Multicenter Trial of a Tubeless, On-Body Automated Insulin Delivery System With Customizable Glycemic Targets in Pediatric and Adult Participants With Type 1 Diabetes

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OBJECTIVE

Advances in diabetes technology have transformed the treatment paradigm for type 1 diabetes, yet the burden of disease is significant. We report on a pivotal safety study of the first tubeless, on-body automated insulin delivery system with customizable glycemic targets.

RESEARCH DESIGN AND METHODS

This single-arm, multicenter, prospective study enrolled 112 children (age 6–13.9 years) and 129 adults (age 14–70 years). A 2-week standard therapy phase (usual insulin regimen) was followed by 3 months of automated insulin delivery. Primary safety outcomes were incidence of severe hypoglycemia and diabetic ketoacidosis. Primary effectiveness outcomes were change in HbA_{1c} and percent time in sensor glucose range 70–180 mg/dL ("time in range").

RESULTS

A total of 235 participants (98% of enrolled, including 111 children and 124 adults) completed the study. HbA_{1c} was significantly reduced in children by 0.71% (7.8 mmol/mol) (mean ± SD: 7.67 ± 0.95% to 6.99 ± 0.63% [60 ± 10.4 mmol/mol to 53 ± 6.9 mmol/mol], $P < 0.0001$) and in adults by 0.38% (4.2 mmol/mol) (7.16 ± 0.86% to 6.78 ± 0.68% [55 ± 9.4 mmol/mol to 51 ± 7.4 mmol/mol], $P < 0.0001$). Time in range was improved from standard therapy by 15.6 ± 11.5% or 3.7 h/day in children and 9.3 ± 11.8% or 2.2 h/day in adults (both $P < 0.0001$). This was accomplished with a reduction in time in hypoglycemia <70 mg/dL among adults (median [interquartile range]: 2.00% [0.63, 4.06] to 1.09% [0.46, 1.75], $P < 0.0001$), while this parameter remained the same in children. There were three severe hypoglycemia events not attributable to automated insulin delivery malfunction and one diabetic ketoacidosis event from an infusion site failure.

CONCLUSIONS

This tubeless automated insulin delivery system was safe and allowed participants to significantly improve HbA_{1c} levels and time in target glucose range with a very low occurrence of hypoglycemia.

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Diabetes care has been transformed by rapid innovation in glucose sensor and insulin pump technology; however, glycemic outcomes continue to be suboptimal across all populations, and the burden of disease for type 1 diabetes is immense (1–5). Automated insulin delivery systems, which combine a subcutaneous insulin infusion pump, glucose sensor, and automated dosing algorithm, have improved glycemic control while reducing hypoglycemia exposure (6–8). Currently, four systems are commercially available in the U.S. and Europe (6,9–12). Each system differs through the combination of specific devices, the system configuration and settings, and the proprietary dosing algorithm. The first automated insulin delivery systems to become available had limited options for customizing glucose targets and interoperability of devices, and so, this has become an area of focus for enhancing the capabilities of more recent systems.

All systems available to date have utilized tethered pumps, which deliver insulin through a length of tubing (46–110 cm) that connects the pump to the infusion site cannula and, therefore, the pump must be located somewhere on the person to accommodate the tubing (e.g., belt, pocket) (13). The algorithm is hosted either on the pump itself, in which case the tethered device must be accessed frequently for user interactions, or on a smartphone that controls the pump, in which case the smartphone must remain within communication range of the pump. In either case, the tubing typically needs to be disconnected for certain activities, such as swimming, exercise, and bathing, during which time no insulin is delivered (12).

The Omnipod 5 Automated Insulin Delivery System (Insulet Corporation, Acton, MA) is a new system that at the time of writing is under review by the U.S. Food and Drug Administration. In addition to a novel algorithm with customizable glucose targets, this system has a unique configuration that utilizes a tubeless insulin pump (Pod), which is a small (3.9 × 5.2 × 1.45 cm) adhesive patch pump worn on the body. The cannula is automatically deployed directly under the Pod, creating an infusion site without external tubing. The Pod is waterproof (IP28) and worn continuously for up to 72 h. All user interactions are conducted wirelessly through a mobile app on a smartphone. The algorithm itself is located on the Pod, and the glucose sensor communicates directly with the Pod through Bluetooth wireless technology. Therefore, the system can continuously provide automated insulin delivery through the wearable on-body components alone (Pod and sensor) without the smartphone needing to be nearby.

We present the results of the first 3-month outpatient pivotal trial of this automated insulin delivery system that uses a wearable tubeless insulin pump with an embedded algorithm that receives communication directly from a glucose sensor through Bluetooth wireless technology (14). The system has been designed to minimize hypoglycemia while maximizing time in glycemic target range, ensuring safety and effectiveness across a broad range of people with diabetes from children to seniors (15,16). Preliminary versions of the algorithm were evaluated in several clinical studies (15–18), and an early trial of the commercial configuration demonstrated positive results (14).

RESEARCH DESIGN AND METHODS

Study Conduct and Oversight

A single-arm, multicenter, prospective clinical study was conducted at 17 sites in the U.S. The protocol was approved by a central institutional review board and relevant local review boards. Informed consent was obtained from participants aged ≥18 years. For participants <18 years, assent and consent were obtained from participants and their parents or guardians, respectively, according to state requirements. The U.S. Food and Drug Administration approved an investigational device exemption. An independent data and safety monitoring board as well as a medical monitor provided trial oversight.

Study Design and Participants

Eligible participants were aged 6–70 years, diagnosed with type 1 diabetes for at least 6 months, had a point-of-care screening HbA_{1c} <10.0% (86 mmol/mol), and did not have a history of severe hypoglycemia or diabetic ketoacidosis in the past 6 months (complete eligibility criteria are listed in Supplementary Table 1). Participants were enrolled into two cohorts: children (age 6–13.9 years) and adolescents/adults (age 14–70 years, subsequently referred to as adults). Both cohorts followed the same protocol and used an identical automated insulin delivery system.

