ORIGINAL ARTICLE

Threshold-Based Insulin-Pump Interruption for Reduction of Hypoglycemia

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ABSTRACT

BACKGROUND

The threshold-suspend feature of sensor-augmented insulin pumps is designed to minimize the risk of hypoglycemia by interrupting insulin delivery at a preset sensor glucose value. We evaluated sensor-augmented insulin-pump therapy with and without the threshold-suspend feature in patients with nocturnal hypoglycemia.

METHODS

We randomly assigned patients with type 1 diabetes and documented nocturnal hypoglycemia to receive sensor-augmented insulin-pump therapy with or without the threshold-suspend feature for 3 months. The primary safety outcome was the change in the glycated hemoglobin level. The primary efficacy outcome was the area under the curve (AUC) for nocturnal hypoglycemic events. Two-hour threshold-suspend events were analyzed with respect to subsequent sensor glucose values.

RESULTS

A total of 247 patients were randomly assigned to receive sensor-augmented insulin-pump therapy with the threshold-suspend feature (threshold-suspend group, 121 patients) or standard sensor-augmented insulin-pump therapy (control group, 126 patients). The changes in glycated hemoglobin values were similar in the two groups. The mean AUC for nocturnal hypoglycemic events was 37.5% lower in the threshold-suspend group than in the control group (980±1200 mg per deciliter [54.4±66.6 mmol per liter] × minutes vs. 1568±1995 mg per deciliter [87.0±110.7 mmol per liter] × minutes, P<0.001). Nocturnal hypoglycemic events occurred 31.8% less frequently in the threshold-suspend group than in the control group (1.5±1.0 vs. 2.2±1.3 per patient-week, P<0.001). The percentages of nocturnal sensor glucose values of less than 50 mg per deciliter (2.8 mmol per liter), 50 to less than 60 mg per deciliter (3.3 mmol per liter), and 60 to less than 70 mg per deciliter (3.9 mmol per liter) were significantly reduced in the threshold-suspend group (P<0.001 for each range). After 1438 instances at night in which the pump was stopped for 2 hours, the mean sensor glucose value was 92.6±40.7 mg per deciliter (5.1±2.3 mmol per liter). Four patients (all in the control group) had a severe hypoglycemic event; no patients had diabetic ketoacidosis.

CONCLUSIONS

This study showed that over a 3-month period the use of sensor-augmented insulin-pump therapy with the threshold-suspend feature reduced nocturnal hypoglycemia, without increasing glycated hemoglobin values. (Funded by Medtronic MiniMed; ASPIRE ClinicalTrials.gov number, NCT01497938.)

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Severe nocturnal hypoglycemia can be catastrophic,[1,2] and hypoglycemia remains one of the most formidable barriers to improving glycemic control in patients with diabetes.[3] Sensor-augmented insulin-pump therapy offers substantial glycemic benefits, as compared with multiple daily insulin injections, but has not been shown to lower the risk of severe hypoglycemia significantly.[4]

The automatic suspension of insulin delivery when a preset sensor glucose threshold is reached has the potential to mitigate hypoglycemia. The low-glucose suspend feature, available in the Medtronic Paradigm Veo pump outside the United States since 2009, was used in this study in the intervention group; the feature allows for suspension of insulin delivery for up to 2 hours at a sensor glucose value that does not require confirmation by the person using the pump. In the United States, this threshold-suspend feature is currently under review by the Food and Drug Administration.

The low-glucose suspend feature has been evaluated in a retrospective analysis,[5] two nonrandomized clinical studies,[6,7] one study of in-clinic induction of hypoglycemia,[8] and an interim cohort analysis.[9] These studies were limited by their short duration,[6-8] relatively small study populations,[6,7,9] or failure to evaluate changes in glycated hemoglobin levels.[5,6,8] We conducted a randomized, controlled, multicenter, open-label trial — ASPIRE (Automation to Simulate Pancreatic Insulin Response) In-Home study — to evaluate the effects of the threshold-suspend feature with sensor-augmented insulin-pump therapy, as compared with sensor-augmented insulin-pump therapy alone, on glycated hemoglobin levels and nocturnal hypoglycemia in patients with documented nocturnal hypoglycemia.

