Table S8).

In the AID group, the median percentage of time that the system was in automated insulin-delivery mode was 93% (interquartile range, 87 to 95), use that was consistent throughout the 13 weeks (Table S9). In the control group, 96% of the patients received multiple daily injections of insulin and 4% used a personal insulin pump without automation; CGM data were available for a median of 96% (interquartile range, 91 to 98) of possible time during 13 weeks of follow-up.

EFFICACY OUTCOMES

Glycated Hemoglobin

The mean glycated hemoglobin level at 13 weeks (primary outcome) decreased by 0.9 percentage points (from 8.2±1.4% at baseline to 7.3±0.9% at week 13) in the AID group and by 0.3 percentage points (from 8.1±1.2% to 7.7±1.1%) in the control group (Table 2 and Fig. S2). The mean adjusted difference in glycated hemoglobin level at 13 weeks in the AID group as compared with the control group was −0.6 percentage points (95% confidence interval [CI], −0.8 to −0.4; P<0.001). Very similar results were obtained in per-protocol analyses, sensitivity analyses, analyses that excluded patients with GAD antibodies, and analyses that were limited to those with a baseline total daily insulin dose of 100 units or more (Tables S10 through S13). Reductions in glycated hemoglobin levels from baseline by more than 0.5 percentage points occurred in 59% of patients in the AID group and in 30% of those in the control group (Table S14).

An evident benefit of AID as compared with only CGM was observed across a broad range of baseline characteristics, including age, sex, race or ethnic group, body-mass index, income, education, pump or injection use, CGM use, total daily insulin dose, and use of noninsulin glucose-lowering medications (Fig. 1). The treatment effect appeared to be greater among patients who had increased glycated hemoglobin levels at baseline. Among the patients with a baseline glycated hemoglobin level of 9.0% or higher, the mean glycated hemoglobin level was reduced from 10.3% to 7.9% in the AID group and from 9.7% to 8.6% in the control group (mean difference, −1.0 percentage point; 95% CI, −1.5 to −0.5). Among the patients who were receiving GLP-1 receptor agonists at baseline, the mean change in the glycated hemoglobin level was −0.8±0.9% in the AID group (85 patients) as compared with −0.3±0.8% in the control group (53 patients). Among the patients who were receiving SGLT2 inhibitors at baseline, the mean change in the glycated hemoglobin level was −0.8±0.9% in the AID group (72 patients) and −0.2±0.7% in the control group (41 patients). Among users of both GLP-1 receptor agonists and SGLT2 inhibitors, the mean change in the glycated hemoglobin level was −0.8±1.0% in the AID group (43 patients) and −0.1±0.7% in the control group (24 patients).

Of note, the treatment effect appeared to be similar among the patients who were receiving fixed doses of insulin and those who were counting carbohydrates for meal boluses before the trial and among the patients with higher as compared with lower numeracy scores at baseline. A similar pattern of benefit for AID across subgroups was seen for the outcome of CGM-measured time in the glucose range of 70 to 180 mg per deciliter (Fig. S3).

CGM-Measured Outcomes

Key secondary multiplicity-controlled CGM-measured outcomes reflective of hyperglycemia were all significantly better in the AID group than in the control group. The percentage of time that patients were in the target glucose range of 70 to 180 mg per deciliter increased from 48±24% at baseline to 64±16% at 13 weeks in the AID group and from 51±21% to 52±21%, respectively, in the control group (mean difference, 14 percentage points; 95% CI, 11 to 17; P<0.001) (Table 2). This difference represents a mean time in the target glucose range that was 3.4 hours per day longer in the AID group than in the control group. The treatment effect was evident in the first week and consistent over 3 months (Fig. 2A). Other secondary outcomes that were lower in the AID group were the mean glucose level at 13 weeks, the percentage of time that patients had a glucose level of more than 180 mg per deciliter or more than 250 mg per deciliter, and the frequency of prolonged hyperglycemia events (Table 2). A similar pattern was observed in other CGM-measured outcomes related to hyperglycemia (Tables S15 and S16). The treatment effect on increasing the percentage of time in the target glucose range and decreasing the mean glucose level was evident during both daytime and nighttime throughout the 24 hours of the day (Fig. 2B, Table S17, and Fig. S4). The frequency of