After screening, participants completed a 2-week standard therapy phase to collect glucose sensor data on their usual diabetes care regimen to be used as a comparator to automated insulin delivery. Participants wore a glucose sensor in blinded mode during the standard therapy phase if a glucose sensor was not part of their usual regimen. Participants were then trained on the investigational system, which consisted of a tubeless insulin pump (Pod) with an embedded automated insulin delivery algorithm (Omnipod 5), an interoperable glucose sensor (Dexcom G6; Dexcom, San Diego, CA), and a mobile app (Omnipod 5 app) on a locked-down Android phone.

Participants controlled the system through the mobile app for daily interactions, including delivering meal and correction boluses and setting target glucose profiles. The mobile app was also used for initial setup and to start automated mode. Both the Pod and the continuous glucose monitor (CGM) were worn on the body, and the CGM

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**A complete list of the Omnipod 5 Research Group can be found in the supplementary material online.*

communicated directly with the algorithm on the Pod. Therefore, the smartphone containing the app did not need to be present for automated insulin delivery to continue once initiated since the algorithm was embedded directly onto the on-body Pod.

During automated mode, each Pod delivers insulin microboluses every 5 min on the basis of current and projected glycemic values to bring the glucose level toward the selected target. The main determinant of automated insulin delivery is the user-selected glucose target, which can range from 110 to 150 mg/dL in 10 mg/dL increments and can be programmed to vary by time of day. The insulin delivery is continuously adjusted to meet this target and is based on an adaptive basal rate determined from the total daily insulin delivered, which is tracked and updated with each subsequent Pod change. The basal rates entered by the user at first-time setup are only relevant for the first Pod use in automated mode or when the system is in manual insulin delivery mode.

Study participants were educated on additional system options, such as the HypoProtect feature that could be used to temporarily set a higher glucose target of 150 mg/dL with additional restrictions on insulin delivery if anticipating lower insulin needs, such as during exercise. Participants were encouraged to use the bolus calculator within the mobile app to deliver meal and correction boluses through the Pod. These boluses were calculated on the basis of user-defined insulin-to-carbohydrate ratios, correction factors, and glucose targets. The bolus calculator adjusted the suggested insulin bolus on the basis of insulin on board as well as the CGM trend arrow in both automated and manual mode. Further details on system function have been previously published (14).

The system was used for 3 months, with nine follow-up study visits occurring in person or by phone (Supplementary Table 2). During each visit, participants were asked about adverse events, medication use, and device issues, and the study team reviewed the system data history and recommended changes to pump settings as needed. Although study teams had access to real-time monitoring of system data, they were not instructed to conduct surveillance outside of study visits, and there were no automated alerts to investigators related to glycemia. Reportable adverse events included adverse device events, adverse events associated with study procedures or hyperglycemia associated with ketosis (>1 mmol/L), or serious adverse events such as severe hypoglycemia, defined as requiring assistance because of altered consciousness, and diabetic ketoacidosis (19).

HbA_{1c} was measured at baseline and the final study visit using laboratory measures, which could differ from point-of-care measures used for eligibility screening. Additional optional measurements were added at the start and end of the study pause (discussed below). HbA_{1c} (Tosoh Bioscience) was measured by a central laboratory (University of Minnesota Advanced Research and Diagnostic Laboratory).

Use of automated insulin delivery was paused study-wide from 28 February 2020 to 4 June 2020 because of a software anomaly with the potential to impact insulin delivery as a result of erroneous system inputs in certain uncommon circumstances. The study was paused as a precaution, and there were no adverse events associated with the anomaly. The median (interquartile range) number of days completed before and after the pause were 46 (36, 56) and 49 (38, 59) for children and 43 (30, 52) and 49 (41, 63) for adults, respectively. During the study pause, participants could continue study system use without activation of automated insulin delivery features where the device functioned as a stand-alone insulin pump (77% of participants), or they could use another insulin regimen (23%). Once the software update was implemented, participants resumed automated delivery, which occurred remotely for most participants because of the COVID-19 pandemic.

Outcomes

The primary safety outcomes were incidence rates of severe hypoglycemia and diabetic ketoacidosis. The primary effectiveness outcomes were change in HbA_{1c} and percentage of time in glucose target range 70–180 mg/dL ("time in range") measured by the glucose sensor during the 3-month automated insulin delivery phase compared with the 2-week standard therapy phase. Secondary outcomes included percent time <70 mg/dL and >180 mg/dL, percent time in additional glycemic ranges (<54 mg/dL, ≥250 mg/dL, ≥300 mg/dL), additional glycemic measures (mean, SD, and coefficient of variation of sensor glucose), and additional clinical measures (total daily dose of insulin, total daily basal or bolus insulin delivery, BMI). Measures related to system use were also assessed (percentage of study time spent in automated mode, number and type of device deficiencies observed).

Statistical Methods

This study was designed to provide 90% power and a one-sided significance level of 2.5% or 1.25% for the two primary effectiveness outcomes. The sample size estimation assumed a mean difference and SD of the difference in HbA_{1c} of 0.5% (5.5 mmol/mol) and 0.8% (8.7 mmol/mol) and time in range of 10% and 15%. Although 35 and 31 participants were required for the two effectiveness outcomes, respectively, enrollment of up to 240 participants was planned for a robust safety evaluation.

Analyses were performed on a modified intention-to-treat data set of participants who entered the automated insulin delivery phase. Any sensor or insulin delivery data collected during the study pause were not included in the analyses of outcomes, and any adverse events or device deficiencies during the pause were listed separately. Sensor data were primarily obtained from the investigational app through cloud-based transmission, with data from Dexcom Clarity as a secondary source. No imputations for missing data were planned or performed.

