Incremental Value of Continuous Glucose Monitoring When Starting Pump Therapy in Patients With Poorly Controlled Type 1 Diabetes

The RealTrend study*

DENIS RACCAH, MD, PHD[1]
VÉRONIQUE SULMONT, MD[2]
YVES REZNIK, MD, PHD[3]
BRUNO GUERCI, MD, PHD[4]
ERIC RENARD, MD, PHD[5]
HÉLÈNE HANAIRE, MD, PHD[6]
NATHALIE JEANDIDIER, MD, PHD[7]
MARC NICOLINO, MD, PHD[8]

OBJECTIVE — To compare the improvements in glycemic control associated with transitioning to insulin pump therapy in patients using continuous glucose monitoring versus standard blood glucose self-monitoring.

RESEARCH DESIGN AND METHODS — The RealTrend study was a 6-month, randomized, parallel-group, two-arm, open-label study of 132 adults and children with uncontrolled type 1 diabetes (A1C ≥8%) being treated with multiple daily injections. One group was fitted with the Medtronic MiniMed Paradigm REAL-Time system (PRT group), an insulin pump with integrated continuous subcutaneous glucose monitoring (CGM) capability, with instructions to wear CGM sensors at least 70% of the time. Conventional insulin pump therapy was initiated in the other group (continuous subcutaneous insulin infusion [CSII] group). Outcome measures included A1C and glycemic variability.

RESULTS — A total of 115 patients completed the study. Between baseline and trial end, A1C improved significantly in both groups (PRT group −0.81 ± 1.09%, $P < 0.001$; CSII group −0.57 ± 0.94%, $P < 0.001$), with no significant difference between groups. When the 91 patients who were fully protocol-compliant (including CGM sensor wear ≥70% of the time) were considered, A1C improvement was significantly greater in the PRT group ($P = 0.004$) (PRT group −0.96 ± 0.93%, $P < 0.001$; CSII group −0.55 ± 0.93%, $P < 0.001$). Hyperglycemia parameters decreased in line with improvements in A1C with no impact on hypoglycemia.

CONCLUSIONS — CGM-enabled insulin pump therapy improves glycemia more than conventional pump therapy during the first 6 months of pump use in patients who wear CGM sensors at least 70% of the time.

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The long-term clinical benefit of tight glycemic control in type 1 diabetic patients has been demonstrated in several reports by the Diabetes Control and Complications Trial (1,2). To achieve this goal, insulin analogs, basal-bolus multiple daily injections (MDI), and insulin pumps for continuous subcutaneous insulin infusion (CSII) have proved to be important tools for lowering glucose variability and improving glycemic control, leading to higher treatment satisfaction in patients with type 1 diabetes (3–5).

Nevertheless, intensive treatment of type 1 diabetes often does not succeed in achieving target A1C levels ≤7.0% (6). Increased self-monitoring of blood glucose (SMBG) levels is correlated with better A1C levels (7,8), but for practical reasons most patients do not perform more than five to seven glucose measurements per day. Consequently, postprandial hyperglycemia and nocturnal hypoglycemia often remain unnoticed, even in individuals with well-controlled diabetes (9–11). Hence, detecting and treating these events might improve the patient's glycemic control and have an impact on quality of life.

Continuous glucose monitoring (CGM) provides information from a subcutaneous glucose sensor on interstitial glucose levels. A typical CGM system incorporates alarms for high and low glucose levels and displays glucose trend information graphically, allowing patients to anticipate hypo- and hyperglycemic events. Recent studies have shown that wearing such devices is associated with improved glycemic control in patients undergoing intensive therapy for type 1 diabetes (12,13) and in patients treated by CSII (14); however, no study has investigated the benefit of CGM in patients with poor metabolic control using MDI upon initiation of pump therapy. In this trial we randomly initiated pump therapy in patients with insufficient metabolic control despite optimized basal-bolus injection regimens with either the MiniMed Paradigm REAL-Time insulin pump (PRT), an insulin pump that can receive and display CGM data from a separate subcutaneous glucose sensor,

