ORIGINAL ARTICLE

Routine Sensor-Augmented Pump Therapy in Type 1 Diabetes: The INTERPRET Study

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Abstract

Background: Sensor-augmented pump (SAP) therapy can improve glycemic control, compared with multiple daily insulin injections or with insulin pump therapy alone, without increasing the risk of hypoglycemia.

Subjects and Methods: A 12-month observational study in patients with type 1 diabetes treated with continuous subcutaneous insulin infusion (CSII), upon the introduction of continuous glucose monitoring (CGM), was conducted in 15 countries (in Europe and in Israel) to document the real-life use of SAP and assess which variables are associated with improvement in type 1 diabetes management.

Results: Data from 263 patients (38% male; mean age, 28.0 ± 15.7 years [range, 1–69 years]; body mass index, 23.3 ± 4.9 kg/m²; diabetes duration, 13.9 ± 10.7 years; CSII duration, 2.6 ± 3 years) were collected. Baseline mean glycated hemoglobin A1c (HbA_{1c}) was $8.1 \pm 1.4\%$; 82% had suboptimal HbA_{1c} ($\geq 7\%$). The average sensor use for 12 months was 30% (range, 0–94%), and sensor use decreased with time (first 3 months, 37%; last 3 months, 27%). Factors associated with improvement in HbA_{1c} after 12 months in patients with baseline HbA_{1c} $\geq 7\%$ were high baseline HbA_{1c} ($P < 0.001$), older age group ($P < 0.001$), and more frequent sensor use ($P = 0.047$). Significantly less hospitalization, increased treatment satisfaction, and reduced fear of hypoglycemia were reported after 12 months of SAP.

Conclusions: This is the largest and longest multicenter prospective observational study providing real-life data on SAP. These results are consistent with those of controlled trials showing the effectiveness of CGM in pump users.

Introduction

CONTINUOUS GLUCOSE MONITORING (CGM) systems represent an important advance in diabetes technology that can facilitate optimal glucose control in type 1 diabetes. Numerous randomized controlled trials have demonstrated the safety and efficacy of real-time CGM in both suboptimally and well-controlled type 1 diabetes patients.^{1–6} In addition, recent studies demonstrated the superiority of sensor-

augmented pump (SAP) therapy versus multiple daily injections,^{7,8} with a mean decrease of 0.8–1.2% in glycated hemoglobin A1c (HbA_{1c}) levels, without increasing the risk of hypoglycemia. In all these trials, the benefits of CGM correlate with frequent sensor wear and more advanced age.^{9,10}

Evaluation of technological interventions is complicated by a frequent lack of generalizability of randomized clinical trial results to everyday clinical settings. Often, randomized clinical trial results reflect not only the technology tested, but also

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*A complete list of the members of the INTERPRET Study Group can be found in the Appendix. This study is registered at ClinicalTrials.gov with trial registration number NCT00790088.

the somewhat rarefied trial setting itself, involving highly qualified healthcare teams with ample skill, time, and resources to assist patients in implementing the technology and to encourage protocol adherence. In clinical practice, SAP therapy is indicated for patients who cannot achieve good metabolic control on continuous subcutaneous insulin infusion (CSII), who have a history of severe hypoglycemia and/or hypoglycemia unawareness, or who desire increased flexibility in their daily lives while maintaining or even improving their HbA_{1c} levels.^{11–13}

The aim of this multicenter prospective observational study was to document in real-life settings the long-term sensor usage and safety of SAP in a broad cohort of patients with type 1 diabetes, to assess which variables are associated with improvement in HbA_{1c}, and to record each patient's self-reported outcomes. Preliminary observations of this study have been presented in abstract form.^{14,15}

Subjects and Methods

The INTERPRET Study was designed as a prospective observational study that included 27 investigational centers in 15 countries (in Europe and in Israel). Physicians treated their enrolled patients under routine care, conducting visits approximately every 3 months over the course of 1 year. Inclusion criteria included a diagnosis of type 1 diabetes mellitus with at least 6 months of CSII treatment prior to enrollment, and the insulin pump had to be compatible with real-time display of CGM data. Only the Paradigm[®] REAL-Time[™] and Paradigm Veo[™] pumps (Medtronic MiniMed, Inc., Northridge, CA) met this criterion at the time of the study; Sof-sensor[™] subcutaneous glucose sensors (Medtronic MiniMed, Inc.) were used exclusively. The usual prescribed blood glucose meter of choice was used. The exclusion criterion was prior use of CGM devices with real-time data display. There were no restrictions on age or baseline HbA_{1c} values. No devices were provided by the study sponsor.