Analyses were conducted separately for children and adults. Results are presented as means with SDs or medians with interquartile ranges as appropriate. The primary safety outcome was considered a success if the incidence rates of severe hypoglycemia and diabetic ketoacidosis were considered acceptable compared with published rates (3,4). Effectiveness outcomes were evaluated using paired *t* tests, or using Wilcoxon

Table 1—Characteristics at baseline of the study participants in the modified intention-to-treat data set

Characteristic	Children (age 6–13.9 years)	Adults (age 14–70 years)
n	112	128
Age (years)	10.3 ± 2.2 (6.0, 14.0#)	36.9 ± 13.9 (14.5, 69.8)
Duration of diabetes (years)	4.7 ± 2.6 (0.6, 11.6)	17.9 ± 11.6 (1.0, 51.0)
BMI (kg/m^2)	18.6 ± 3.2 (13.7, 32.4)	26.6 ± 4.7 (18.9, 41.4)
Female sex, *n* (%)	60 (53.6)	78 (60.9)
Race/ethnicity, *n* (%)‡		
White	104 (92.9)	117 (91.4)
Hispanic or Latino	8 (7.1)	6 (4.7)
Not Hispanic or Latino	96 (85.7)	111 (86.7)
Black or African American, White	3 (2.7)	—
Black or African American	2 (1.8)	5 (3.9)
Hispanic or Latino	—	1 (0.8)
Not Hispanic or Latino	2 (1.8)	4 (3.1)
Asian	—	2 (1.6)
Asian, White	2 (1.8)	—
Asian, Native Hawaiian or Pacific Islander, White	1 (0.9)	—
American Indian or Alaska Native, White	—	1 (0.8)
American Indian or Alaska Native	—	3 (2.3)
Hispanic or Latino	—	3 (2.3)
Not Hispanic or Latino	—	0 (0.0)
HbA_{1c} (%)§	7.67 ± 0.95 (5.80, 10.30)	7.16 ± 0.86 (5.20, 9.80)
HbA_{1c} (mmol/mol)§	60 ± 10.4 (40, 89)	55 ± 9.4 (33, 84)
Daily insulin dose (units/kg)‖	0.85 ± 0.24 (0.25, 1.47)	0.61 ± 0.22 (0.16, 1.31)
Previous¶ or current CGM use, *n* (%)	108 (96.4)	126 (98.4)
Previous¶ or current pump use, *n* (%)	100 (89.3)	115 (89.8)
Use of multiple daily injections as standard therapy method, *n* (%)	13 (11.6)	20 (15.6)

Data are mean ± SD (minimum, maximum) unless otherwise indicated. #Age was determined at the date of informed consent. The birth date of one participant fell immediately after the informed consent date, resulting in inclusion in the children cohort despite the age being 14.0 years after rounding. ‡Race and ethnicity were reported by the participants and are displayed exactly as reported. As shown, several participants chose more than one racial category. Ethnicity delineation is shown for racial categories where at least one person identified as Hispanic or Latino. §Participant eligibility for the study was determined using a point-of-care HbA_{1c} measurement performed at screening, which in some cases differed from the laboratory assessment displayed here and used for analysis. ‖Baseline total daily insulin dose was determined from data collected during the standard therapy phase. ¶Previous use is defined as having used the device for any duration in the past.

signed rank tests if there were <10 participants in a group or if Shapiro-Wilk tests of normality were significant ($P < 0.05$). All *P* values were considered significant at a two-sided level of 0.05. Analysis was performed using SAS 9.4 statistical software.

RESULTS

Participant Characteristics

Between 19 December 2019 and 28 February 2020, 241 participants were enrolled, and 240 entered the automated insulin delivery phase and were included in the modified intention-to-treat data set. Baseline characteristics are included in Table 1. Ninety-eight percent of enrolled participants completed the main study (Supplementary Fig. 1). Of these, 224 (95%) elected to participate in an ongoing extension phase.

Effectiveness Outcomes

HbA_{1c} was reduced in children by 0.71% (7.8 mmol/mol) (7.67 ± 0.95% to 6.99 ± 0.63% [60 ± 10.4 to 53 ± 6.9 mmol/mol], $P < 0.0001$) and in adults by 0.38% (4.2 mmol/mol) (7.16 ± 0.86% to 6.78 ± 0.68% [55 ± 9.4 to 51 ± 7.4 mmol/mol], $P < 0.0001$) (Table 2). Improvement was seen in both age-groups regardless of their baseline glycemic control (20) (Fig. 1).

Time in range increased by 15.6% in children (52.5 ± 15.6% to 68.0 ± 8.1%, $P < 0.0001$) and 9.3% in adults (64.7 ± 16.6% to 73.9 ± 11.0%, $P < 0.0001$) (Table 2 and Supplementary Table 3). Sensor glucose profile by time of day is presented in Fig. 2. Improvement in time in range was achieved rapidly, with adults achieving 73.5% over days 1–3 after system initiation and children achieving 62.6% in days 1–3 and 68.0% in days 4–6. Time in range remained stable thereafter. The number of participants who met the established clinical targets (1,2) for glycemic measures is included in Supplementary Table 4.