From the [1]University Hospital Sainte Marguerite, Marseille, France; the [2]American Memorial Hospital, Children's Hospital, Reims, France; the [3]Côte de Nacre Hospital, Caen, France; [4]Centre Hospitalier Universitaire de Nancy and University of Nancy, Nancy, France; [5]Centre Hospitalier Universitaire de Montpellier and University of Montpellier, Montpellier, France; [6]Centre Hospitalier Universitaire de Toulouse and University of Toulouse, Toulouse, France; [7]University Louis Pasteur Hospital, Strasbourg, France; and [8]Hospital Femme-Mère-Enfant, Lyon, France.
Corresponding author: Denis Raccah, denis.raccah@mail.ap-hm.fr.
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*Additional study investigators are listed in the APPENDIX.

or conventional CSII, and compared glycemic outcomes after 6 months.

RESEARCH DESIGN AND METHODS

— A total of 132 patients (51 children and 81 adults) with type 1 diabetes were recruited in eight centers (six adult and two pediatric centers). Inclusion criteria required age between 2 and 65 years, type 1 diabetes diagnosed for ≥12 months, follow-up by the respective investigator for at least 3 months, A1C ≥8%, and treatment with basal/bolus MDI with rapid insulin analogs at mealtimes. Unbiased biochemical hyper- and hypoglycemia parameters were collected using a blinded Holter-type CGM device at the beginning and the end of the trial. Patients randomly assigned into the PRT group agreed to wear an unblinded glucose sensor during at least 70% of the study period. All patients continued to perform fingerstick measurements for glucose self-monitoring as they did before the study.

The trial was approved by the ethics committee, Comité de Protection des Personnes Sud-Méditerranée II. All patients (or the parents of minor patients) read the patient information and signed informed consent forms.

Study treatment

Physicians and patients were blinded to centralized A1C data from baseline to completion of the study. A1C levels were measured at screening, baseline, 3 months, and 6 months.

Two weeks after screening (visit 1), eligible patients were randomly assigned to one of the two groups (PRT or CSII) and fitted with a Holter-type CGM device for 3 days. Blinded CGM data were retrieved at the end of this period (visit 2). Patients in the PRT group were asked to start using only the (unblinded) CGM function of their insulin pump at this time and were free to use the CGM information provided to them as they desired, while continuing MDI treatment for 9 days. Default settings for the high- and low-glucose alarms could be adjusted by the physician for individual patients.

At baseline (visit 3, 12 days after randomization), insulin pump therapy was initiated in both groups. Patients in the PRT group started using the pump function of their device, whereas patients in the CSII group were fitted with a Medtronic MiniMed Paradigm 512/712 insulin pump. All patients continued to use their usual blood glucose meter to obtain at least three readings daily. Patients in the PRT group were required to use glucose sensors at least 70% of the time and replace the sensor every 3 days and were instructed on appropriate responses to CGM information. A confirmatory blood glucose reading served as reference for therapeutic decisions.

One month after pump therapy initiation (visit 4), device data were downloaded for both groups, and patients discussed treatment with the physician. Therapy could be adjusted for all patients and alarm targets reset for the PRT group.

After 3 months of pump therapy (visit 5), pump and CGM data were downloaded again, blood samples were taken for A1C determination, and treatment guidelines were adjusted as needed.

Three days before the final study visit after 6 months of pump therapy (visit 6), all patients again wore a blinded Holter-type CGM device. Blinded CGM, PRT, and CSII data were downloaded at study end.

The primary objective of the trial was to determine whether pump therapy initiation in patients with A1C values ≥8%, being currently treated with MDI, could result in improved metabolic control after 24 weeks of continuous use of either a sensor-augmented or a conventional insulin pump. The secondary objective was to evaluate change in glycemic variability. The primary outcome was A1C change from baseline (visit 3) to 6 months (visit 6). Secondary outcomes included mean glucose change and descriptive parameters for biochemical hyperglycemia (>190 mg/dl) and hypoglycemia (<70 mg/dl). Daily insulin use was also compared.

