Reduction in Hypoglycemia With the Predictive Low-Glucose Management System: A Long-Term Randomized Controlled Trial in Adolescents With Type 1 Diabetes

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OBJECTIVE

Short-term studies with automated systems that suspend basal insulin when hypoglycemia is predicted have shown a reduction in hypoglycemia; however, efficacy and safety have not been established in long-term trials.

RESEARCH DESIGN AND METHODS

We conducted a 6-month, multicenter, randomized controlled trial in children and adolescents with type 1 diabetes using the Medtronic MiniMed 640G pump with Suspend before low (predictive low-glucose management [PLGM]) compared with sensor-augmented pump therapy (SAPT) alone. The primary outcome was percentage time in hypoglycemia with sensor glucose (SG) <3.5 mmol/L (63 mg/dL).

RESULTS

In an intent-to-treat analysis of 154 subjects, 74 subjects were randomized to SAPT and 80 subjects to PLGM. At baseline, the time with SG <3.5 mmol/L was 3.0% and 2.8% in the SAPT and PLGM groups, respectively. During the study, PLGM was associated with a reduction in hypoglycemia compared with SAPT (% time SG <3.5 mmol/L: SAPT vs. PLGM, 2.6 vs. 1.5, $P < 0.0001$). A similar effect was also noted in time with SG <3 mmol/L ($P < 0.0001$). This reduction was seen both during day and night ($P < 0.0001$). Hypoglycemic events (SG <3.5 mmol/L for >20 min) also declined with PLGM (SAPT vs. PLGM: events/patient-years 227 vs. 139, $P < 0.001$). There was no difference in glycated hemoglobin (HbA_{1c}) at 6 months (SAPT 7.6 ± 1.0% vs. PLGM 7.8 ± 0.8%, $P = 0.35$). No change in quality of life measures was reported by participants/parents in either group. There were no PLGM-related serious adverse events.

CONCLUSIONS

In children and adolescents with type 1 diabetes, PLGM reduced hypoglycemia without deterioration in glycemic control.

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The integration of real-time continuous glucose monitoring (CGM) systems and pump therapy has been an important milestone in the management of type 1 diabetes (1), and the more recent incorporation of control algorithms has offered potential to further improve clinical outcomes. For example, the "Low glucose suspend" algorithm shuts off basal insulin delivery with sensor-detected hypoglycemia and has been shown to reduce the duration and severity of hypoglycemia (2,3). The next step has been the development of an algorithm that predicts impending hypoglycemia based on CGM and suspends basal insulin before the occurrence of hypoglycemia. The predictive low-glucose management (PLGM) system, the only commercially available sensor-integrated insulin delivery system, has been shown to reduce hypoglycemia in in-clinic conditions (4–6), in short-term outpatient observational studies (7–11), and recently in a 2-week randomized controlled trial (12). The important question as to whether the system is effective and safe in long-term use, and by inference in clinical practice, is however untested, especially as long-term CGM use has been challenging for many patients. Short-term studies have not provided information as to whether the system results in deterioration in glycemic control. Finally, it is not known whether behavioral changes develop in an individual using these systems over long-term and whether these in turn will impact on outcomes. A 6-month study attempts to address these questions.

The PLGM system is incorporated in the MiniMed 640G pump (Medtronic, Northridge, CA). The pump, when used in conjunction with the Medtronic Enlite Sensor and Guardian 2 Link transmitter, has the "Suspend before low" feature, which suspends insulin infusion when hypoglycemia is predicted. In order to test the effectiveness and safety of the system over the long-term, we conducted a 6-month randomized controlled home trial in real-life conditions in older children and adolescents. This age-group is at significant risk of hypoglycemia (13) and in most surveys has higher glycated hemoglobin (HbA_{1c}) and potentially has the most to gain from strategies that potentially could improve glycemic control.

RESEARCH DESIGN AND METHODS

Study Design and Participants

A detailed description of the study protocol has been published (14). This was a multicenter, unblinded, parallel, randomized controlled phase 3 home trial conducted by five tertiary pediatric diabetes centers in Australia. Ethics approval was received at each site. Eligible patients were 8–20 years of age, had type 1 diabetes of at least 1 year duration, with HbA_{1c} of $<$10% ($<$86 mmol/mol), and had used insulin pump therapy for $>$6 months. Patients were excluded if they had any medical condition predisposing to hypoglycemia, were on oral hypoglycemic agents, were pregnant, or were not able to comply and meet the protocol requirements. Participants were screened through the diabetes clinics for eligibility in the study. Written informed consent was obtained from participants aged $\geq$18 years and written parental consent and participant assent for those $<$18 years of age.