Participating physicians were required to have experience in treating patients with real-time CGM and to recommend that sensors be worn for at least 10% of the time per year. The decision to initiate SAP therapy was made prior to and independently of the study. The devices were prescribed according to their instructions for use. Pump settings, operations with the CGM, and alarms for hypoglycemia and hyperglycemia were set by the treating healthcare professional according to the patients' individual needs and could be freely adjusted during the course of the study. HbA_{1c} values were centrally determined from samples obtained at baseline and at 3, 6, 9, and 12 months with a Diabetes Control and Complication Trial-aligned high-performance liquid chromatography method (Laboratorium für Klinische Forschung, Schwentimental, Germany). The HbA_{1c} values were available to investigators, staff, and patients. Validated versions of Diabetes Treatment Satisfaction Questionnaires Status and Change versions (DTSQs and DTSQc, respectively)^{16,17} and Hypoglycemia Fear Survey-II (HFS) questionnaires¹⁸ were administered to adults in Danish, Hungarian, and Spanish centers only, where validated translated versions of the questionnaires were available at that time. The DTSQc questionnaire was used to assess the perceived relative change in satisfaction compared with the previous treatment that could perhaps not be detected by the DTSQs in the case of a relatively high level

of patient satisfaction at baseline (ceiling effect). The questionnaires were handed out at baseline (DTSQs and HFS), 3 months (DTSQs), 6 months (HFS), and 12 months (DTSQs, DTSQc, and HFS).

Management decisions were made as per routine practice by the patients and physician-investigators and were based in part on CGM and HbA_{1c} data. Patients could upload data from their devices using CareLink[™] Personal therapy management software (Medtronic MiniMed, Inc.) for additional data visualization options, as needed.

The study was conducted according to the principles of the Declaration of Helsinki on biomedical research involving human patients and the respective local national regulations. Each center obtained local Ethics Committee approval before beginning patient recruitment. Written informed consent was obtained from all patients before enrollment. For the participants <18 years of age, both children (whenever possible) and parents (or legal representative) signed informed consent forms. Baseline data included pump and compatible blood glucose meter data, which were uploaded to CareLink Clinical software (Medtronic MiniMed, Inc.). Safety data including serious adverse events, whether related or unrelated to the study device, were also recorded. Serious adverse events included severe hypoglycemia (defined as an episode absolutely requiring assistance from another person and preferably accompanied by a confirmatory blood glucose value of <50 mg/dL [<2.8 mmol/L]) and diabetic ketoacidosis/severe hyperglycemia (defined as a blood glucose value of >250 mg/dL [>13.9 mmol/L] with either low serum bicarbonate [<15 mEq/L] or low pH [<7.3] and either ketonemia or ketonuria and requiring treatment within a healthcare facility).

To calculate the percentage of time that sensors were used, the number of valid sensor readings was expressed as a percentage of the maximum possible number of daily readings (i.e., 288) during the observation period. Patients were categorized in different sensor usage frequency subgroups as 0 to <10%, 10 to <25%, 25 to <50%, 50 to <75%, and 75–100%. Similarly, age was treated as a categorical variable using different subgroups (Table 1). To assess whether there are factors predictive of changes in HbA_{1c} value from the start of SAP therapy to the last visit at 12 months, a multiple regression model was used with baseline HbA_{1c} value, sensor usage group during 12 months, age group, the main indication for SAP initiation, the duration of CSII prior to CGM initiation, retraining on sensor use during the study, Bolus Wizard[®] (Medtronic MiniMed, Inc.) use, and CareLink Personal use. The regression model was fitted for patients with a baseline HbA_{1c} value of $\geq 7\%$. Patient demographics and baseline characteristics have been presented using appropriate summary statistics. Patient-reported outcomes (DTSQs and HFS) were analyzed with linear mixed models with subject-specific random intercepts and mean structure consisting of the fixed effects: visit, sensor usage group, baseline HbA_{1c} value, and the main indication for SAP initiation. Dunnett's test was used for pairwise comparisons. For analysis of the DTSQc data, where scores were assessed at the 12-month visit, a multiple regression model was used. A negative binomial model with subject-specific random intercepts was used for the analysis of hospitalizations. At the end of the study, patients were asked to complete a user survey to collect their feedback on the SAP treatment. The items were scored from 0 (strongly disagree) to