The sample size calculation was based on change in A1C levels between baseline and trial end. A difference of ≥0.5% between the treatment groups was considered clinically meaningful. To have a 95% chance of detecting a 0.5% difference with an assumed SD of 0.9, using a two-sided two-sample *t* test with a power of 80%, 52 patients were required for each group. A total of 132 patients were randomly assigned to allow for a normal dropout rate. Because of the nature of the treatments, the study was not blinded.

Statistical analysis

The primary covariance analysis was based on the comparison of A1C changes between the PRT and CSII groups using the last observation carried forward method on the full analysis set (FAS) of patients (all patients with two A1C results from baseline to the end of the study). $P \leq 0.05$ was considered statistically significant. Analyses were adjusted for age as patients were randomly assigned within the age-groups: <19 and ≥19 years. In light of sensor use heterogeneity in the PRT group, a separate analysis was conducted using data from only those subjects who adhered to the protocol requirements (the per-protocol data subset).

Secondary outcomes analyzed the changes in glucose concentration (hyperglycemia and hypoglycemia above and below the target range) calculated from blinded CGM data using the covariance analysis model. Daily use of insulin calculated from pump downloads was compared between groups using an ANOVA adjusted for age-groups.

RESULTS

— Between May 2006 and December 2007, 148 patients were assessed for eligibility and 132 (81 adults and 51 children) fulfilling the inclusion criteria were randomly assigned. The safety population ($n = 128$) was identical to the randomized population except for four adults who withdrew before visit 3. The FAS population ($n = 115$) excluded an additional 13 patients who did not have A1C measured after the baseline visit. The FAS population included 55 patients in the PRT arm (22 children and 33 adults) and the 60 patients in the CSII arm (24 children and 36 adults). Analysis on this population was intention to treat. The per protocol population excluded 24 FAS patients because of major protocol deviations (1 screening failure in the CSII group and 23 patients in the PRT group who failed to wear glucose sensors at least 70% of the time). The per protocol population included 32 patients in the PRT group (11 children and 21 adults) and 59 patients in the CSII group (24 children and 35 adults).

A total of 20 patients abandoned the study: 14 from the PRT group (6 children and 8 adults) and 6 from the CSII group (6 adults). The trial ran from May 2006 to May 2008, with the first patients recruited in June 2006. Patient characteristics at baseline were comparable in both study arms for all analyzable populations (Table 1).

A1C levels

In the FAS population, A1C levels were significantly reduced in both groups (PRT $-0.81 \pm 1.09\%$, $P < 0.001$; CSII

Table 1—*Baseline and demographic characteristics*

	FAS		Per protocol	
	PRT	CSII	PRT	CSII
n	55	60	32	59
Age (years)	28.1 ± 15.1	28.8 ± 16.7	30.9 ± 16.2	28.1 ± 15.7
Age ≥19 years	33 (60.0)	36 (60.0)	21 (65.6)	35 (59.3)
Male sex	30 (54.5)	34 (56.7)	19 (59.4)	33 (55.9)
Weight (kg)	65.7 ± 17.4	62.6 ± 18.6	66.8 ± 19.9	62.3 ± 18.7
Height (cm)	166.0 ± 12.3	164.6 ± 14.4	166 ± 13.6	164.5 ± 14.5
BMI (kg/m^2)	23.5 ± 4.1	22.5 ± 4.4	23.8 ± 4.7	22.5 ± 4.4
Screening A1C (%)	9.4 ± 1.1	9.3 ± 1.1	9.2 ± 1.0	9.3 ± 1.1
Baseline A1C (%)	9.11 ± 1.28	9.28 ± 1.19	8.9 ± 1.12	9.25 ± 1.19
Baseline MAGE (mg/dl)	188.5	192.9	194.4	192.2
Baseline SD (mg/dl)	74.4	75.1	72.1	75.1
Type 1 diabetes duration (years)	11.2 ± 9.0	12.3 ± 8.8	13.7 ± 10.2	12.2 ± 8.9
Daily insulin doses (units/day)	42.9 ± 17.5	42.2 ± 17.0	40.2 ± 14.8	42.8 ± 16.5

Data are means ± SD, *n* (%), or mean.