Participants were randomized to either the control group with sensor-augmented pump therapy (SAPT) alone (Suspend on low and Suspend before low not enabled) or to the intervention group with SAPT and Suspend before low enabled (PLGM). Participants were allocated to either SAPT or PLGM using minimization incorporating a random element. Each site had their own minimization schedule based on the following equally weighted factors: sex, age, HbA_{1c}, and hypoglycemia awareness score. Participants were allocated to the minimization-preferred group at a probability of 0.7. The program Minimpy (version 0.3) was used to allocate participants (15).

PLGM System

Suspend before low feature is a SmartGuard function on the MiniMed 640G pump. The low limit was set for the entire study duration at 3.4 mmol/L (61 mg/dL), and the pump would therefore suspend insulin infusion when sensor glucose (SG) was $\leq$7.3 mmol/L or 131 mg/dL (70 mg/dL above the low limit) and predicted to be $\leq$4.5 mmol/L or 81 mg/dL (20 mg/dL above the low limit) in 30 min. In the absence of patient interference, after pump suspension, the insulin infusion resumes after a maximum suspend period of 2 h or earlier if the autoresumption parameters are met. The low limit alarm was by default active when PLGM was on. In the control group on SAPT, all participants were advised to keep the low limit alarm on. In both groups, the alerts on high, before high, and before low were optional for the participant. The basal resume alert (on autoresumption) was an optional alert in patients using PLGM; however, the system always alerted the patient if basal infusion resumes after the 2-h maximum suspend period.

Study Visits

The first and second visits were for pump start and sensor training, respectively. A minimum of a 2-week run-in period was required to demonstrate confidence in using the system and to ensure eligibility for randomization. All participants were required to use CGM for $>$80% of the time and demonstrate hypoglycemia (at least one SG $<$3.5 mmol/L) or risk of hypoglycemia (one or more SG $<$4.4 mmol/L on at least three different days). At visit three, eligible participants were randomly assigned to standard SAPT or PLGM. The study visit schedule was identical in both groups, and the participants were followed up at 3 and 6 months after randomization (visits four and five). Pump data were uploaded to Medtronic CareLink Therapy Management Software for Diabetes. HbA_{1c} levels were measured at randomization and at visits four and five. Validated questionnaires were administered to participants and/or their parents at the first visit and repeated at visits four and five. These included the hypoglycemia awareness questionnaire from Clarke et al. (16), EQ-5D-Y and pediatric-specific diabetes quality of life (PedsQL) questionnaires (17), hypoglycemia fear survey (18), and CGM satisfaction questionnaire (19). Apart from ketone testing as part of routine care during sick days, participants were instructed to test for ketones before breakfast and prebed in both groups, and after pump resumption after 2 h of suspend in the intervention group during the awake hours.

Study Outcomes

The primary objective of the study was the comparison of the average percentage of time spent in hypoglycemia (SG $<$3.5 mmol/L) with PLGM versus SAPT. The secondary objectives were comparisons of events of hypoglycemia, defined as 20 min or more with SG $<$3.5 mmol/L and the average percentage of time spent with SG $<$3.0 mmol/L and in hyperglycemia (SG 10–15 mmol/L and $>$15 mmol/L) with and without PLGM. The study also evaluated the time spent in hypoglycemia during the day (06:00 A.M. to 10:00 P.M.)

and night (10:00 P.M. to 6:00 A.M.). The percentage time in the glucose range of interest was calculated at each visit by dividing the number of observed CGM readings falling within the respective range by the total number of readings for the time period.

In addition, the safety of the system was determined by evaluating the number of ketosis events (blood ketones >0.6 mmol/L) and glycemic control (HbA_{1c}) at the end of 6 months. Using validated questionnaires, the study also evaluated the impact of PLGM on the patient's quality of life, fear of hypoglycemia, satisfaction and acceptability of the system, and hypoglycemia awareness. A data safety and monitoring board independently reviewed the data arising from the study.