Methods

Patients

Eligible patients were 16 to 70 years of age and had type 1 diabetes of at least 2 years' duration, had a glycated hemoglobin value of 5.8 to 10.0%, and had used insulin-pump therapy for more than 6 months. Patients were excluded if they had had more than one episode of severe hypoglycemia (resulting in coma or seizures or requiring medical assistance) in the previous 6 months; were pregnant; had received a diagnosis of macrovascular disease, thyroid disease, or chronic renal disease in the previous 12 months; had been hospitalized or had visited the emergency room for symptoms related to uncontrolled diabetes in the previous 6 months; or had red-cell disease affecting glycation of hemoglobin. Validated quality-of-life surveys — the Hypoglycemia Fear Survey[10] and the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D)[11] — were administered before randomization and at study end. Written informed consent was obtained from adults and from parents or guardians of minors, and assent was obtained from minors.

Run-in and Study Phases

The study had a 2-week run-in phase, which could be repeated, and a 3-month study phase (see Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM .org). During the run-in phase, patients used the Paradigm Revel 2.0 insulin pump and Enlite glucose sensors (both Medtronic MiniMed). These sensors, which were used throughout the study, were calibrated with the study meter (Bayer Contour Next Link, Bayer HealthCare) and have a previously established mean absolute relative difference between sensor and reference blood glucose values of 13.6%.[12] To be eligible for randomization, patients wore sensors for at least 80% of the time and had at least two nocturnal hypoglycemic events during the run-in phase. A nocturnal hypoglycemic event was defined as sensor glucose values of 65 mg per deciliter (3.6 mmol per liter) or less between 10 p.m. and 8 a.m. for more than 20 consecutive minutes in the absence of a pump interaction (i.e., meter blood glucose entries, carbohydrate entries, and insulin-delivery changes) within 20 minutes, as determined by reviews of data uploaded with the use of Medtronic CareLink Therapy Management Software for Diabetes.

Patients were randomly assigned to receive sensor-augmented insulin-pump therapy with the threshold-suspend feature (threshold-suspend group) or standard sensor-augmented insulin-pump therapy (control group). The study-visit schedule was identical in the two groups (Fig. S1 in the Supplementary Appendix). The threshold-suspend group used the Paradigm Veo insulin pump with its threshold-suspend feature initially set to suspend insulin delivery at sensor glucose values of 70 mg per deciliter (3.9 mmol per liter) or less, after which the setting could

range from 70 mg per deciliter to 90 mg per deciliter (5.0 mmol per liter). Patients assigned to the control group continued to use the Paradigm Revel 2.0 insulin pump, which does not have the threshold-suspend feature. Patients in the threshold-suspend group were instructed to have the threshold-suspend feature on between 10 p.m. and 8 a.m.; it was optional at other times. A representation of the equipment is shown in Figure S2 in the Supplementary Appendix. Urinary ketone concentrations were assessed every morning, and blood ketone concentrations were measured if meter glucose values were more than 300 mg per deciliter (16.7 mmol per liter) or in the event of symptomatic ketosis. Pump data were uploaded with the use of Medtronic CareLink Therapy Management Software for Diabetes at weekly intervals. Glycated hemoglobin levels were measured at a central laboratory (Quest Diagnostics); values at randomization and at the end of the study were compared for the safety end point.

END POINTS

The primary safety end point was the change in the glycated hemoglobin level from randomization to study end. The primary efficacy end point was the area under the curve (AUC) for nocturnal hypoglycemic events (events between 10 p.m. and 8 a.m.). Secondary and other end points included the percentage of sensor glucose values that were less than 70 mg per deciliter, rates of hypoglycemic events, characteristics of automatic pump-suspension events, and quality-of-life and treatment-related measures.