TABLE 1. BASELINE CHARACTERISTICS OF ELIGIBLE PATIENTS

	All (n = 263)	Young children (0–7 years) (n = 28)	Children (8–12 years) (n = 21)	Adolescents (13–17 years) (n = 35)	Young adults (18–24 years) (n = 27)	Adults (≥ 24 years) (n = 152)
Age (years)	28.04 ± 15.55	4.25 ± 1.46	10.62 ± 1.32	14.57 ± 1.40	21.15 ± 2.07	39.15 ± 10.24
Males/females [n (%)]	99/164 (38%/62%)	15/13 (54%/46%)	9/13 (43%/57%)	15/20 (43%/57%)	9/18 (33%/67%)	51/101 (33%/67%)
Weight (kg)	63.11 ± 21.62	18.53 ± 2.87	40.90 ± 9.38	62.29 ± 12.55	69.26 ± 11.46	73.5 ± 13.68
Body mass index (kg/m ²) ^a	23.26 ± 4.92	16.31 ± 1.62	18.28 ± 2.70	21.92 ± 3.92	23.41 ± 2.82	25.51 ± 4.23
Duration of diabetes (years)	13.87 ± 10.67	2.54 ± 1.23	3.81 ± 2.44	6.71 ± 3.42	11.93 ± 4.10	19.34 ± 10.51
Duration of CSII treatment (years)	2.65 ± 2.97	1.61 ± 1.20	1.00 ± 1.10	1.91 ± 1.87	3.07 ± 2.96	3.17 ± 1.52
HbA _{1c} (%)	8.10 ± 1.40	8.38 ± 1.14	7.89 ± 1.39	9.03 ± 2.16	8.30 ± 1.23	7.84 ± 1.15
Median (minimum–maximum) (%)	7.95 (4.8–15.8)	8.6 (6.3–10.5)	7.9 (5.6–11.2)	8.5 (6.1–15.8)	8 (6.5–11.8)	7.8 (4.8–11.5)
Patients with baseline HbA _{1c} < 7% (%)	18%	18%	24%	14%	7%	22%

Data are mean ± SD values as indicated.

^aBody mass index z-score at baseline for pediatric groups can be found in Supplementary Table S1 (Supplementary Data are available online at www.liebertonline.com/dia). CSII, continuous subcutaneous insulin infusion; HbA_{1c}, glycated hemoglobin A_{1c}.

10 (strongly agree). An average score of ≥ 8 was considered as “strongly agree.”

Results

The 27 active sites in 15 countries recruited a total of 274 patients. At baseline, few patients had to be excluded from analyses because of major protocol deviations such as missing patient informed consent (one patient), CSII therapy for less than 6 months (two patients), prior experience with SAP therapy (seven patients), and no electronic Case Report Form data information available (one patient). Hence 263 patients were eligible for analyses at baseline; among these individuals, 84 were < 18 years of age. Baseline characteristics of eligible patients are summarized in Table 1. On average, the patients had 2.65 ± 2.97 years of CSII experience (95% confidence interval [CI] 2 years). Mean ± SD HbA_{1c} levels at the time of initiation of CGM were 8.1 ± 1.4% (range, 4.8–15.8%); 212 (81.5%) subjects had a baseline HbA_{1c} value of ≥ 7.0%. The main indications for SAP therapy initiation were glycemic instability (38%), persistently high HbA_{1c} (30%), recurrent hypoglycemia (8%), hypoglycemia unawareness (8%), and flexibility/lifestyle or patient choice (10%). The study was completed by 235 (89%) of the 263 subjects; four patients stopped CSII therapy during the 12-month study period, seven patients were lost to follow-up despite every attempt from the treating physician to contact them, and 17 enrolled subjects did not continue the study for other reasons (e.g., changed treating physician, left the clinic, lack of time, moved countries).