Statistical Analysis

A modified intent-to-treat (ITT) approach was used for analysis. The ITT population was defined as all patients who were randomized and had at least one visit (visit four) after randomization. The percentages of time in hypoglycemia and hyperglycemia were calculated for each visit after randomization and were analyzed using likelihood-based, linear mixed-effect model repeated measurement. Models included fixed-effect terms for group, visit, site, baseline time in range, and group by visit interaction. Choice of correlation matrix was based on Akaike information criterion; in all models, the unstructured matrix resulted in the best model fit. Least squares (LS) means, based on the fixed terms in the model, and differences in least square mean change along with their 95% CIs were calculated. Incidence of severe hypoglycemia and SG-defined hypoglycemic events were analyzed as unadjusted incidence rates based on the Poisson distribution. Ketosis events are presented as percentage of total ketone measurements that were >0.6, and an incidence rate ratio was derived from a negative binomial mixed model analyzing the number of ketosis events with the total number of ketone measurements as the exposure variable. (One participant in the PLGM group on low-carbohydrate diet was excluded from analysis.) Mixed-effect model repeated measurements were conducted using SAS (version 9.4), and all other analyses were conducted

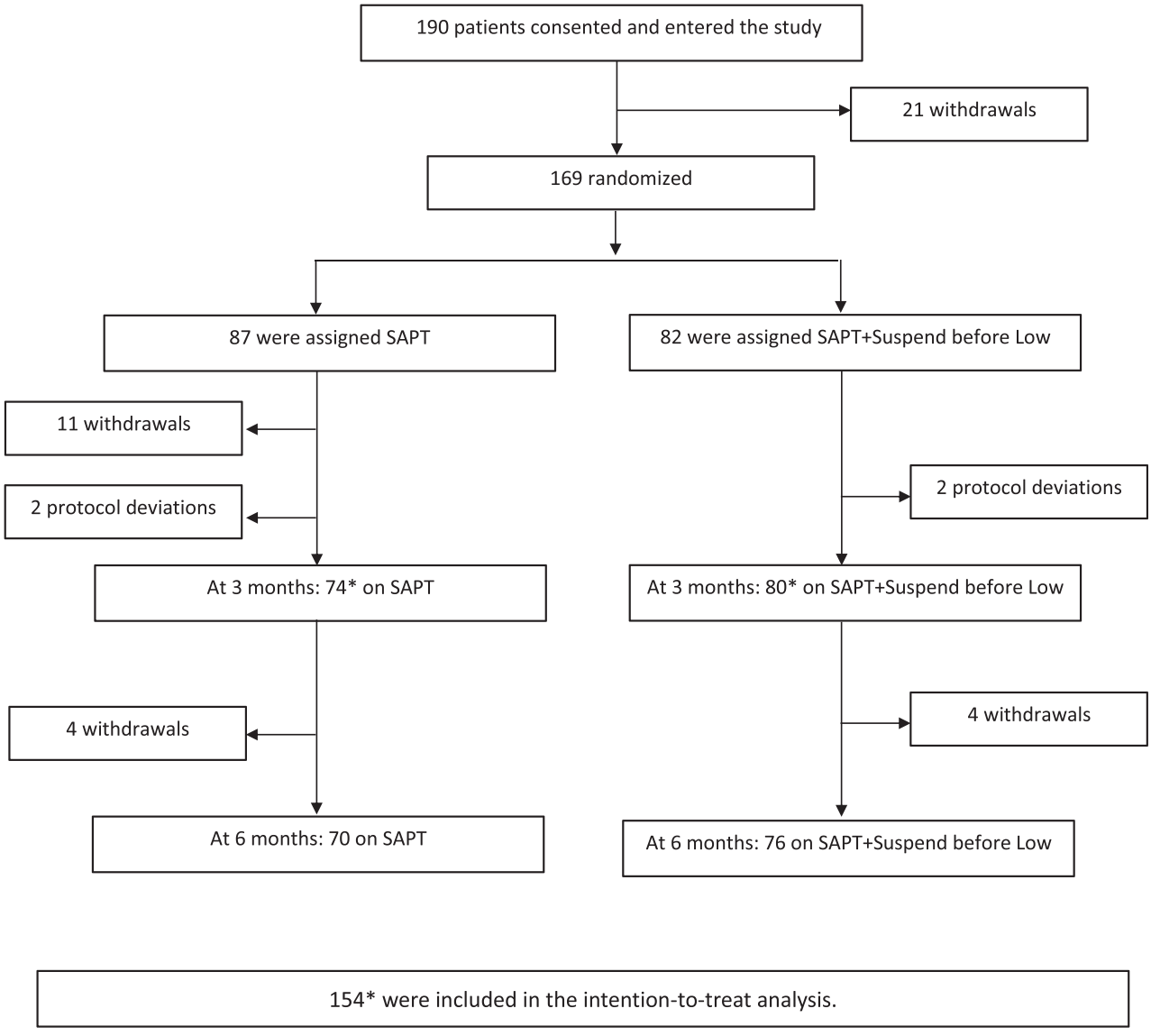

Figure 1—The consort diagram for participants in the trial.

using Stata (version 13.0). A P value <0.05 was considered statistically significant.