−0.57 ± 0.94%, $P < 0.001$), but the difference in favor of the PRT group failed to reach statistical significance ($P = 0.087$) (Fig. 1*A*). Among patients who were fully compliant with the protocol, however, the reduction in A1C was significantly greater in the PRT group (PRT −0.96 ± 0.93%, $P < 0.001$; CSII −0.55 ± 0.93%, $P < 0.001$; intergroup comparison, $P = 0.004$) (Fig. 1*B*).

Glycemic control

In the FAS population, the mean glucose concentration decreased in both groups between baseline and study end (Table 2). The reduction was significantly greater in the PRT group (−30.6 ± 54.0) than in the CSII group (−10.8 ± 39.6) ($P = 0.005$). Significant differences in favor of the PRT group were also observed with respect to duration of hyperglycemic events, in the hyperglycemic area under the curve per day, in the mean amplitude of glycemic excursions (MAGE) (15), and in overall SD of blood glucose values. Similar trends of improved glycemic variability were observed in the per protocol population, although some failed to reach statistical significance because of the small sample size. All hypoglycemia parameters remained constant and comparable in both groups.

Insulin doses and use

In the FAS population, there was a significant increase in total daily doses (TDDs) of insulin between baseline and after 1 month of treatment in both the PRT group (ΔTDD = 5.8 ± 12.8 units) and the CSII group (ΔTDD = 2.2 ± 8.4 units, $P = 0.032$). Likewise, doses increased significantly between baseline and study end (PRT 6.8 ± 17.3 units, CSII 1.5 ± 9.1 units; $P = 0.036$). Patients in the PRT group delivered bolus doses more frequently after 1 month of treatment (PRT 4.8 ± 1.5, CSII 4.1 ± 1.2; $P = 0.002$) and at study end (PRT 4.7 ± 1.4, CSII 3.9 ± 1.4; $P = 0.005$). A higher percentage of insulin delivered as bolus (53.8 ± 10.0%) in the PRT group versus CSII (49.8 ± 15.8%) reflects these behavioral changes.

In the per protocol population, TDDs increased between baseline and 1 month (by 6.1 ± 9.5 units in the PRT group and by 1.7 ± 7.6 units in the CSII group; $P = 0.028$), but the difference, although of comparable magnitude, failed to reach significance at 3 and 6 months. Patients in the PRT group delivered bolus doses more frequently at 3 months (PRT 4.8 ± 1.2, CSII 4.1 ± 1.2; $P = 0.002$) and at study end (PRT 4.9 ± 1.4, CSII 3.9 ± 1.4; $P = 0.002$). Bolus delivery accounted for 53.3 ± 9.3% of total insulin in the PRT group versus 49.7 ± 15.9% in the CSII group.

Ancillary analyses

Between the screening visit and the end of the study, A1C levels fell significantly in both groups of the FAS population (PRT −1.14 ± 1.21%, $P < 0.001$; CSII 0.57 ± 0.91%, $P < 0.001$), and the difference in favor of the PRT group compared with the CSII group was statistically significant ($P = 0.006$). A1C levels also fell in the per protocol population (PRT −1.23 ± 1.08%, $P < 0.001$; CSII −0.55 ± 0.90%, $P < 0.001$); the intergroup difference was again significant and in favor of the PRT group ($P < 0.001$) (Fig. 1).

The probability of failing to comply with agreed-upon sensor wear was not constant among different age cohorts. Analysis according to the age categories proposed by the Juvenile Diabetes Research Foundation (JDRF) (13) revealed the highest sensor compliance in the adult age-group (>25 years, $n = 25$, sensor wear 74.9% of time), followed by the pediatric population (5–14 years, $n = 14$, sensor wear 68.4% of time). Compliance was lowest in adolescents (15–25 years, $n = 15$, sensor wear 52.4% of time). Because of the small sample size of the age subgroups, no decrease in A1C was significantly different compared with that of the CSII group.