STUDY OVERSIGHT

The study was sponsored by Medtronic. Representatives of Medtronic, along with the study investigators, performed the data collection and the interpretation and analysis of the data, and all authors vouch for the accuracy and completeness of the data presented and for the fidelity of this report to the study protocol, available at NEJM.org. An independent data and safety monitoring board analyzed the data for safety. All the authors wrote and revised the manuscript and made the decision to submit it for publication. All authors signed nondisclosure agreements with Medtronic. Employees of Medtronic provided editorial assistance with an earlier version of the manuscript.

STATISTICAL ANALYSIS

We analyzed data for the intention-to-treat cohort, which included all randomly assigned patients. For the primary safety end point, a linear regression model was used with the change in the glycated hemoglobin level from the time of randomization to 3 months as the dependent variable; covariates were treatment group and glycated hemoglobin level at randomization. The 97.5% upper confidence limit for the between-treatment difference was estimated and compared with the predefined 0.4% noninferiority margin. The multiple-imputation method (described in the Supplementary Appendix) was adopted to handle missing data.

For analysis of the primary efficacy end point, only events that did not include a pump interaction, that were not preceded by a nonphysiologic sensor glucose rate of change (>5 mg per deciliter [0.3 mmol per liter] per minute), and that lasted for more than 20 minutes after the first sensor glucose value was 65 mg per deciliter or less were analyzed. Events separated by less than 30 minutes were counted as a single event.

The magnitude and duration of each qualified hypoglycemic event were used to calculate the AUC for sensor glucose values of 65 mg per deciliter or less. Event AUC data were analyzed with the use of both original and log-transformed scales. Mean log-transformed event AUCs were estimated and compared by means of a superiority test with a one-sided significance level of 0.025.

The analysis of the primary efficacy end point was performed on the basis of the conditional power procedure,[13-15] with nocturnal hypoglycemic events treated as independent events within the same patient. In addition, a supportive analysis was performed with the use of a mixed-effects model incorporating within-patient correlation.

RESULTS

STUDY RECRUITMENT AND BASELINE CHARACTERISTICS

A total of 414 patients were assessed for eligibility, and 320 entered the run-in phase (Fig. 1). Seventy-three patients did not undergo randomization: 57 did not meet the requirements for the number of nocturnal hypoglycemic events or for sensor wear, and 16 were withdrawn during the