Table 2. Primary and Secondary Hierarchical Efficacy Outcomes.*

Outcome	At Baseline		At 13 Weeks		Adjusted Difference between Groups (95% CI)	P Value
	AID Group	Control Group	AID Group	Control Group		
Primary outcome						
No. of patients evaluated	214†	104	209‡	102§		
Glycated hemoglobin level — %	8.2±1.4	8.1±1.2	7.3 ±0.9	7.7 ±1.1	–0.6 (–0.8 to –0.4)	<0.001
Secondary hierarchical outcomes						
No. of patients evaluated	215	104	214¶	104		
Percentage of time with glucose level in range of 70 to 180 mg/dl	48±24	51±21	64±16	52±21	14 (11 to 17)	<0.001
Mean glucose level — mg/dl	194±43	190±35	170±23	188±34	–21 (–26 to –15)	<0.001
Percentage of time with glucose level of >180 mg/dl	51±25	49±21	35±16	48±21	–14 (–17 to –11)	<0.001
Percentage of time with glucose level of >250 mg/dl‖	19.5±17.3	15.8±13.6	9.7±7.8	16.7±14.1	–9.1 (–11.7 to –6.6)	<0.001
No. of prolonged hyperglycemia events per wk‖**	1.7±1.7	1.6±1.7	0.9±0.9	1.6±1.5	–0.7 (–1.0 to –0.4)	<0.001
Percentage of time with glucose level of <70 mg/dl‖	0.7±0.8	0.3±0.3	0.4±0.4	0.4±0.4	–0.1 (–0.4 to 0.1)	NS††
Percentage of time with glucose level of <54 mg/dl‖	0.16±0.16	0.05±0.05	0.09±0.09	0.09±0.10	–0.02 (–0.09 to 0.04)	NA
No. of CGM-measured hypoglycemia events per wk‖‡‡	0.2±0.3	0.1±0.0	0.1±0.2	0.1±0.2	0.0 (–0.1 to 0.0)	NA
Coefficient of variation in glucose levels — %	28±6	27±5	30±5	29±5	0.3 (–0.5 to 1.2)	NA

* Plus–minus values are means ±SD. To convert the values for glucose to millimoles per liter, multiply by 0.05551. NA denotes not applicable, and NS not significant.
† Data were missing because the sample that was obtained from one patient could not be analyzed.
‡ Four patients withdrew from the trial before the 13-week final visit. The sample for one patient could not be analyzed, and the sample for one patient was obtained outside the prespecified analysis window and thus was not included. Missing data were handled by direct-likelihood analysis so that all the patients who had undergone randomization were included in the analysis.
§ Two patients withdrew from the trial before the 13-week final visit.
¶ One patient withdrew immediately after randomization to the AID group and did not have enough follow-up CGM data.
‖ In this calculation, the outcome was skewed, so to down-weigh the outliers, the SDs were calculated with the use of a t-distribution with 10 degrees of freedom for the error distribution.
** A prolonged hyperglycemia event was defined as at least 90 cumulative minutes with a CGM glucose level of more than 300 mg per deciliter within a 120-minute period. A subsequent prolonged hyperglycemia event could be measured after the CGM glucose level was less than 180 mg per deciliter for at least 15 consecutive minutes.
†† A hierarchical procedure was used to control for the overall type I error. Since the P value for this outcome was more than 0.05, no additional P values are provided for subsequent secondary outcomes.
‡‡ A CGM-measured hypoglycemia event was defined as at least 15 consecutive minutes with a CGM glucose level of less than 54 mg per deciliter. A subsequent hypoglycemia event could be measured after the CGM glucose level was at least 70 mg per deciliter for at least 15 consecutive minutes.