RESULTS

Study Recruitment and Baseline Characteristics

As illustrated in Fig. 1, 190 participants consented and entered the study. Twenty-one participants withdrew in the run-in period. Eligible participants were randomized with 87 to the control arm and 82 to the intervention arm. Eleven participants withdrew between randomization (visit three) and visit four, with a further eight withdrawals between visit four and end of the study. The reasons for withdrawal were multifactorial. While difficulty in inserting sensors, pain and bleeding at sensor site, sensor life, inaccuracies, and tape reactions were some of the reasons cited by participants, the intensity of the study, the need for increased parental support in younger children, and ability to comply with uploading the devices were reported by the others. Two participants in the intervention arm were excluded due to a protocol deviation (Suspend on low was activated instead of Suspend before low). The baseline CGM data were missing in two participants in the control arm and were excluded from analysis. The ITT population comprised all participants who were randomized and attended visit four. The data were therefore analyzed in 154 participants (age 13.2 ± 2.8 years, duration of diabetes 7.1 ± 3.8 years, HbA_{1c} 7.5 ± 0.8% [mean ± SD]): 74 participants in the control arm and 80 participants in the intervention arm.

Table 1 shows the baseline characteristics of the 154 participants. There were no differences in baseline characteristics between the two groups. At baseline, time spent <3.5 mmol/L in the SAPT group was 3.0 ± 3.2% and in the PLGM group was 2.8 ± 2.9%. All participants had >80% sensor use prior to randomization according to the eligibility criteria (SAPT 88% vs. PLGM 83%). The proportion of time with available sensor data was 72 ± 0.02% and 73 ± 0.02% between baseline and 3 months and 59 ± 0.03% and 63 ± 0.03% between 4 and 6 months in participants in the control and intervention groups, respectively. Sensor use remained similar in both groups during the duration of the study (P = 0.93). Participants on PLGM had an average of 2.35 suspend events per day.

Table 1—Baseline characteristics of the participants*

Characteristic	Control (SAPT)	Intervention (PLGM)	Total
n	74	80	154
Age (years)	13.3 ± 2.8	13.1 ± 2.8	13.2 ± 2.8
Males (%)	53	54	53
Duration of diabetes (years)	6.9 ± 3.8	7.2 ± 3.7	7.1 ± 3.8
HbA_{1c} (%)	7.4 ± 0.7	7.5 ± 0.8	7.5 ± 0.8
Duration of pump therapy (years)	4.5 ± 2.7	4.6 ± 2.8	4.6 ± 2.7
BMI**	21.4 ± 3.9	21.3 ± 3.5	21.3 ± 3.7
% time <3.5 mmol/L			
Day + night	3.0 ± 3.2	2.8 ± 2.9	2.5 ± 2.8
Day	2.5 ± 2.7	2.4 ± 2.7	2.5 ± 2.7
Night	3.8 ± 5.1	3.4 ± 4.2	3.3 ± 4.4
% time <3.0 mmol/L			
Day + night	1.4 ± 1.9	1.3 ± 1.7	1.1 ± 1.8
Day	1.1 ± 1.7	1.0 ± 1.5	1.1 ± 1.6
Night	2.0 ± 3.2	1.7 ± 2.7	1.8 ± 3.0

Values are means ± SD. There were no significant differences between the groups ($P > 0.05$). *Participants in the ITT analysis. **BMI is the weight in kilograms divided by the square of the height in meters.

Time Spent in Hypoglycemia

A reduction in time spent in hypoglycemia (SG <3.5 mmol/L) from the commencement of the study was demonstrated in both groups (SAPT 3% to 2.6%, P = 0.03 vs. PLGM 2.8% to 1.4%, $P < 0.0001$) but was greater with PLGM than SAPT during the entire study period (difference in LS means: −0.95% [95% CI −1.30, −0.61], $P < 0.0001$). The reduction in hypoglycemia with PLGM was persistent across the 6-month study duration. Over the study period, this equated to 37.7 min/day of time <3.5 mmol/L with SAPT and 20 min/day with PLGM. A similar effect was also noted in time spent with SG <3 mmol/L (SAPT 1.4% to 1.2%, P = 0.04 vs. PLGM 1.3% to 0.6%, $P < 0.0001$), with a greater reduction with PLGM than SAPT (difference in LS means: −0.44% [−0.64, −0.24], $P < 0.0001$). This corresponds to 17.6 min/day of time <3 mmol/L on SAPT and 9 min/day on PLGM (Fig. 2). SAPT alone was not associated with a statistically significant reduction in hypoglycemia during daytime (2.5% to 2.3%; difference in LS means: 0.23 [−0.48, 0.02], P = 0.07), although it was accompanied by a small reduction in nocturnal hypoglycemia (3.8% to 3.3%; difference in LS means: −0.45% [−0.88, −0.02], P = 0.04). In contrast, PLGM use resulted in hypoglycemia reduction both during day and night (day 2.4% to 1.3%; difference in LS means: −1.09% [−1.33, −0.85], $P <$ 0.001; vs. night 3.4% to 1.6%; difference in LS means: −1.96% [−2.37, −1.54], $P < 0.0001$), with a difference in LS means of 1.51% (0.92, 2.10; $P < 0.001$) between both groups.