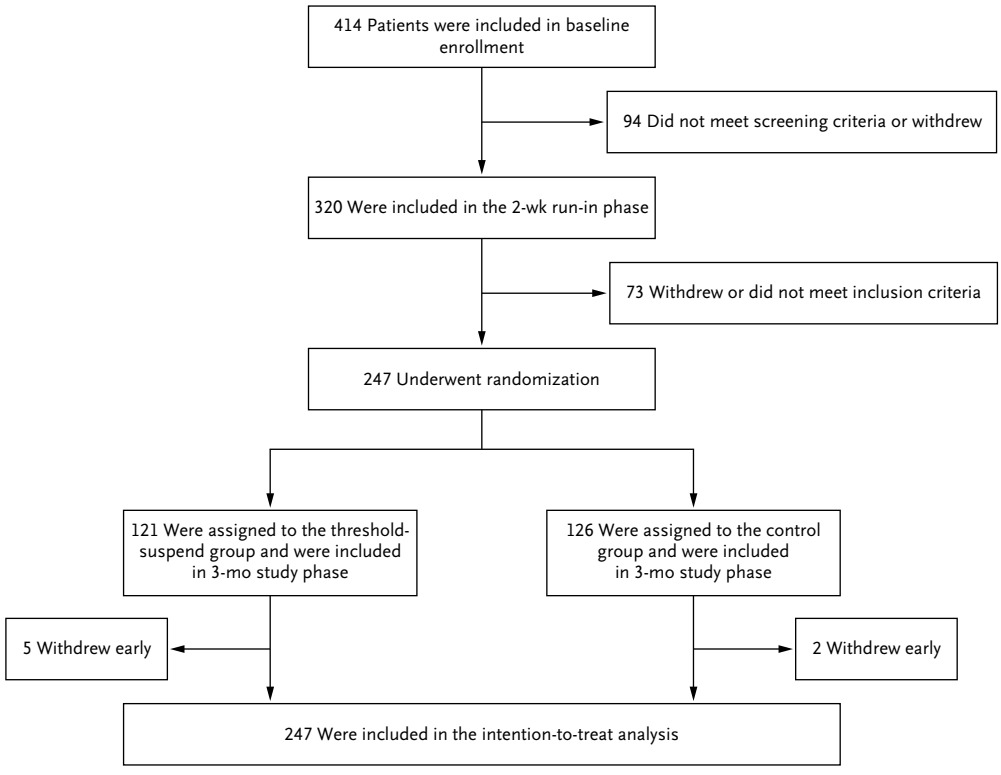

Figure 1. Enrollment, Randomization, and Inclusion in the Study Phase.

A total of 320 patients participated in the run-in phase. To advance to the study phase, patients had to have worn glucose sensors at least 80% of the time, and sensor data had to have shown at least two nocturnal hypoglycemic events. A total of 247 patients were randomly assigned to a study group: 121 to the threshold-suspend group and 126 to the control group.

run-in phase. A total of 68 patients repeated the run-in phase, of whom 40 underwent randomization. Glycated hemoglobin values and rates of nocturnal hypoglycemia were similar in the two groups during the run-in phase (Table S1 in the Supplementary Appendix). Table 1 shows the characteristics of the 247 randomly assigned patients. During the study phase, 7 patients were withdrawn early: 3 did not adhere to the protocol, 2 declined to use features of the study device, 1 had personal reasons, and 1 had dizziness.

PRIMARY SAFETY END POINT

As shown in Figure 2A (and Table S1 in the Supplementary Appendix), the change in the glycated hemoglobin level from randomization to study end was negligible in both groups, and the between-group difference was 0.05 percentage points. The upper limit of the 95% confidence interval (–0.05 to 0.15) for the difference in the change in the glycated hemoglobin level was lower than the prespecified noninferiority margin of 0.4 percentage points and met the primary safety criterion.

EFFICACY END POINTS

As shown in Figure 2B, the mean (±SD) AUC for nocturnal hypoglycemic events in the threshold-suspend group was 37.5% less than that of the control group (980±1200 mg per deciliter [54.4±66.6 mmol per liter] × minutes vs. 1568±1995 mg per deciliter [87.0±110.7 mmol per liter] × minutes). This reduction was significant ($P<0.001$) with the use of either a two-sample t-test or a mixed-effects model that included within-patient clustering effects, thus meeting the criterion for the efficacy end point. The mean sensor glucose value was 62.6 mg per deciliter (3.5 mmol per liter) at

Table 1. Baseline Characteristics of the Patients Who Underwent Randomization.*

Characteristic	Threshold-Suspend Group (N=121)	Control Group (N=126)
Age (yr)		
Mean	41.6±12.8	44.8±13.8
Range	16–69	16–70
Duration of diabetes (yr)	27.1±12.5	26.7±12.7
Male sex (%)	38.0	39.7
Weight (kg)	79.6±15.9	79.1±15.1
Body-mass index†	27.6±4.7	27.1±4.3
Glycated hemoglobin at randomization (%)	7.26±0.71	7.21±0.77

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

the beginning of nocturnal hypoglycemic events in both groups and at 4 hours was 162.3 mg per deciliter (9.0 mmol per liter) in the threshold-suspend group as compared with 140.0 mg per deciliter (7.8 mmol per liter) in the control group. The mean AUC for combined daytime and nighttime hypoglycemic events was 31.4% lower in the threshold-suspend group than in the control group (798±965 mg per deciliter [44.3±53.6 mmol per liter] × minutes vs. 1164±1590 mg per deciliter [64.6±88.3 mmol per liter] × minutes, P<0.001) (Table S1 in the Supplementary Appendix). These safety and efficacy results were consistent in subgroups of patients who were stratified according to age, glycated hemoglobin level at randomization, and duration of diabetes (Tables S3, S4, and S5 in the Supplementary Appendix).