CGM use

The average sensor use for the complete observation period was 30% of the time (range, 0–94%). Usage decreased over time from 37% in the first 3 months to 27% in the last 3 months ($P < 0.0001$) (Fig. 1). Twenty-four percent of the patients used the sensor at least half of the time during the 12-month observation period, and 19% of the patients used it for < 10% of the time. At the beginning of the study, 40% of the patients were advised by their physicians to wear sensors more than 75% of the time, wearing the sensor was recommended to 18% for 50–74% of the time, 8% for 25–49% of the time, and 29% for 10–24% of the time, and 5% of the patients received the recommendation to wear the sensor less than 5% of the time for the first 3 months. These recommendations were sometimes changed during the course of the study. The sensor training was performed during the baseline visit for 98.9% of the patients and was delivered as one unique session in most of the cases (81.5%). During this training, 85.9% of the participants were trained on the use of the real-time information (trends and alerts) to which CGM gives them access on their pump screen. The characteristics of participants were analyzed to identify potential predictors of long-term high sensor use (≥ 75% of the time). A low baseline HbA_{1c} and high sensor use during the first 3 months were factors significantly associated with high sensor use during the 12-month period ($P = 0.015$ and $P = 0.001$, respectively). No significant effect of age, gender, duration of diabetes or CSII therapy, main indication for SAP therapy initiation, diabetes-related complications, way of funding the sensor, retraining on sensor, number of self-monitoring of blood glucose measurements, or CareLink Personal use was evident. The patients participating to the user survey on SAP treatment ($n = 190$) strongly agreed that

FIG. 1. Sensor use and percentage of the population with glycated hemoglobin A1c (HbA1c) levels of <7% and <7.5%.

the alarms were good at telling them if their glucose was high or low (average score, 8.2 ± 2.4 on a 10-point Likert-scale questionnaire) and that the SAP assisted them in achieving better glycemic control (average score, 8.6 ± 2.0).

HbA_{1c} outcome

The proportion of patients well-controlled with an HbA_{1c} value of <7% remained stable throughout the 12-month observation period (Fig. 1). There were significantly more patients with an HbA_{1c} value of <7.5% after 3 months of SAP therapy than at baseline (baseline, 29%; 3 months, 37%; Bonferroni corrected $P=0.009$). The percentage of patients with an HbA_{1c} value of <7.5% decreased with the decrease of sensor usage during the 12-month observation period. The percentage of patients with an HbA_{1c} value of <7.5% after 12 months was higher than at baseline, but the difference was not statistically significant (12 months, 33%; Bonferroni corrected $P=0.185$). The decrease in HbA_{1c} from baseline to 12 months in patients with a baseline HbA_{1c} value of $\geq 8\%$ was 0.43% ($P=0.0014$). A multiple regression analysis conducted on patients with a baseline HbA_{1c} value of $\geq 7\%$ showed that factors associated with improvement in HbA_{1c} after 12 months were high baseline HbA_{1c} levels ($P<0.001$), older age group ($P<0.001$), and more frequent use of sensor ($P=0.047$). The main indication for initiation of SAP therapy, the duration of CSII therapy, the retraining on sensor during the study, Bolus Wizard use, and CareLink Personal use were not factors associated with HbA_{1c} decrease after 12 months.

Hospitalization and serious adverse events

The average number of diabetes-related hospital admissions per 100 patients-years and the average length of stay

over the 12-month observation period were significantly reduced compared with the 12 months before starting SAP therapy (25.9 vs. 13.9 per 100 patients-years [$P=0.0002$] and 1.7 ± 5.0 vs. 0.6 ± 2.6 days [$P<0.001$], respectively). There was a decrease in the number of admissions/100 patients-years in the overall population when sensor use increased, although the difference was not significant ($P=0.0697$). During the 12 months prior to initiation of SAP therapy, five patients were hospitalized because of diabetic ketoacidosis (DKA), whereas no hospitalizations for severe hypoglycemia were reported. During the observation period, three patients required a total of three hospital admissions for treatment of DKA, and nine patients reported 13 episodes of severe hypoglycemia, of which only four events required emergency room visit or hospitalization. The change in the rate of DKA and severe hypoglycemia was not statistically significant. The overall incidence of severe hypoglycemic events was 6.3 events per 100 patient-years, and the ketoacidosis rate was 1.1 per 100 patient-years. Six other diabetes-related (angioplasty, diabetic foot ulcer, ischemic heart disease, pancreas and liver transplantations, suicide attempt, and poor glycemic control) and six non-diabetes-related serious adverse events that were not related to the study device were reported.