Hypoglycemic Events

Both groups had a similar number of sensor-defined hypoglycemic events (SG <3.5 mmol/L for >20 min) during the run-in period (SAPT vs. PLGM, events/patient-years: 232 vs. 245 [95% CI 217, 248 vs. 230, 261], P = 0.245). However, at the end of the study, the PLGM group had fewer hypoglycemic events compared with those on SAPT (SAPT vs. PLGM, events/patient-years: 227 vs. 139 [95% CI 221, 234 vs. 134, 143], $P < 0.001$). There were no episodes of severe hypoglycemia in either group during the 6-month study period.

Impaired Awareness of Hypoglycemia

At baseline, there were 90 participants ≥12 years of age. Of these, impaired awareness of hypoglycemia (IAH; Clarke score ≥4) was present in 17% at baseline (n = 15), with a similar number in each group (SAPT 16% vs. PLGM 18%). At the end of 6 months, the prevalence of IAH in the SAPT group was 13% and 4% in the PLGM group. A mixed-effects logistic regression did not demonstrate a significant effect of intervention group (odds ratio 0.25 [0.03, 1.84], P = 0.17; reference category was SAPT). There was no effect of PLGM on the mean Clarke scores in the aware and IAH group (−0.04 [0.52, 0.43], P = 0.86).

Safety and Adverse Events

An increase in time spent in 10–15 mmol/L was seen with SAPT and PLGM (SAPT 27% to 31%, $P < 0.0001$ vs. PLGM 29% to 31%,