Subgroup	Mean Glycated Hemoglobin Level: AID group (no.) percentage at baseline/percentage at 13 wk	Mean Glycated Hemoglobin Level: Control group (no.) percentage at baseline/percentage at 13 wk	Treatment Effect (95% CI) percentage points
Overall	(208) 8.2/7.3	(102) 8.0/7.7	−0.6 (−0.8 to −0.4)
Sex			
Female	(100) 8.4/7.4	(48) 8.0/7.7	−0.5 (−0.8 to −0.2)
Male	(108) 8.0/7.2	(54) 8.0/7.8	−0.6 (−0.9 to −0.3)
Age at enrollment			
<50 yr	(48) 8.7/7.2	(29) 8.2/7.9	−1.0 (−1.5 to −0.6)
50 to <65 yr	(83) 8.3/7.3	(48) 8.0/7.6	−0.5 (−0.8 to −0.1)
≥65 yr	(77) 7.8/7.3	(25) 7.9/7.8	−0.4 (−0.9 to 0.0)
Race or ethnic group			
White, non-Hispanic	(125) 8.0/7.1	(65) 7.9/7.8	−0.7 (−1.0 to −0.4)
Other	(82) 8.6/7.6	(37) 8.2/7.7	−0.3 (−0.7 to 0.0)
Body-mass index			
<30	(58) 8.3/7.4	(30) 8.2/7.7	−0.4 (−0.8 to 0.0)
30 to <35	(71) 8.3/7.3	(24) 8.3/7.9	−0.5 (−1.0 to −0.1)
35 to <40	(32) 7.9/7.1	(26) 7.7/7.5	−0.5 (−1.0 to 0.0)
≥40	(47) 8.3/7.3	(22) 7.9/7.9	−0.9 (−1.4 to −0.4)
Glycated hemoglobin level			
<7.0%	(28) 6.4/6.4	(15) 6.5/6.5	−0.1 (−0.7 to 0.5)
7.0 to <8.0%	(71) 7.5/7.0	(40) 7.5/7.4	−0.4 (−0.7 to 0.0)
8.0 to <9.0%	(65) 8.4/7.5	(24) 8.3/8.1	−0.7 (−1.1 to −0.3)
≥9.0%	(44) 10.3/7.9	(23) 9.7/8.6	−1.0 (−1.5 to −0.5)
Time in glucose range of 70–180 mg/dl			
≥60%	(79) 7.4/7.0	(39) 7.3/7.0	−0.1 (−0.5 to 0.2)
30 to <60%	(77) 8.2/7.4	(44) 8.1/7.9	−0.5 (−0.9 to −0.2)
<30%	(52) 9.5/7.6	(19) 9.4/8.8	−1.2 (−1.7 to −0.8)
Use of noninsulin glucose-lowering medications			
None	(46) 8.7/7.3	(12) 8.7/8.4	−1.0 (−1.6 to −0.4)
Other, but no SGLT2i or GLP-1ra	(48) 8.3/7.3	(20) 8.3/8.0	−0.7 (−1.2 to −0.2)
GLP-1ra, but no SGLT2i	(42) 8.1/7.3	(29) 7.8/7.5	−0.3 (−0.7 to 0.1)
SGLT2i, but no GLP-1ra	(29) 8.2/7.5	(17) 7.8/7.6	−0.3 (−0.8 to 0.3)
Both GLP-1ra and SGLT2i	(43) 7.9/7.1	(24) 7.8/7.7	−0.6 (−1.1 to −0.2)
Total daily insulin intake			
<100 units/day	(125) 8.3/7.3	(57) 7.9/7.6	−0.5 (−0.8 to −0.2)
100 to <150 units/day	(55) 8.1/7.2	(27) 8.2/7.9	−0.6 (−1.1 to −0.2)
150 to <200 units/day	(14) 8.0/7.5	(12) 7.7/7.9	−0.7 (−1.4 to 0.0)
≥200 units/day	(14) 7.9/7.0	(6) 8.7/7.7	−0.1 (−1.0 to 0.8)
Duration of diabetes at enrollment			
<5 yr	(10) 8.5/7.3	(9) 8.3/8.0	−0.9 (−1.7 to −0.1)
5 to <10 yr	(29) 8.5/7.2	(10) 8.4/7.8	−0.7 (−1.3 to 0.0)
10 to <20 yr	(69) 8.2/7.3	(38) 8.1/7.9	−0.7 (−1.0 to −0.3)
≥20 yr	(100) 8.1/7.3	(45) 7.8/7.5	−0.4 (−0.7 to −0.1)
Use of fixed dosing to calculate meal bolus			
Yes	(158) 8.2/7.3	(75) 8.1/7.8	−0.6 (−0.9 to −0.3)
No	(50) 8.2/7.2	(27) 7.9/7.6	−0.5 (−0.9 to −0.1)
C-peptide level			
<0.8 nmol/liter	(108) 8.3/7.3	(46) 8.3/7.9	−0.6 (−0.9 to −0.3)
≥0.8 nmol/liter	(100) 8.2/7.3	(55) 7.8/7.6	−0.5 (−0.8 to −0.2)
Score on the subjective numeracy survey			
<4.5	(89) 8.2/7.4	(43) 8.1/7.8	−0.5 (−0.9 to −0.2)
≥4.5	(119) 8.2/7.2	(59) 8.0/7.7	−0.6 (−0.9 to −0.3)
Insulin delivery before enrollment			
Multiple daily injections	(199) 8.2/7.3	(98) 8.0/7.7	−0.6 (−0.8 to −0.3)
Pump	(9) 8.1/7.2	(4) 8.2/7.9	−0.6 (−1.8 to 0.5)
Use of CGM before enrollment			
Yes	(141) 8.1/7.3	(77) 7.9/7.7	−0.5 (−0.8 to −0.3)
No	(67) 8.5/7.3	(25) 8.5/7.9	−0.6 (−1.1 to −0.2)