Patient-reported outcomes

The DTSQs and DTSQc questionnaires were administered to 66 eligible patients; 40 patients returned the entire HFS questionnaire at 12 months, and 20 patients completed only the Worry subscale as the translation of the Behavior subscale was not fully validated in one of the selected languages. Patients reported highly favorable scores for treatment satisfaction on the DTSQs questionnaire at baseline (average score, 32 out of 36 possible points), and this score remained

unchanged throughout the study period. In addition, patients reported a significant decrease in the perceived frequency of hyperglycemic episodes after 12 months ($P=0.047$). All patients gave favorable responses to the treatment satisfaction questions at 12 months on the DTSQc questionnaire (average score, 13.6 ± 5.7 out of 18; 95% CI [12.2, 14.9]), indicating improved treatment satisfaction compared with previous treatment. The perceived frequency of hyperglycemia did not change (average score, -0.4 ; 95% CI $[-0.8, 0.0]$), and the perceived frequency of hypoglycemia was reduced (average score, -0.62 ; 95% CI $[-1.0, -0.2]$).

The total HFS score was significantly improved versus baseline after 12 months of treatment (Fig. 2). The model-based average change on the total HFS score at 12 months was -6.87 (95% CI $[-11.54, -2.20]$; $P=0.003$). Scores in the “behaviors to avoid hypoglycemia” and “worries about hypoglycemia” subscales were significantly improved over the 12 months of treatment with CGM: the model-based average changes were -2.6 and -4.1 (95% CI $[-4.87, -0.31]$, $P=0.024$ and $[-6.91, -1.30]$, $P=0.003$, respectively). There was significant improvement in the “worry” subscale between 12 months and baseline (average change -5.21 , 95% CI $[-9.71, -0.70]$, $P=0.021$ after adjustment for sensor use).

Discussion

This is the largest and longest observational study of real-life SAP use in Europe and Israel to date. Our study confirms the incremental benefit of sensor use in the population of CSII-treated patients requiring the use of CGM for various indications. Higher baseline HbA_{1c}, older age at initiation of SAP therapy, and high sensor use were associated with greater HbA_{1c} improvements. There were no demographic characteristics that were associated with continuous use of sensor (more than 75% of the time) for a period of 12 months. Only

patients with high sensor use at the beginning of SAP as well as patients with lower HbA_{1c} at baseline tended to wear the sensor more often in the 12-month observation period. One can hypothesize that well-controlled patients are likely to seek continuous protection against hypoglycemia or hypoglycemia and hyperglycemia (a strict control). By contrast, patients who do not understand or practice the basics of intensive insulin therapy still have the greatest challenges with efficient adoption of SAP therapy. These results are consistent with recent controlled studies comparing CGM versus self-monitoring of blood glucose⁹ and SAP versus multiple daily injections.¹⁹ Ours is the first study to identify continuous use of sensor for 3 months as a factor predictive of high use in the long term, suggesting that patients’ willingness to wear the sensor consistently is influenced by the initial favorable experiences with high use. No other parameters have been detected to help physicians at the outset of the therapy in identifying the best candidates for SAP. Further observational studies with large enough and more refined populations could potentially answer this still-open question.

Despite evidence that a clinically relevant benefit can be expected if the patient wears the sensor more than 70% of the time^{5,6} and clinical guidelines emphasizing the need to use the sensor continuously,^{11,13} this study reports a low sensor use in this population. This is only partly explained from the lack of reimbursement of sensors in most of the countries participating in the study because some hospital and charity organizations are able to fund sensors. One interesting finding of this report is the wide range of sensor usage recommendations given by physicians. Some physicians were potentially unaware of the benefits of CGM technology or are still not compellingly advising the use of sensors according to guidelines and published recommendations. The lack of sensors reimbursement may be a disincentive. Other physicians did not recommend continuous use because of flexibility/lifestyle concerns or skin irritation.