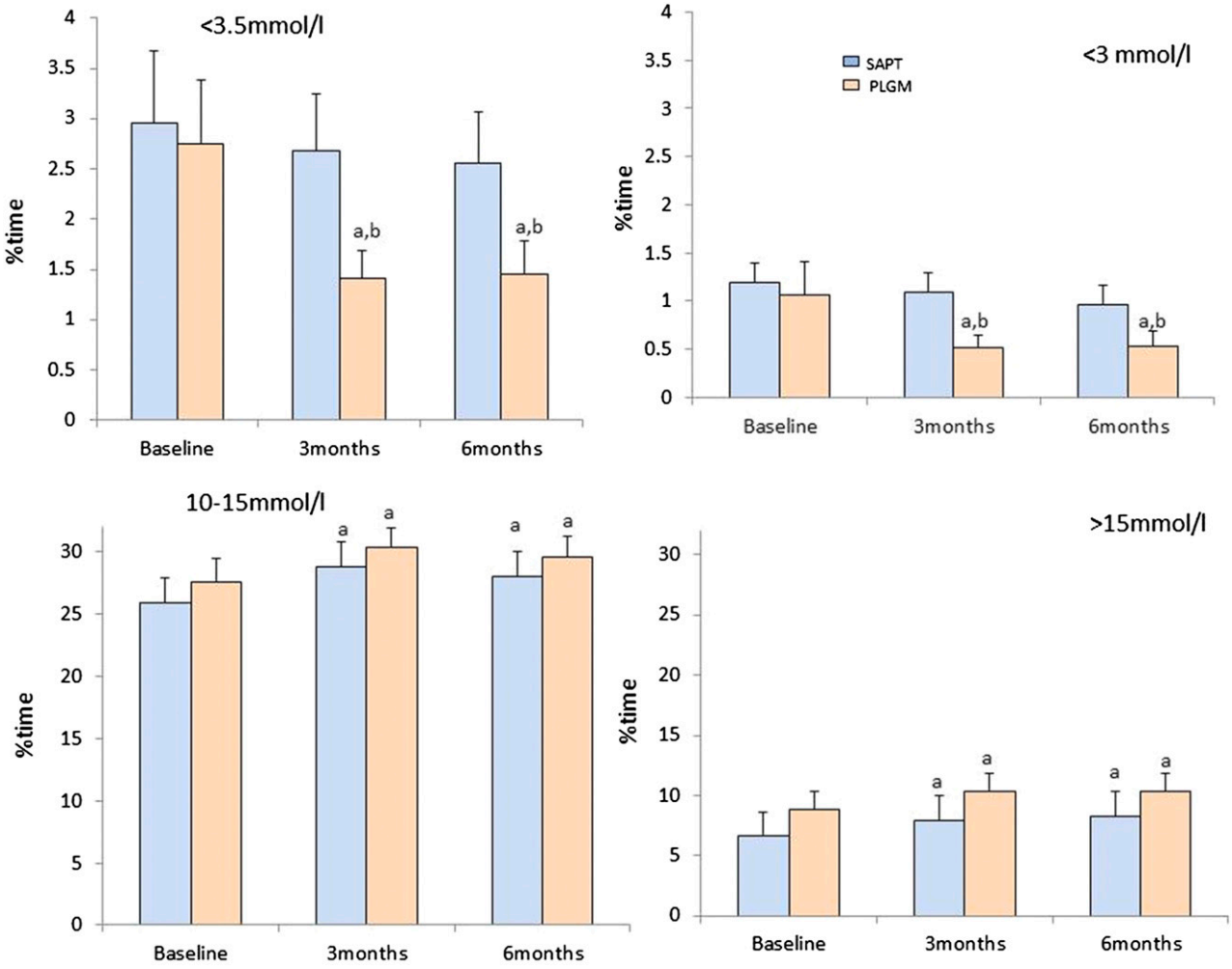

Figure 2—The time in hypoglycemia (SG <3.5 mmol/L and <3 mmol/L) and hyperglycemia (SG 10–15 mmol/L and >15 mmol/L). a, change from baseline ($P < 0.005$); b, difference between groups ($P < 0.005$). (A high-quality color representation of this figure is available in the online issue.)

$P < 0.0001$). However, there was no effect of the intervention on time spent in 10–15 mmol/L at the end of the study (difference in LS means: 0.47 [95% CI −1.1, 2.1], $P = 0.56$). Similarly, an increase in time >15 mmol/L was seen in both groups (SAPT 7% to 10%, $P < 0.0001$ vs. PLGM 9% to 10%, $P < 0.0001$), although there was no difference between the two groups at the end of the study (difference in LS means: 0.52 [−0.73, 1.78], $P = 0.40$). The mean SG was 9.3 mmol/L (9.1, 9.5) and 9.8 mmol/L (9.5, 10) in the control and intervention groups, respectively ($P < 0.005$). However, the HbA_{1c} level from randomization to study end was unchanged in both study groups (SAPT 7.4 ± 0.7% to 7.6 ± 1.0%, $P = 0.20$ vs. PLGM 7.5 ± 0.8% to 7.8 ± 0.8%, $P = 0.008$), with the difference in LS means of 0.09 (−0.10, 0.27; $P = 0.35$). There was no difference in the ketosis events (>0.6 mmol/L) between the two groups (SAPT 2.2% vs. PLGM 2.6%; incidence rate ratio 0.96 [0.52, 1.76], $P = 0.89$). Apart from one episode of diabetic ketoacidosis due to pump failure and poor management in the PLGM group, there were no severe adverse events in the study period.

Quality of Life and Fear of Hypoglycemia

At the end of the study, participants and their parents reported no change in quality of life measures in either group. Similarly, there was no difference in fear of hypoglycemia between the two groups. Table 2 provides the scores of the participants and their parents in both groups.

CONCLUSIONS

This study highlights an almost twofold reduction in hypoglycemia exposure in children and adolescents with type 1 diabetes using PLGM during a 6-month, multicenter, randomized controlled home trial. These results support the findings of the in-clinic studies that used the investigational PLGM system (4–6) and the short-term observational studies and trials that used the MiniMed 640G pump with the SmartGuard function in children and adults (7–12). In our study, both groups demonstrated a reduction in hypoglycemia, although the magnitude of reduction was greater with PLGM. The use of SAPT did not significantly reduce the time spent in hypoglycemia during the day but showed a mild reduction at night. In contrast, PLGM was associated with reduced day and night time hypoglycemia, with greater reduction at night. Children and adolescents spent approximately half the time in hypoglycemia with fewer hypoglycemic events with PLGM as compared with SAPT alone. The lower hypoglycemia exposure was consistent in subgroups of participants

Table 2—IAH, quality of life, fear of hypoglycemia, and CGM satisfaction in participants and parents in the trial