Secondary outcomes demonstrated a reduction in hypoglycemia for adults and a reduction in hyperglycemia in both age-groups. Time <70 mg/dL for adults declined by a median of 0.89% (interquartile range 2.00%, 1.09%; $P < 0.0001$). Adults also had a median reduction of 0.08% in time spent <54 mg/dL ($P < 0.0001$). Time <54 mg/dL and <70 mg/dL remained unchanged for children. Time

Table 2—Primary and secondary effectiveness outcomes

Parameter	Cohort							
	Children (age 6–13.9 years, n = 112)				Adults (age 14–70 years, n = 128)			
	Baseline§ or standard therapy phase	Follow-up§ or automated insulin delivery phase	Change	P value‖	Baseline§ or standard therapy phase	Follow-up§ or automated insulin delivery phase	Change	P value‖
Overall (24 h)								
Primary effectiveness outcome, HbA_{1c}† %	7.67 ± 0.95, 7.50 (7.00, 8.30)	6.99 ± 0.63, 6.90 (6.50, 7.40)	−0.71 ± 0.63, −0.65 (−1.10, −0.30)	<0.0001	7.16 ± 0.86, 7.10 (6.60, 7.60)	6.78 ± 0.68, 6.70 (6.40, 7.15)	−0.38 ± 0.54, −0.30 (−0.70, −0.00)	<0.0001
mmol/mol	60 ± 10.4, 58 (53, 67)	53 ± 6.9, 52 (48, 57)	−7.8 ± 6.9, −7.1 (−12, 3.3)	—	55 ± 9.4, 54 (49, 60)	51 ± 7.4, 50 (46, 55)	−4.2 ± 5.9, −3.3 (−7.7, 0.0)	—
Primary effectiveness outcome, time 70–180 mg/dL, %	52.5 ± 15.6, 52.8 (39.3, 63.2)	68.0 ± 8.1, 68.2 (63.3, 73.5)	15.6 ± 11.5, 15.0 (7.8, 24.6)	<0.0001	64.7 ± 16.6, 67.1 (51.3, 77.6)	73.9 ± 11.0, 75.8 (68.0, 81.1)	9.3 ± 11.8, 7.9 (0.9, 15.5)	<0.0001
Mean sensor glucose, mg/dL	183 ± 32, 181 (163, 205)	160 ± 15, 159 (150, 171)	−23 ± 23, −21 (−37, −7)	<0.0001	161 ± 28, 156 (138, 178)	154 ± 17, 151 (143, 163)	−8 ± 20, −6 (−16, 7)	0.0002
SD of sensor glucose, mg/dL	68 ± 13, 68 (59, 77)	60 ± 10, 59 (52, 65)	−9 ± 8, −8 (−14, −3)	<0.0001	57 ± 14, 55 (46, 67)	49 ± 11, 48 (42, 55)	−8 ± 9, −7 (−13, −1)	<0.0001
CV of sensor glucose, %‡	37.5 ± 5.1, 37.1 (33.8, 41.0)	37.0 ± 3.9, 37.6 (34.3, 39.8)	−0.4 ± 4.2, −0.6 (−3.5, 2.5)	0.2893	35.2 ± 5.7, 34.6 (31.2, 37.9)	31.7 ± 4.7, 32.1 (28.5, 34.6)	−3.5 ± 4.3, −3.7 (−6.0, −0.3)	<0.0001
Time in glucose range, %								
<54 mg/dL	0.41 ± 0.83, 0.10 (0.00, 0.41)	0.32 ± 0.33, 0.23 (0.08, 0.42)	−0.08 ± 0.66, 0.04 (−0.12, 0.20)	0.1132	0.62 ± 1.24, 0.22 (0.00, 0.77)	0.23 ± 0.27, 0.17 (0.06, 0.28)	−0.39 ± 1.16, −0.08 (−0.46, 0.04)	<0.0001
<70 mg/dL	2.21 ± 2.66, 1.38 (0.42, 2.67)	1.78 ± 1.37, 1.48 (0.65, 2.23)	−0.43 ± 2.01, 0.06 (−0.66, 0.68)	0.8153	2.89 ± 3.07, 2.00 (0.63, 4.06)	1.32 ± 1.10, 1.09 (0.46, 1.75)	−1.57 ± 2.55, −0.89 (−2.23, −0.01)	<0.0001
>180 mg/dL	45.3 ± 16.7, 44.8 (35.2, 58.9)	30.2 ± 8.7, 29.7 (24.1, 35.5)	−15.1 ± 12.2, −14.3 (−24.5, −6.8)	<0.0001	32.4 ± 17.3, 28.9 (17.6, 46.6)	24.7 ± 11.2, 22.8 (17.0, 31.4)	−7.7 ± 12.1, −6.2 (−13.9, 1.6)	<0.0001
≥250 mg/dL	19.1 ± 13.1, 15.9 (9.7, 26.3)	9.6 ± 5.4, 8.9 (5.7, 12.4)	−9.4 ± 9.8, −6.1 (−14.4, −2.1)	<0.0001	10.1 ± 10.5, 6.6 (2.3, 15.4)	5.8 ± 5.5, 3.9 (2.2, 7.7)	−4.3 ± 7.7, −2.3 (−6.9, 0.3)	<0.0001
≥300 mg/dL	8.5 ± 8.9, 5.8 (2.5, 11.5)	3.5 ± 2.9, 2.7 (1.4, 4.8)	−5.1 ± 7.1, −2.6 (−7.5, −0.5)	<0.0001	3.7 ± 5.5, 1.5 (0.2, 5.0)	1.7 ± 2.5, 0.8 (0.3, 2.2)	−2.0 ± 4.3, −0.4 (−2.8, 0.1)	<0.0001