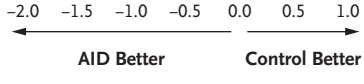

Figure 1 (facing page). Glycated Hemoglobin Level, According to Baseline Subgroup.

The forest plot shows the treatment effect on the glycated hemoglobin level in the automated insulin delivery (AID) group and in the control group that continued their pretrial insulin-delivery method, according to subgroup variable. Both groups received continuous glucose monitoring (CGM). The overall treatment effect is the between-group difference at 13 weeks, as measured in percentage points (the overall primary outcome). Point estimates to the left of the vertical dashed line indicate a lower glycated hemoglobin level in the AID group than in the control group. The numeracy survey assessed the patients' beliefs about their ability to perform mathematical tasks and preference for numerical data as compared with prose information; the results were scored from 1 to 6, with higher scores indicating greater belief in ability. Race or ethnic group was reported by the patients. The body-mass index is the weight in kilograms divided by the square of the height in meters. To convert the values for glucose to millimoles per liter, multiply by 0.05551. GLP-1ra denotes glucagon-like peptide 1 receptor agonist, and SGLT2i sodium–glucose cotransporter 2 inhibitor.

CGM-measured hypoglycemia was low at baseline and changed little in each group over the 13 weeks, with a between-group difference in the percentage of time spent with a glucose level of less than 70 mg per deciliter of −0.1 percentage points (95% CI, −0.4 to 0.1).

Other Outcomes

The results suggested a reduction in total daily insulin dose in the AID group as compared with the control group but also suggested a slight increase in weight with AID. The mean total insulin dose changed from 95±47 units per day at baseline to 87±46 units per day at 13 weeks in the AID group and from 102±50 units per day to 104±56 units per day, respectively, in the control group (Table S18). The mean change from baseline in weight was 2.4±4.4 kg in the AID group and 0.9±3.3 kg in the control group (Table S19).

Most of the patient-reported outcome surveys did not show meaningful differences between treatment groups. There was a trend toward more positive responses in the AID group for device satisfaction on the Diabetes Impact and Satisfaction Scale and sleep quality on the Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep-Related Impairment Questionnaire (Table S20).

ADVERSE EVENTS

A total of 106 adverse events were reported in 64 patients in the AID group (30%, most of which were unrelated to the AID system) and 26 events in 19 patients in the control group (18%) (Table 3 and Table S21). In the AID group, one patient had a severe hypoglycemia event of indeterminate cause, which was treated with oral carbohydrate (without glucagon). In this instance, the AID system had functioned as intended. In the AID group, 20 nonserious device-related hyperglycemia events, related primarily to infusion-set failures, occurred in 13 patients (6%). No severe hypoglycemia events were reported in the control group. There were no cases of diabetic ketoacidosis or hyperosmolar hyperglycemic syndrome in either group. Other serious adverse events, all unrelated to the trial devices, occurred in 16 patients (7%) in the AID group and in 7 patients (7%) in the control group. In the latter group, one serious event related to pancreatitis and multiorgan failure resulted in death.