The threshold-suspend group had significantly lower weekly rates of both nighttime hypoglycemic events and combined daytime and nighttime events than the control group (P<0.001 for both comparisons) (Table S1 in the Supplementary Appendix). The rate of nighttime hypoglycemic events was reduced by 31.8% (1.5±1.0 vs. 2.2±1.3 per patient-week). The distribution of sensor glucose values differed significantly between the groups with regard to the percentage of sensor glucose values of less than 50 mg per deciliter (2.8 mmol per liter), 50 to less than 60 mg per deciliter (3.3 mmol per liter), and 60 to less than 70 mg per deciliter (Fig. 2C). For the nocturnal hours, there was a 26.8% reduction in the percentage of sensor glucose values of 60 to less than 70 mg per deciliter, a 41.9% reduction in values of 50 to less than 60 mg per deciliter, and a 57.1% reduction in values of less than 50 mg per deciliter in the threshold-suspend group as compared with the control group (Table S2 in the Supplementary Appendix).

AUTOMATIC PUMP-SUSPENSION EVENTS

In the threshold-suspend group, the mean per-patient number of automatic pump-suspension events mediated by the threshold-suspend feature (threshold-suspend events) was 2.08 in each 24-hour interval and 0.77 in each nighttime (10 p.m. to 8 a.m.) interval. The median duration of nighttime threshold-suspend events was 11.9 minutes (mean, 39.4); 43.1% lasted for less than 5 minutes, and 19.6% lasted for 2 hours. The median duration of combined daytime and nighttime threshold-suspend events was 1.42 minutes (mean, 25.5); 56.3% lasted for less than 5 minutes, and 9.4% lasted for 2 hours (±2 minutes). For 96.9% of the threshold-suspend events, the threshold-suspend feature was set at 70 mg per deciliter; the feature was turned on for 85.5% of the time.

There were 1873 threshold-suspend events that lasted for 2 hours (±2 minutes); of these, 1444 were nocturnal. A total of 111 of 121 patients in the threshold-suspend group had at least one nocturnal event lasting for 2 hours. The mean sensor glucose values before, during, and after the 1438 2-hour nocturnal events that could be evaluated (6 were excluded owing to insufficient sensor data) are summarized in Figure 3. The mean sensor glucose value at the end of these 2-hour threshold-suspend events was 92.6±40.7 mg per deciliter (5.1±2.6 mmol per liter), and the distribution of values was as follows: less than 70 mg per deciliter, 33.1%; 70 to 200 mg per deciliter (11.1 mmol per liter), 64.8%; and more than 200 mg per deciliter, 2.2%. Two hours after insulin delivery was resumed (4 hours after the beginning of the threshold-suspend event), the mean sensor glucose value was 168.8±64.6 mg per deciliter (9.4±3.6 mmol per liter). The percentages of sensor glucose values at 4 hours after pump suspension were as follows: less than 70 mg per deciliter, 3.9%; 70 to 200 mg per deciliter, 70.2%; and more than 200 mg per deciliter, 26.0% (Fig. S3 in the Supplementary Appendix). It is unknown