Continued on p. 1635

Table 2—Continued

Parameter	Cohort							
	Children (age 6–13.9 years, $n = 112$)				Adults (age 14–70 years, $n = 128$)			
	Baseline§ or standard therapy phase	Follow-up§ or automated insulin delivery phase	Change	*P* value‖	Baseline§ or standard therapy phase	Follow-up§ or automated insulin delivery phase	Change	*P* value‖
Overnight (00:00–06:00 h)								
Primary effectiveness outcome, time 70–180 mg/dL, %	55.3 ± 19.0, 55.8 (41.2, 70.6)	78.1 ± 10.8, 79.4 (70.9, 85.9)	22.9 ± 14.8, 23.5 (12.8, 33.8)	<0.0001	64.3 ± 19.5, 66.7 (50.1, 79.5)	78.1 ± 13.9, 79.9 (69.4, 89.6)	13.8 ± 14.0, 12.3 (4.5, 20.7)	<0.0001
Mean sensor glucose, mg/dL	177 ± 35, 173 (154, 200)	149 ± 17, 147 (136, 158)	−29 ± 27, −27 (−48, −9)	<0.0001	160 ± 34, 158 (134, 178)	149 ± 21, 147 (134, 161)	−11 ± 24, −7 (−23, 4)	<0.0001
SD of sensor glucose, mg/dL	61 ± 15, 61 (50, 73)	48 ± 12, 46 (39, 56)	−13 ± 13, −13 (−22, −5)	<0.0001	56 ± 17, 55 (43, 67)	44 ± 13, 42 (34, 52)	−12 ± 12, −12 (−18, −5)	<0.0001
CV of sensor glucose, %‡	34.6 ± 7.1, 34.2 (29.0, 38.7)	31.9 ± 5.6, 31.5 (28.2, 35.6)	−2.8 ± 7.5, −2.5 (−7.5, 1.9)	0.0002	35.0 ± 7.9, 34.4 (29.8, 39.2)	28.9 ± 5.8, 29.1 (24.8, 32.8)	−6.2 ± 7.0, −6.1 (−9.7, −1.4)	<0.0001
Time in glucose range, %								
<54 mg/dL	0.57 ± 1.65, 0.00 (0.00, 0.30)	0.22 ± 0.31, 0.09 (0.02, 0.32)	−0.35 ± 1.52, 0.02 (−0.18, 0.13)	0.9451	0.95 ± 1.86, 0.00 (0.00, 1.06)	0.24 ± 0.38, 0.09 (0.02, 0.30)	−0.70 ± 1.74, 0.00 (−0.85, 0.09)	0.0002
<70 mg/dL	2.51 ± 4.21, 0.78 (0.00, 2.84)	1.17 ± 1.19, 0.78 (0.37, 1.49)	−1.34 ± 3.81, 0.01 (−1.56, 0.55)	0.0456	3.64 ± 4.49, 2.07 (0.50, 5.54)	1.17 ± 1.27, 0.82 (0.31, 1.62)	−2.46 ± 4.03, −0.86 (−3.76, 0.14)	<0.0001
>180 mg/dL	42.2 ± 20.0, 40.1 (27.1, 57.9)	20.7 ± 10.8, 18.6 (12.7, 26.6)	−21.5 ± 16.0, −21.8 (−33.7, −12.1)	<0.0001	32.1 ± 20.2, 29.3 (15.6, 44.5)	20.7 ± 14.1, 18.8 (8.7, 29.8)	−11.3 ± 14.4, −9.1 (−18.9, −2.2)	<0.0001
≥250 mg/dL	16.3 ± 15.0, 11.7 (5.1, 26.4)	5.4 ± 5.1, 3.5 (1.9, 7.3)	−10.9 ± 12.0, −7.2 (−18.2, −2.3)	<0.0001	10.6 ± 12.7, 6.6 (1.5, 15.0)	4.8 ± 7.0, 2.5 (0.9, 6.7)	−5.7 ± 8.9, −3.2 (−9.0, 0.0)	<0.0001
≥300 mg/dL	6.7 ± 9.1, 3.1 (0.5, 10.2)	1.8 ± 2.5, 0.9 (0.3, 2.6)	−4.8 ± 7.5, −1.7 (−7.3, 0.0)	<0.0001	4.2 ± 8.0, 0.7 (0.0, 4.9)	1.5 ± 3.1, 0.5 (0.0, 1.7)	−2.7 ± 6.4, 0.0 (−2.7, 0.2)	<0.0001

Data are mean ± SD, median (interquartile range). To convert the values for glucose to mmol/L, multiply by 0.05551. CV, coefficient of variation. †Baseline HbA_{1c} values were available for 112 children and 128 adults. Final HbA_{1c} values were available for 108 children and 124 adults who completed the study. The change and *P* values were calculated only for those who had values available at both baseline and end of study (see Supplementary Table 7 for HbA_{1c} outcomes at additional time points). ‡CV of sensor glucose is SD divided by the mean. §Baseline and follow-up data were used for the primary effectiveness outcome of HbA_{1c}; the remaining outcomes are described for the standard therapy phase and the automated insulin delivery phase. ‖*P* value determined using unadjusted two-sided paired *t* tests, unless otherwise specified as follows: two-sided Wilcoxon signed rank tests were used for HbA_{1c} for adults, mean sensor glucose (except for children overnight), SD for adults overnight, CV for adults overnight, and percentage of time in glucose ranges 70–180 mg/dL for adults, <54 mg/dL, <70 mg/dL, >180 mg/dL for adults, ≥250 mg/dL, and ≥300 mg/dL.

>180 mg/dL declined by a mean of 15.1% (from 45.3% to 30.2%, $P < 0.0001$) for children and by 7.7% (from 32.4% to 24.7%, $P < 0.0001$) for adults. Mean sensor glucose was also reduced in both groups (Table 2). Subgroup analysis by baseline demographic characteristics, including device-naive participants, demonstrated glycemic improvement similar to the overall study cohort (Supplementary Table 5).

Most participants selected the glucose target of 110 mg/dL for automated insulin delivery (61% of cumulative person-days for children and 80% for adults). Patterns in glycemic outcomes at the 110 mg/dL target for both groups were similar to those overall (Supplementary Table 6). With the 110 mg/dL target, time in range was 68.4 ± 9.1% for children and 75.6 ± 9.9% for adults. Glycemic outcomes when using the other targets are listed in Supplementary Tables 8 and 9.