DISCUSSION

In this multicenter, randomized, controlled trial involving adults with type 2 diabetes, the reduction in glycated hemoglobin levels was significantly greater among patients in the AID group than among those in a control group who used real-time CGM and continued their pretrial insulin-delivery method. A similar benefit of AID was reported in CGM-measured hyperglycemia and related outcomes. The mean time that patients had a glucose level of 70 to 180 mg per deciliter was 3.4 hours per day longer with AID than with CGM alone. The frequency of hypoglycemia was low at baseline and remained low during the trial, a finding that was consistent with other studies involving patients with type 2 diabetes.[9,11,14,16,17,20,21]

Results appeared to be robust across a range of per-protocol and sensitivity analyses. The frequency of GAD antibodies (in 8% of the trial patients, although only 4% had a GAD level of more than 250 IU per milliliter) was not surprising, given that some patients with type 2 diabetes may be misdiagnosed and have a form of type 1 diabetes or features of both type 2 and type 1 diabetes.[22,23] Results were unchanged when the patients with GAD antibodies were excluded from the analyses.

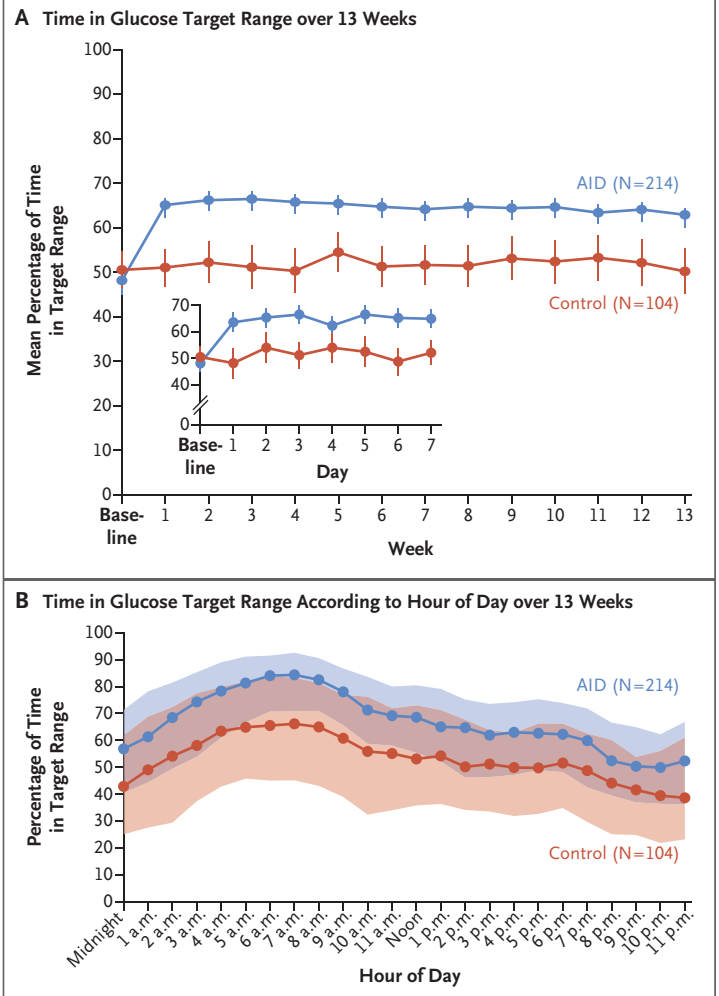

Figure 2. Mean Percentage of Time in the Glucose Target Range during the 13-Week Trial and According to the Time of Day.

Panel A shows the mean percentage of time that patients' glucose levels were in the target range of 70 to 180 mg per deciliter each week during the 13 weeks of the trial in each treatment group. The inset shows the mean time that the patients were in the target range each day for the first 7 days. The vertical lines denote 95% confidence intervals. Panel B shows an envelope plot of the percentage of time that patients were in the glucose target range according to the time of day, as measured by CGM during the 13-week period. Solid circles denote the hourly median values, and the shaded regions represent the interquartile ranges. To convert the values for glucose to millimoles per liter, multiply by 0.05551.

Consistent reduction in glycated hemoglobin levels was observed across a wide range of demographic and diabetes-related characteristics, including among patients with a high glycated hemoglobin level at baseline. Many patients with type 2 diabetes are being treated with GLP-1 receptor agonists or other noninsulin glucose-lowering medications. Our trial results indicate that AID can further reduce glycated hemoglobin levels when added to a diabetes management regimen that includes one or more of these medications.