At each visit after treatment initiation, physicians recorded whether patients had modified their treatment regimens. Whereas 20% of patients in the PRT group reported making modifications to their nutritional habits and/or their lifestyle, only 10% of patients in the CSII group did so. In addition, 93.2% of all patients in the PRT group reported using CGM data to adjust their insulin doses, and 59.5% reported that they used CGM data to modify their responses to glycemic excursions.

Adverse events

Adverse event data were collected and analyzed for the safety population. Ten serious adverse events were reported: three in the PRT group and seven in the CSII group. Two episodes of ketoacidosis occurred in the PRT group when patients failed to react to the device's hyperglycemic alarms. One episode of severe hypoglycemia with loss of consciousness also occurred in the PRT group. In this instance, the device was improperly calibrated, and acute alcohol intoxication may have played a role in the adverse event. Three episodes of ketoacidosis occurred in the CSII group. The overall ketoacidosis rate was 3.2 per 100 patient-years, and the overall rate of severe hypoglycemia was 0.64 per 100 patient-years. Four other serious adverse events occurred in the CSII group that were unrelated to the study devices or the protocol.

CONCLUSIONS — Six months after transitioning from MDI to pump therapy, patients with poorly controlled type 1 diabetes achieved significantly improved A1C values whether they used a sensor-augmented insulin pump or a conventional pump (the PRT and CSII groups,