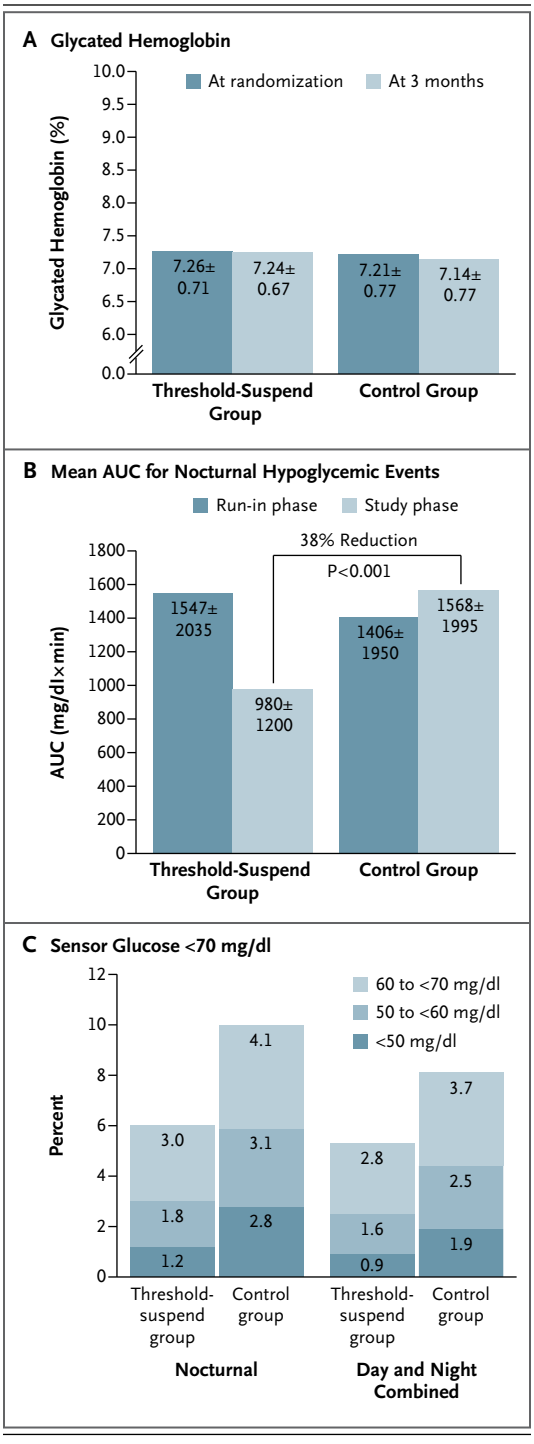

Figure 2. Primary and Key Secondary End Points.

As shown in Panel A, the mean (±SD) changes in glycated hemoglobin concentrations during the study phase (the primary safety end point) were similar in the threshold-suspend and control groups (0.00±0.44% vs. −0.04±0.42%; difference, 0.05 percentage points; 95% confidence interval [CI], −0.05 to 0.15). As shown in Panel B, the mean area under the curve (AUC) for nocturnal hypoglycemic events during the study phase (the primary efficacy end point) was 37.5% lower in the threshold-suspend group than in the control group (P<0.001). As shown in Panel C, the percentage of sensor glucose values that were less than 70 mg per deciliter was lower in the threshold-suspend group than in the control group, whether during nighttime hours (6.0% vs. 10.0%) or during daytime and nighttime hours combined (5.3% vs. 8.1%). The P value was less than 0.001 for each range in the panel. (See Table S2 in the Supplementary Appendix for the percentages of sensor glucose values in all ranges.) To convert values for glucose to millimoles per liter, multiply by 0.05551.

whether patients ingested food or glucose during the 4-hour time period.

QUALITY-OF-LIFE MEASURES AND TREATMENT-RELATED VARIABLES

Scores on the Hypoglycemia Fear Survey[10] and the EQ-5D[11] did not show any difference in trends between groups. The mean sensor life during the study period was 4.8 days in both groups. There were no significant differences in insulin dosage (total, basal, and bolus); the number of boluses and use of the bolus calculator; sensor wear, sensor life, and sensor calibrations; or change in body weight (Table S6 in the Supplementary Appendix). The number of finger-stick blood glucose measurements per day was 6.2 at the beginning and 5.6 at the end of the study in the threshold-suspend group and 5.9 and 5.3, respectively, in the control group (Table S6 in the Supplementary Appendix).

SAFETY AND ADVERSE EVENTS

No episodes of diabetic ketoacidosis occurred in either group. In the threshold-suspend group, there were no severe hypoglycemic events (resulting in coma or seizures or requiring medical assistance) in the 3-month study phase. The rate of severe hypoglycemic events was 0.13 per patient-year in the control group (four events, starting at 6 p.m., 9 p.m., 8 a.m., and 12:30 a.m., in four patients). Nadir sensor glucose values during these events were 56 mg per deciliter (3.1 mmol per liter), 40 mg per deciliter (2.2 mmol per liter), 76 mg per deciliter (4.2 mmol per liter), and 40 mg per deciliter, respectively. Morning urinary ketones were undetectable 94.8% of the time and large ketones were present 0.2% of the time in the thresh-