FIG. 2. Hypoglycemia Fear Survey-II (HFS) scores at baseline, 6 months, and 12 months.

Despite the relatively low sensor use on average, the assessment of patients' perceived fear of hyperglycemia or severe hypoglycemia improved significantly. This study indicates that CGM in real-life settings led to a significant decrease in patients' fear of hypoglycemia and provides additional evidence of the favorable impact of CGM on patients' treatment satisfaction. We were not able to administer the questionnaires in all countries participating to the study because of language validation restriction at the time of study start; hence the generalizability of these findings should be interpreted in the context of the characteristics of these study participants. Nevertheless our findings are in line with previous studies.^{8,25} The rates of severe hypoglycemia and DKA found in our study are relatively low versus rates reported in the literature²⁰ but similar to those observed in a study in a large cohort of children evaluated retrospectively in a real-life setting.²¹ The number of severe hypoglycemic episodes that did not lead to hospitalization in the previous 12 months before the study was not collected, although we asked for severe hypoglycemia reporting at each patient visit. Therefore, we cannot draw strong conclusions on the effect of SAP therapy on severe hypoglycemia. We observed that a small number of events happened while the sensor was supposedly protecting the patient from severe hypoglycemia. None of these patients was using a pump equipped with a shut-off system that could have automatically suspended insulin delivery when sensor values reached critical lows.^{22,23} The use of SAP revealed similar results concerning the incidence of DKA, with slightly lower rates of diabetic acidosis reported during the observation period and only one occurring on a day the patient was wearing a sensor. We observed significantly lower hospitalization rates and lengths of stay when comparing the 12-month data collected at baseline (retrospective collection) versus the 12-month observation, suggesting that physicians did not consider it necessary to hospitalize the patients for pump training, glycemic variability assessment, or education and used the sensor for therapy adjustments in outpatient care.

It has previously been reported that regular clinician-patient contact is time- and labor-intensive and that there are no agreed strategies for incorporating CGM use into routine clinical care.²⁴ We believe that the understanding and interpretation of data from CGM and the relevance of therapeutic interventions are all key elements for the effectiveness of SAP. Because of its real-life setting, our study provides important data in this respect as it highlights several factors associated with successful SAP therapy. Because of its observational nature, it did not have a prospective control group, and hence it was not possible to control for potential confounding factors such as study effects or regression to the mean; as a result, the findings related to effectiveness can be considered to be hypothesis-generating only. A before/after approach was applied to several outcomes such as adverse events and rate of hospitalizations. Furthermore, it is noteworthy that the results are consistent with those of controlled trials^{9,19} showing that pump therapy with CGM can achieve effective glycemic control with low risks of hypoglycemia and other complications.

Appendix: The INTERPRET Study Group

Investigators are listed as (PI) for Principal Investigator, (I) for co-investigator, and (C) for Coordinator: Merete Meld-

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Author Disclosure Statement

K.N. participates in advisory boards and as a consultant for Roche and for Medtronic. A.S. receives research support and participates in advisory boards for Medtronic. O. Cohen

declares advisory services, research fees, and study coordination with Medtronic. P.J.-C. received honoraria from Medtronic, Roche, NovoNordisk, Sanofi-Aventis, and Lilly for delivering lectures and workshops. N.B. receives honoraria from Medtronic and NovoNordisk. O. Carrette is an employee of Medtronic International Trading Sàrl. J.C. is an employee of the Medtronic Bakken Research Center. N.M.L., G.C., E.J., and C.D.B. declare no competing financial interests exist. K.N., A.S., and O. Cohen discussed and designed the study protocol and researched data. J.C. was in charge of the statistical analyses. O. Carrette coordinated the study and drafted the manuscript. N.B., N.L., P.J.-C., E.J., C.D.B., and G.K. researched data and contributed to the interpretation of results. All authors contributed to the discussion and interpretation of results and reviewed and approved the final manuscript.

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