BMI increased slightly in children (18.6 ± 3.2 to 19.2 ± 3.6 kg/m^2, $P < 0.0001$ by paired *t* test), although the BMI *z*-score was the same at baseline and follow-up (0.4 ± 0.8), indicating that the increase in BMI was related to normal growth. There was no change in BMI in adults. Total daily insulin requirements increased in children (0.85 ± 0.24 to 0.92 ± 0.25 units/kg, $P < 0.0001$) and decreased slightly in adults (0.61 ± 0.22 to 0.59 ± 0.21 units/kg, $P = 0.02$) (Supplementary Table 10).

Safety Outcomes

The observed incidence rates of severe hypoglycemia and diabetic ketoacidosis during the automated insulin delivery phase were 4.8 and 1.2 events per 100 person-years, respectively (Supplementary Table 11). These are lower than the respective rates of 25.2 severe hypoglycemia events and 10.8 diabetic ketoacidosis events per 100 person-years reported in the U.S. T1D Exchange Registry (3,4). There were three severe hypoglycemia events: two in adults following user-initiated boluses, with appropriate insulin suspension by the system, and one in a child following delayed eating after a preprandial bolus. There was one case of diabetic ketoacidosis in a child because of a suspected infusion site failure. Additional details on all adverse events recorded during the automated insulin delivery phase in each age-group and overall are available in Supplementary Table 11.

System Use

Children spent median 96.4% (interquartile range: 93.8 to 97.9%) and adults spent median 96.7% (interquartile range: 93.4 to 98.0%) of total study time in automated mode (mean±SD: 95.2 ± 4.0% and 94.8 ± 6.0% of time in children and adults, respectively). There was approximately 1 device deficiency per person-month of system use: 608 related to the Pod, 83 to the app/handheld device, 20 to the glucose sensor, and 1 each to the glucose and ketone meters.

CONCLUSIONS

This multicenter trial of adults and children with type 1 diabetes using a tubeless automated insulin delivery system for 3 months demonstrated the safety of the system in this population. We also observed significant and clinically important improvements in glycemic outcomes with system use compared with participants' standard therapy. Adults and children achieved a mean HbA_{1c} of 6.78% (51 mmol/mol) and 6.99% (53 mmol/mol), respectively. Adults attained a time in range of 73.9% (an improvement of 2.2 h/day from standard therapy) or 75.6% when using the 110 mg/dL target, with a reduction in hypoglycemia (<70 mg/dL) exposure by 13 min/day. Children attained a time in range of 68.0%, which increased their time in range by 3.7 h/day from standard therapy without an increase in hypoglycemia. In both age-groups, the glycemic improvements were particularly prominent overnight and were driven by a clinically meaningful reduction in hyperglycemia. While using the system, 82% of children and 69% of adults met established clinical targets for time in range (children >60%, adults >70%) (2), and 53% of children and 66% of adults had an HbA_{1c} <7% (<53 mmol/mol) (1). Importantly, gains in glycemic control were not associated with a concomitant rise in hypoglycemia. Median percent time <70 mg/dL was 1.48% and 1.09% for children and adults, respectively, which is well below the recommendation of <4% (2). In fact, 93% of children and 95% of adults achieved this target. The safety outcomes of severe hypoglycemia and diabetic ketoacidosis incidence were below observed rates in type 1 diabetes (3–5) and were not attributable to automated insulin delivery malfunction.

These results are consistent with published findings of similar systems. The pivotal trials for two systems commercially available in the U.S. reported improved HbA_{1c} and time in range in both adults and children after 3–6 months of use (6,7,10,21). One system resulted in an HbA_{1c} of 6.9% (change from baseline of −0.5%) in adults and 7.5% (−0.4%) in children after 3 months, with improved time in range, achieving 72.2% (+5.5%) and 65% (+8.8%) for adults and children, respectively (10,21). Another system resulted in an HbA_{1c} of 7.06% (−0.34%) in adults and 7.0% (−0.6%) in children after 6 and 4 months, respectively, and an improved time in range, achieving 71% (+10%) and 67% (+14%) (6,7). The results of the current study show notably low rates of hypoglycemia, with the majority of participants reaching glycemic targets for their age. While differences in study design limit direct outcome comparisons, the results presented here indicate that the present system compares favorably with current commercially available devices.

An unexpected challenge to this study was the 3-month pause that was initiated once a software anomaly was detected. System use evaluation time was no longer continuous and thus, presented a complication for the planned analysis. For some participants, the final HbA_{1c} was preceded by as few as 28 days of continuous system use, while HbA_{1c} is known to reflect glycemic changes over longer periods of time (22); thus, our results may provide an underestimation of effectiveness. Nevertheless, a stable time in range was achieved quickly after system initiation, and outcomes that were based on sensor data are not expected to have been affected by the pause.

During this first outpatient evaluation of the system, there was about one device deficiency recorded per person-month of use, with the majority of these relating to the Pod. Pod deficiencies were generally related to hazard alarms occurring before the end of the