Previous studies involving patients with type 2 diabetes have shown beneficial glycemic effects of AID, including in small randomized crossover trials[9,10,12,13,15] and in single-group trials evaluating the AID system that was used in this trial or other AID systems.[11,14,16,17] The beneficial effect of AID that we observed in an insulin-treated type 2 diabetes cohort was similar to the benefit observed in randomized, controlled trials involving adults with type 1 diabetes.[4,8]

The use of the AID system in our trial led to no new safety signals unique to a population with type 2 diabetes. Device-related adverse events were similar to those observed in type 1 diabetes AID studies and were mainly due to infusion-set failures.[4,8] Only 4% of the patients had experience using an insulin pump before the trial, and the patients did not receive formal training in traditional carbohydrate-counting methods or nutritional management of diabetes during the trial. Most patients elected to use a simple fixed-bolus regimen that allowed for minor adjustments for meal carbohydrate content. Consequently, the results of this trial suggest that previous experience with an insulin pump or in-depth training in carbohydrate-counting methods are not prerequisites to the successful and safe use of AID to improve glycemia in patients with type 2 diabetes. Although we do not know the mechanism for the slight weight gain that was observed in the context of a reduction in total daily insulin delivery, possible explanations include decreased glycosuria, especially among the patients who had higher baseline glycated hemoglobin levels or increased calorie intake.

Strengths of the trial include its randomized design; substantially larger sample size than in previous randomized, controlled trials of AID systems in patients with type 2 diabetes; a racially and socioeconomically diverse patient population across a wide age range from 19 to 87 years, which was representative of adults with type 2 diabetes and enhanced the generalizability of the results; broad use of GLP-1 receptor agonists and SGLT2 inhibitors; high retention rate among the patients; and use of real-time CGM by the control group. The last factor is a particularly important

Table 3. Safety Outcomes during the 13-Week Trial Period.

Adverse Event	AID Group (N=215)		Control Group (N=104)	
	no. of events	*no. of patients (%)*	*no. of events*	*no. of patients (%)*
Any adverse event*	106	64 (30)	26	19 (18)
Specific event				
Severe hypoglycemia	1	1		0
Diabetic ketoacidosis or hyperosmolar hyperglycemic syndrome		0		0
Other serious adverse event†	18	16 (7)	7	7 (7)
Other adverse event				
Hyperglycemia with or without ketosis				
Related to trial device	20	13 (6)		0
Not related to trial device	1	1 (<1)	2	2 (2)
Nonsevere hypoglycemia	10	9 (4)	2	2 (2)
Other reportable adverse event	56	37 (17)	15	14 (13)

* Reportable adverse events included those that met the criteria for a serious adverse event, were associated with an emergency department visit, led to temporary or permanent discontinuation of the trial device, affected the patient's ability to complete a trial procedure, or met the criteria for severe hypoglycemia, for diabetic ketoacidosis or hyperosmolar hyperglycemic syndrome, or for certain adverse device effects.

† In the AID group, the serious adverse events occurred in 15 patients who were hospitalized for a nonglycemia-related systemic medical condition and 1 each with vitreous hemorrhage, breast cancer, and inadvertent overdelivery of insulin because of a user error without development of hypoglycemia. In the control group, the 7 serious adverse events all occurred in patients who were hospitalized with a nonglycemia-related systemic medical condition, one of which resulted in death from pancreatitis and multiorgan failure.

aspect of the trial in showing the reduction in glycated hemoglobin levels that occurs with AID over and above the use of CGM without AID.

Our trial had certain limitations, including the restriction of enrollment to adults with insulin-treated type 2 diabetes, a follow-up duration of only 13 weeks, and lack of data on the amount of time required for device training in this cohort. Although only 4% of the patients were using an insulin pump before the trial, 71% were using CGM, a percentage that may be higher than what would be expected in an insulin-treated population with type 2 diabetes.

In a diverse population of adults with insulin-treated type 2 diabetes, the use of AID safely reduced glycated hemoglobin levels and hyperglycemia without increasing hypoglycemia as compared with a control group using CGM.

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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.

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