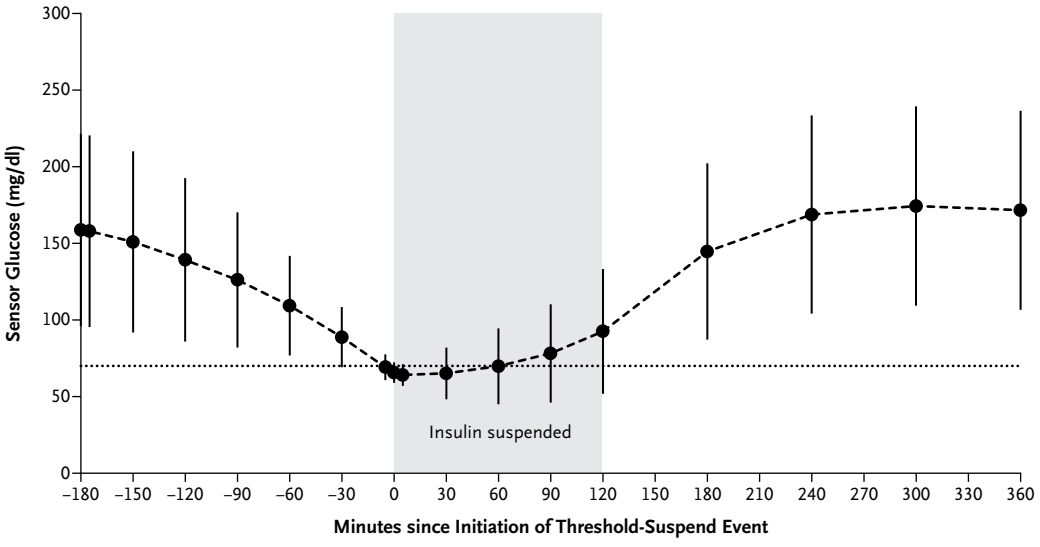

Figure 3. Sensor Glucose Values during Threshold-Suspend Events.

Shown are mean (±SD) sensor glucose values during 1438 nocturnal threshold-suspend events lasting for 2 hours. Time 0 indicates the time that the pump suspension started, and 120 minutes indicates the resumption of insulin delivery. The dotted line is at 70 mg per deciliter. See Figure S3 in the Supplementary Appendix for the percentages of sensor glucose values in various ranges at 2 and 4 hours after the beginning of nocturnal 2-hour threshold-suspend events.

old-suspend group; morning urinary ketones were undetectable 96.2% of the time and large ketones were present 0.2% of the time in the control group. The mean blood ketone levels were similar in the threshold-suspend and control groups (0.31 and 0.28 mmol per liter, respectively). There were 340 ketone measurements for elevated glucose levels in the threshold-suspend group, of which 8.8% were more than 0.6 mmol per liter, and 242 measurements in the control group, of which 7.0% were more than 0.6 mmol per liter.

There were no deaths or device-related serious adverse events. There were 19 device- or procedure-related adverse events during the study phase (Table 2). One patient had prolonged pump suspensions (a device-performance issue) that did not result in an adverse event.

DISCUSSION

This multicenter, open-label, randomized, controlled trial showed that use of the threshold-suspend feature in sensor-augmented insulin-pump therapy significantly reduced the AUC for rigorously defined nocturnal hypoglycemic events (a proxy for the severity and duration of such events), the weekly rate of nighttime hypoglycemic events, and the percentage of nocturnal time spent with sensor glucose values in the hypoglycemic range. In addition, these reductions in measures of hypoglycemia with the threshold-suspend feature were observed for the full 24-hour period. Lower exposure to hypoglycemia was consistent in subgroups of patients stratified according to age, duration of diabetes, and glycated hemoglobin level at randomization and was achieved without significant changes in glycated hemoglobin levels, severe hypoglycemic events, ketosis, or diabetic ketoacidosis. The finding that there were no significant between-group differences in the number of study visits, insulin use, sensor wear and calibrations, or number of blood glucose determinations suggests that the reduction in hypoglycemia was due to the threshold-suspend feature itself.