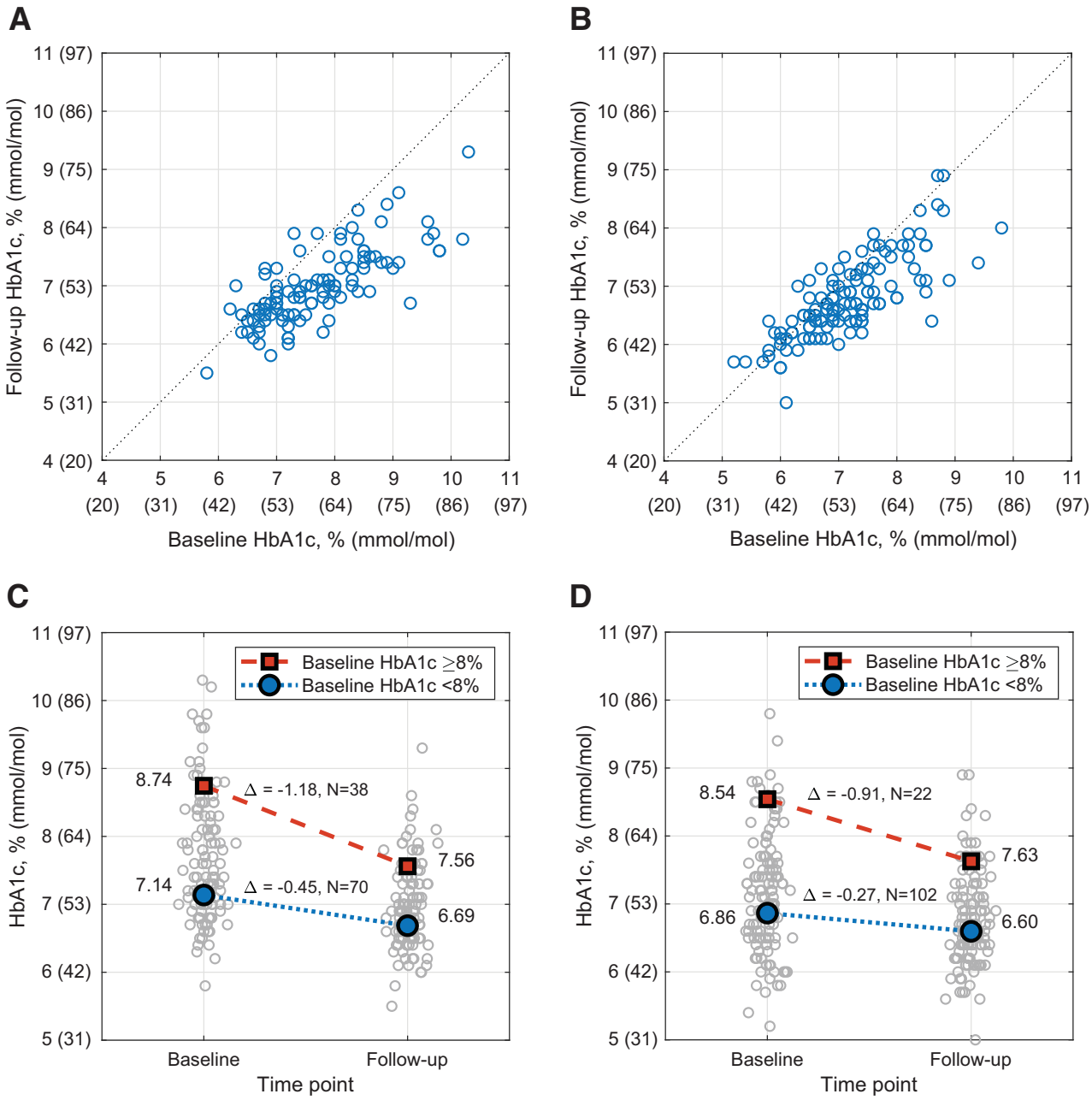

Figure 1—Changes in HbA_{1c}. Individual participant HbA_{1c} results are shown before (baseline) and after (follow-up) the 3-month automated insulin delivery phase for all participants with measurements available at both time points. HbA_{1c} at follow-up plotted vs. HbA_{1c} at baseline for children age 6–13.9 years ($n = 108$) (*A*) and adults age 14–70 years ($n = 124$) (*B*), with each circle representing a single participant. Mean HbA_{1c} (%) values at baseline and follow-up when stratified into two groups by baseline HbA_{1c} <8% (blue circle) and ≥8% (red square) for children ($n = 108$) (*C*) and adults ($n = 124$) (*D*), with the distribution of individual participant results at each time point shown as gray circles. Mean HbA_{1c} (mmol/mol) values for children (*C*) with baseline HbA_{1c} <64 mmol/mol (blue circle) and ≥64 mmol/mol (red square) are 55 and 72 mmol/mol at baseline and 50 and 59 mmol/mol at follow-up (change −4.9 and −12.9 mmol/mol), respectively. HbA_{1c} values for adults (*D*) with baseline HbA_{1c} <64 mmol/mol (blue circle) and ≥64 mmol/mol (red square) are 51 and 70 mmol/mol at baseline and 49 and 60 mmol/mol at follow-up (change −3.0 and −9.9 mmol/mol), respectively. In the analysis of change in HbA_{1c} stratified by baseline HbA_{1c}, the change was significant for each combination of age-group and baseline HbA_{1c} category (all $P < 0.0001$ by paired *t* test). The cutoff of HbA_{1c} <8.0% (<64 mmol/mol) was selected as a measure of adequate HbA_{1c} control set by the Comprehensive Diabetes Care Healthcare Effectiveness Data and Information Set (20).

expected 72-h duration of use. These alarms indicate to the user that the Pod must be replaced. Many of these alerts are standard for insulin pump systems and arise from fault detection, such as detection of an occlusion, low battery voltage, or interference in electrical circuit integrity. Pod change is routine, and the rate of Pod device deficiencies equated to approximately an additional 2.5 Pod changes throughout the duration of the study. This would have a negligible effect on the study results. Information from the device deficiencies observed in this study was used to make improvements to the system. Thus, there is expected to be a much lower rate of error occurrences in future uses of the system.