			Baseline		6 months		
Questionnaire			SAPT	PLGM	SAPT	PLGM	*P*
Time <3 mmol/L							
IAH (*n*)	*n*	Child*	7	8	6	2	0.17
	Score		2.0 ± 1.7	1.8 ± 1.5	1.7 ± 1.5	1.7 ± 1.2	0.86
Quality of life	VAS	Child*	81.8 ± 14.3	85.4 ± 9.3	85.7 ± 14.0	81.5 ± 17.2	0.69
		Parent	84.8 ± 11.9	85.2 ± 11.4	84.2 ± 13.5	85.5 ± 11.9	0.61
	Index	Child*	0.86 ± 0.11	0.90 ± 0.13	0.83 ± 0.25	0.85 ± 0.24	0.45
		Parent	0.84 ± 0.17	0.87 ± 0.14	0.81 ± 0.22	0.90 ± 0.11	0.50
Pediatric quality of life	Total	8–12 years	72.5 ± 13.3	72.7 ± 11.4	71.0 ± 13.2	71.9 ± 11.5	0.65
		>12 years	68.1 ± 13.2	68.6 ± 11.0	69.7 ± 15.3	68.3 ± 11.7	0.55
		Parent	65.1 ± 13.9	68.3 ± 12.1	63.2 ± 13.8	66.2 ± 12.1	0.45
Fear of hypoglycemia	Total	Child*	35.3 ± 13.5	34.5 ± 14.4	32.6 ± 11.9	31.8 ± 14.8	0.40
		Parent	46.7 ± 15.1	44.8 ± 16.0	44.9 ± 14.5	42.1 ± 14.7	0.29
	Behavior	Child*	18.9 ± 5.2	17.0 ± 6.4	19.2 ± 6.0	16.8 ± 6.5	0.82
		Parent	23.1 ± 6.6	21.9 ± 7.2	23.4 ± 7.0	20.8 ± 7.0	0.20
	Worry	Child*	16.3 ± 10.8	17.5 ± 10.3	13.4 ± 8.0	15.0 ± 10.5	0.16
		Parent	23.6 ± 11.8	22.9 ± 11.3	21.5 ± 10.3	21.3 ± 10.2	0.53
CGM satisfaction	Total	Child*	3.5 ± 0.3	3.6 ± 0.3	3.4 ± 0.4	3.5 ± 0.4	0.46
		Parent	3.6 ± 0.3	3.7 ± 0.3	3.5 ± 0.4	3.5 ± 0.3	0.12

IAH is expressed in numbers (*n*) and score; quality of life, fear of hypoglycemia, and CGM satisfaction are expressed as scores. $P < 0.05$: significant, derived from mixed models including data from 3 months and 6 months adjusting for baseline. VAS, visual analogue scale. *Self-reported by children >12 years of age.

irrespective of the age, duration of diabetes, HbA_{1c} level, and hypoglycemia awareness status. In our study, the baseline time in hypoglycemia was relatively low (38 min/day with SG <3.5 mmol/L or 18 min/day with SG <3 mmol/L); this contrasts with older studies but is similar to other recent studies with 73 min/day with SG <3.9 mmol/L in a German study (7) and 45 and 29 min/day, respectively, with SG <3.6 and <3.3 mmol/L in a study from Slovenia and Israel (12). These groups also showed a significant reduction in hypoglycemia by at least 50%. This does highlight that hypoglycemia has reduced in contemporary samples perhaps with improved modalities of treatment.

The decline in hypoglycemia exposure was not associated with an increase in hyperglycemia with PLGM as compared with SAPT. Although the time spent between 10–15 mmol/L and >15 mmol/L increased from baseline in both groups, there was no evidence for a difference between the control and intervention arm in spite of automated insulin suspends with PLGM. It is reassuring to note that insulin suspension by itself may not be the cause of the increase in hyperglycemia, and the observation that an increase in SG >10 mmol/L was noted in both groups could possibly be due to carbohydrate consumption with downward trend arrows in an attempt to prevent hypoglycemia. In contrast to the previously conducted short-term studies, the 6-month study duration provided us with the opportunity to follow the glycemic outcomes. Although there was an increase in HbA_{1c} from baseline with PLGM, there was no difference in the HbA_{1c} between the two groups at the end of 6 months. The safety of the system was further established with a similar proportion of ketosis in both groups. This is in accordance with previous studies that, although using a different predictive algorithm (Kalman filter predictive model), demonstrated a reduction in overnight hypoglycemia with predictive suspends without conferring an increased risk of morning ketosis (20,21). This further reinforces the efficacy of the system in reducing the time spent in hypoglycemia without deterioration of glycemic control.