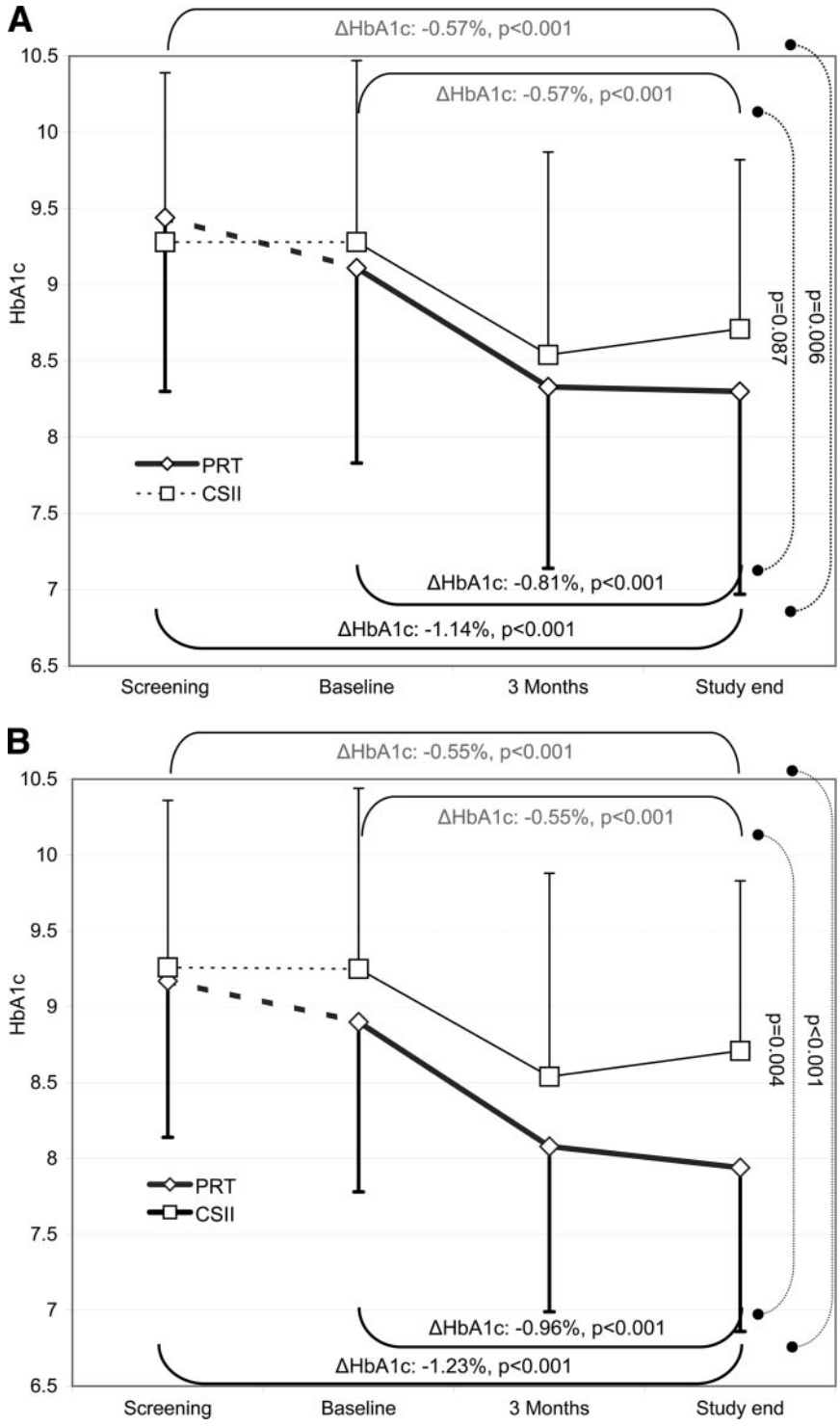

Figure 1—*Change in A1C during the study period.* A*: A1C levels in the intention-to-treat population measured at screening and visits 3, 5, and 6 in the FAS population* (n = *115*). Δ*A1C intergroup visit 3–to–visit 6 ratio: 0.24%,* P = *0.08;* Δ*A1C intergroup screening–to–visit 6 ratio: 0.57%,* P = *0.006.* B*: A1C levels in the per protocol population (compliant patients,* n = *91),* Δ*A1C intergroup visit 3–to–visit 6 ratio: 0.41%,* P = *0.004;* Δ*A1C intergroup screening–to–visit 6 ratio: 0.68%,* P < *0.001. All values are means ± SD.*

respectively). The magnitude of improvement within each group was comparable to published data on the efficacy of pump therapy (16), confirming the superiority of pump therapy over MDI in patients with poorly controlled diabetes.

Among patients who complied with the study protocol, there was a significant between-group difference favoring the sensor-augmented over the conventional insulin pump. However, when protocol-noncompliant patients were included, the A1C improvement was not significant between the PRT and CSII groups.

During the 9-day period between screening and study baseline, the PRT group was trained on sensor use and allowed to modify their MDI dosing regimens based on CGM readings. The decrease observed in A1C levels during this short interval may represent the immediate benefit of exposure to CGM data, even in the absence of an insulin pump. The initial decline in A1C levels seen in the PRT group may also explain the blunting of the difference observed between baseline and study end. A more meaningful comparison may, therefore, be between screening and study end.

MAGE and SD calculations revealed a significantly greater reduction in the PRT group compared with that in the CSII group for the entire study population. The improvements in MAGE and SD values were reached without any increase in the number or duration of hypoglycemic events.

Improvements in glycemic control in the PRT group beyond those seen in the CSII group may be attributable to alarms and glucose trend information available to patients during the study, prompting patients in the PRT group to engage in more lifestyle modifications and insulin treatment adjustments.

Recent studies reported that CGM was beneficial in lowering A1C. In the GuardControl study (12), A1C was reduced by ≥2% in 26% of patients after 3 months of continuous sensor use but not by intermittent use. Hirsch et al. (14) reported that the effectiveness of sensor-augmented pump therapy was contingent on patients' compliance with glucose sensor use. Wearing a CGM sensor >60% of the time was associated with lowered A1C levels. The JDRF study (13) recently showed that CGM improved A1C in adults with well-controlled type 1 diabetes wearing the continuous glucose sensor for 83% of the requested time. Although sensor compliance was less consistent in other age-groups, compliant patients still benefited from the technology (13).