Prior limited observational and interventional studies of the low-glucose suspend feature showed that it was acceptable to patients, reduced hypoglycemia (including in patients prone to hypoglycemia and in children and adolescents), and was associated with a low risk of severe rebound hyperglycemia.[5-9] In our study,

as in these previously published studies,[5,9] sensor glucose values at 2 and 4 hours after automatic pump suspensions did not result in hyperglycemia, and the distribution of the duration of time that insulin was suspended was also similar, with 45 to 55% of the suspensions lasting up to 10 minutes and 11 to 13% lasting the full 2 hours in the prior studies.[5,6,9]

Use of the threshold-suspend feature reduced the weekly rate of hypoglycemic events, suggesting that it prevented hypoglycemia. The observation that recent episodes of hypoglycemia predispose patients to subsequent episodes that are longer and more severe has been made previously.[16-18] The underlying mechanism (or mechanisms) for this preventive effect were not investigated in this study, but avoidance of hypoglycemia may spare glycogen stores, allow for an improved counterregulatory hormone response, and minimize hypoglycemia-associated autonomic failure.[16] The four episodes of severe hypoglycemia during the study phase all occurred in the control group, at a rate of 0.13 per patient-year, which was identical to the rate among patients who received multiple daily injections and those who received sensor-augmented insulin-pump therapy in the Sensor-Augmented Pump Therapy for A1C Reduction (STAR) 3 study.[4]

Our study had several limitations. First, sensor glucose values were used for all analyses without validation by another reference method. Second, according to the definition used for hypoglycemic events that could be evaluated, runs of sensor glucose values of 65 mg per deciliter or less lasting less than 20 minutes and those with evidence of a pump interaction were not analyzed. Had these been included, the weekly rate of hypoglycemic events probably would have increased and the mean event AUC probably would have decreased. Third, the generalizability of the study results may be limited because only hypoglycemia-prone patients were enrolled. Finally, the 3-month duration of the study may have been too short to show a benefit with respect to the quality of life. Our quality-of-life assessment showed no benefit in the threshold-suspend group as compared with the control group. In contrast, the STAR 3 study showed an improvement in the quality of life after a year with the use of sensor-augmented insulin-pump therapy as compared with multiple daily insulin-injection therapy.[19]

Table 2. All Adverse Events during the Run-In and Study Phases.

Event	Run-In Phase	Study Phase	
		Threshold-Suspend Group	Control Group
		no. of events	
Serious adverse events related to study device or study procedure	0	0	0
Serious adverse events not thought to be related to study device or study procedure	4*	0	2†
Adverse events not related to study device or study procedure	114	46	53
Adverse events related to study device or study procedure			
Skin-related	20	4	12
Related to infusion-set malfunction and resulting in severe hyperglycemia (blood glucose >300 mg/dl [16.7 mmol/liter], with ketones >0.6 mmol/liter)	2	3	0
Related to the infusion set and resulting in hyperglycemia	1	0	0
Syncope	1	0	0
Emesis from mixed-meal tolerance test used to assess C-peptide level	1	0	0
Pump-priming issue and hypoglycemia	1	0	0
Total	144	53	67

* The four reported serious adverse events in the run-in phase were radiculopathy resulting in laminectomy in one patient, coronary ischemia and stent placement in one patient, coronary artery disease in one patient, and atypical chest pain in one patient.

† The two reported serious adverse events in the study phase were severe hypoglycemia in one patient and pneumonia in one patient.

In the STAR 3 study, sensor-augmented insulin-pump therapy allowed for rapid, significant, and durable reductions in glycated hemoglobin levels, as compared with multiple daily insulin-injection therapy.[4] Results from the present study show that over a 3-month period, the addition of automatic pump suspension with the threshold-suspend feature can reduce episodes of hypoglycemia, especially at night, without any apparent loss in overall glucose control.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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