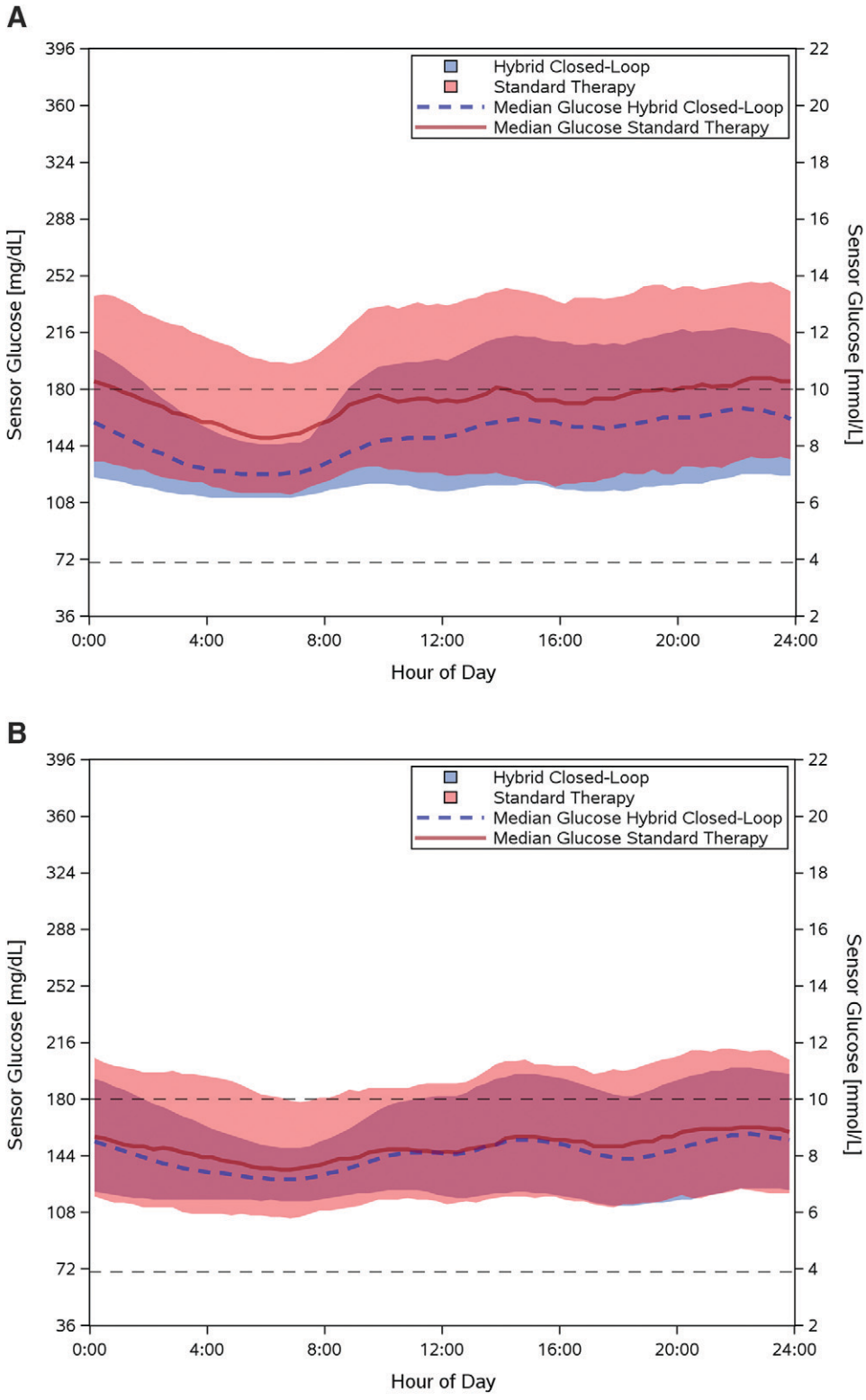

Figure 2—Sensor glucose measurements. Median sensor glucose measurements are shown for children (age 6–13.9 years, $n = 112$) (*A*) and adults (age 14–70 years, $n = 128$) (*B*) during the automated insulin delivery phase (blue dashed line) and the standard therapy phase (red line), with blue and red shaded areas indicating the interquartile range for each phase. The target range (70–180 mg/dL) is indicated by black dashed lines. Measurements represent a 24-h period from midnight to midnight.

Strengths of this study include the wide range of participant ages (6–70 years) and baseline HbA_{1c} levels (5.2–10.3% [33–89 mmol/mol]). In addition, the trial enrolled both pump and multiple daily injection users with no requirement for prestudy sensor use, with successful implementation across diverse pediatric and adult centers. Participant engagement and endorsement of the system was evident, with 95% choosing to enroll in

the extension phase of the trial. Connectivity of the on-body devices was excellent, allowing use of automated insulin delivery for median 96.4% and 96.7% of the possible time for children and adults, respectively. Furthermore, the study used a remote data monitoring system that allowed for cloud-based transmission of data, obviating the need for manual uploads initiated by the user. This critical component of care to allow for seamless data review may help to alleviate the burden sometimes generated by diabetes technologies. While in this study a mobile app on a provided locked-down Android phone was used to interact with the system, it is planned for this app to be available for download and use on compatible personal smartphones when the system becomes commercially available.

Limitations of this study include the single-arm design without a control group that did not account for effects related to participation in a study. This important design limitation could result in overestimation of effectiveness outcomes because it does not account for potential improvements through study-related interactions alone. The standard therapy comparator phase was also of shorter duration than the treatment phase. This limitation is mitigated in part by using glycemic measures that have been validated to reflect underlying glycemia across shorter durations (10–14 days of sensor use) (2,23). Participants had relatively well-controlled baseline glycemic metrics, with many already using insulin pumps and glucose sensors, which may limit generalizability. However, the fact that there were improvements in this generally well-controlled group is encouraging.

In conclusion, this tubeless, on-body automated insulin delivery system with customizable targets was safe, achieving significant improvements in HbA_{1c} and glycemic measures with a low rate of hypoglycemia in a heterogeneous participant group with varied age, baseline glycemia, and prior device use. This system allowed the majority of participants to achieve current glycemic targets set by the American Diabetes Association and international consensus guidelines (1,2).

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