Failure to adhere to many aspects of diabetes management is recognized as an obstacle for successful treatment in adolescents and young adults (17,18). In the present study, subjects in the 15- to 24-year-old age-group had the highest prob-

Table 2—*Measured A1C, glycemic, and insulin parameter changes, baseline to end of study*

	FAS		Per protocol	
	PRT	CSII	PRT	CSII
n	46	54	30	53
Δ Blood glucose (mg/dl)	−30.6 ± 54.0*	−10.8 ± 39.6	−39.6 ± 55.8*	−9.0 ± 39.6
Δ Hyperglycemia >190 mg/dl (h/day)	−3.5 ± 4.8*	−0.7 ± 3.8	−4.1 ± 5.1*	−0.6 ± 3.8
Δ Hyperglycemia AUC (mg · dl^{-1} · day^{-1})	−17.1 ± 31.7†	−5.8 ± 26.7	−19.1 ± 35.5†	−5.2 ± 26.5
Δ Hyperglycemia (episodes/day)	−0.2 ± 0.7	−0.2 ± 0.7	−0.2 ± 0.7	−0.2 ± 0.7
Δ Hypoglycemia <70 mg/dl (h/day)	0.3 ± 1.4	0 ± 1.2	0.6 ± 1.3	0.0 ± 1.2
Δ Hypoglycemia AUC (mg · dl^{-1} · day^{-1})	0.4 ± 1.3	0.0 ± 1.8	0.7 ± 1.3	0.0 ± 1.8
Δ Hypoglycemia (episodes/day)	0.1 ± 0.9	0.1 ± 0.7	0.2 ± 1.0	0.1 ± 0.7
Δ MAGE (mg/dl)	−27.5*	−16.2	−20.4	−16.2
Δ SD	−15.8*	−5.7	−11.3	−5.7
Δ Daily insulin doses (units/day)	6.8 ± 17.3†	1.5 ± 9.1	6.2 ± 14.8	1.1 ± 8.4
Bolus insulin (%/day)	53.8 ± 10.0	49.8 ± 15.8	53.3 ± 9.3	49.7 ± 15.9
Number of boluses/day	4.7 ± 1.4	3.9 ± 1.4	4.9 ± 1.4	3.9 ± 1.4

Data are means ± SD or means. *$P \leq 0.005$ vs. CSII group. †$P \leq 0.05$ vs. CSII group.

ability of being noncompliant with the sensor protocol. Our findings support the fact that CGM should be used at least 70% of the time to improve metabolic control when pump therapy is initiated and show that even patients whose diabetes had been poorly controlled previously with intensified MDI regimens may realize A1C reductions. Patients' motivation to use CGM as an adjunct to insulin pump therapy is crucial for device effectiveness. Trained health care provider teams should focus on how to adequately select, train, manage, and motivate patients to optimize benefits from CGM.

The high attrition rate of this study can be considered as a limitation of this trial and is best explained by the lack of a run-in period, which could have been used to select the most well-motivated patients. In addition, the short duration of this trial does not provide information on the long-term impact of the treatment.

In summary, patients who use CGM-enabled pumps and who wear sensors at least 70% of the time realize glycemic benefits beyond those who do not wear sensors or who use conventional insulin pumps. Exposure to CGM data, even before transitioning from MDI to an insulin pump, can lead to A1C reductions. Reduction of hyperglycemia without an increased risk of hypoglycemia can be achieved by a combination of modified insulin administration and lifestyle changes.

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APPENDIX — Other investigators involved in the study were P. Schaepelynk, MD, University Hospital Sainte Marguerite, Marseille, France; P.F. Souchon, MD, American Memorial Hospital, Children's Hospital, Reims, France; M. Joubert, MD, Hospital Côte de Nacre, Caen, France; D. Lauton, MD, Centre Hospitalier Universitaire Montpellier and University of Montpellier, Montpellier, France; V. Melki, MD, Centre Hospitalier Universitaire Toulouse and University of Toulouse, Toulouse, France; L. Meyer, MD, University Hospital Louis Pasteur, Strasbourg, France; and N. Bendelac, MD, University Hospital Femme-Mère-Enfant, Lyon, France.

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