The 6-month study duration further helped us to explore the impact of this technology on various psychosocial parameters in both children and their caregivers. Most participants were sensor naïve at the commencement of the study, and both groups used the same pump and sensors with PLGM enabled in the intervention group. The need of an additional sensor site, troubleshooting sensor problems, and coping with alarms and alerts with additional pump suspends and resumptions in the intervention group could potentially increase the burden of the disease. Hence, it is reassuring to note that there was no deterioration in the quality of life in both groups during the study. Furthermore, the expected reduction in fear of hypoglycemia was not evidenced in our cohort. There was no difference between the control and intervention groups at the end of the study in both children and their caregivers. This could be as PLGM does not completely abolish hypoglycemia, although it reduces the number of hypoglycemic events.

The SmartGuard option with the Suspend on low and Suspend before low functions empower the user to individualize diabetes management. A CareLink review of the MiniMed 640G pump demonstrated that at least 99% of all users used one or both suspend functions and 59% used Suspend before low exclusively (9). The threshold level for pump suspend can be individualized by the user for different times of the day. A higher threshold has a greater chance to abort an impending hypoglycemic event, albeit with an increase in the number of alarms, suspensions, hyperglycemia post-resumption, and possible patient fatigue.

On the contrary, a lower threshold could avoid the multiple suspensions but may not eliminate the risk of hypoglycemia. In recent studies, either the low limit was chosen by the participant (10) or the hypoglycemia threshold (3.9 mmol/L) was set for the whole study (7). In our study, we set the lower limit at 3.4 mmol/L (pump suspend if SG $\leq$4.5 mmol/L in 30 min). We used this low limit as a result of our experience in the in-clinic studies (4,5) and the PILGRIM study (6). We maintained the same threshold throughout the study to provide uniformity to the entire intervention group and to establish a threshold that would not be associated with clinically significant post-suspend hyperglycemia. However, in real-life, these thresholds can be altered and individualized depending on the glycemic excursions related to food and exercise in day-to-day life.

The reduction in the duration of hypoglycemia and hypoglycemic episodes was accompanied by a nonstatistically significant trend toward reduced prevalence of IAH with the use of PLGM. Although this result did not reach statistical significance, this outcome was only available for a smaller subpopulation of the sample. The observed, albeit nonsignificant, trend suggests that the reduced prevalence of IAH is potentially a clinically important secondary outcome that requires further study. Therapeutic options for patients with IAH remain limited and challenging, and although some individuals may gain benefit from structured education, the use of CGM, and SAPT with low glucose suspension, many do not respond to these approaches (22). Hypoglycemia avoidance is the basis of restoring awareness in patients with IAH (23,24), and systems like PLGM, by almost eliminating hypoglycemia, have the potential to improve awareness in this high-risk group and provide a valuable addition to the current armamentarium of available therapies.

Sustained frequent use of CGM is challenging in children and adolescents compared with adults, with sensor uptake higher in adults than among children. The Star 3 trial continuation phase reported a mean sensor wear time of 61% among adults and 45% among pediatric subjects (25). Similarly, the JDRF-CGM follow-up trial reported sensor wear of 6.5, 3.3, and 3.7 days/week in the 6th month in participants $>$25 years, 15–24 years, and 8–14 years, respectively (26). In our study, time commitment, technical challenges, sensor alerts, sensor efficacy, sensor life, and skin irritation were described as some of the barriers identified through open-ended questionnaires (27). These challenges are potentially compounded in the adolescent age-group, a physical and emotional growth phase associated with risk taking and vulnerability (28). Hence, it is vital to address these issues with participants and their families to provide them with education and support to overcome and troubleshoot these issues.

This study is the first randomized controlled home trial and provides high-quality evidence of the efficacy and safety of the PLGM system in the prevention of hypoglycemia in real-life situations. The strength of our study is in its ability to provide this clinical insight about the use of PLGM in free-living conditions. A limitation of our study is that the important clinical observation of reduced prevalence of IAH in participants on PLGM did not reach statistical significance. We were also unable to corroborate it with improved counterregulatory hormones as originally planned in our study design, as the prevalence of IAH in this cohort was 17% as compared with the expected 25% of patients (29), which affected recruitment for this outcome. Hence, the small sample size of this high-risk group provides only observational inferences.

To conclude, PLGM reduced hypoglycemia exposure without compromising glycemic control or quality of life in children and adolescents with type 1 diabetes and thereby is an important technological device to reduce hypoglycemia in their day-to-day lives.

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Author Contributions. M.B.A. conducted and coordinated the studies, collected data, and wrote the manuscript. G.J.S. collected data, conducted the analyses, and provided statistical input. J.A.N. contributed to the design of the study, conducted and coordinated the studies, and reviewed the manuscript. J.M.F., B.R.K., G.R.A., F.J.C., E.A.D., and T.W.J. contributed to the design of the study, supervised the study at each site and reviewed the manuscript. T.W.J. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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