Continuous Subcutaneous Insulin Infusion (CSII) of Insulin Aspart Versus Multiple Daily Injection of Insulin Aspart/Insulin Glargine in Type 1 Diabetic Patients Previously Treated With CSII

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OBJECTIVE — Multiple daily injection (MDI) therapy of bolus insulin aspart and basal insulin glargine was compared with continuous subcutaneous insulin infusion (CSII) with aspart in type 1 diabetic patients previously treated with CSII.

RESEARCH DESIGN AND METHODS — One hundred patients were enrolled in a randomized, multicenter, open-label, crossover study. After a 1-week run-in period with aspart by CSII, 50 subjects were randomly assigned to MDI therapy (aspart immediately before each meal and glargine at bedtime) and 50 subjects continued CSII. After 5 weeks of the first treatment, subjects crossed over to the alternate treatment for 5 weeks. During the last week of each treatment period, subjects wore a continuous glucose monitoring system for 48–72 h.

RESULTS — Mean serum fructosamine levels were significantly lower after CSII therapy than after MDI therapy (343 ± 47 vs. 355 ± 50 μmol/l, respectively; $P = 0.0001$). Continuous glucose monitoring profiles over a 24-h time period showed that glucose exposure was 24 and 40% lower for CSII than MDI as measured by area under the curve (AUC) glucose ≥80 mg/dl (1,270 ± 742 vs. 1,664 ± 1,039 mg · h · dl^{-1}; $P < 0.001$) and AUC glucose ≥140 mg/dl (464 ± 452 vs. 777 ± 746 mg · h · dl^{-1}, CSII vs. MDI, respectively; $P < 0.001$). Similar percentages of subjects reported hypoglycemic episodes (CSII: 92%, MDI: 94%) and nocturnal (12:00 A.M. to 8:00 A.M.) hypoglycemic episodes (CSII: 73%, MDI: 72%). Major hypoglycemia was infrequent (CSII: two episodes, MDI: five episodes).

CONCLUSIONS — In a trial of short duration, CSII therapy with insulin aspart resulted in lower glycemic exposure without increased risk of hypoglycemia, as compared with MDI with insulin aspart and glargine.

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Abbreviations: AUC, area under the curve; CGMS, continuous glucose monitoring system; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injection; SMBG, self-measured blood glucose.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Multiple daily injection (MDI) therapy and continuous subcutaneous insulin infusion (CSII) with an external pump are two current methods of intensive insulin therapy for diabetes. MDI therapy requires bolus injection of short- or rapid-acting insulin at each meal, along with long-acting insulin once or twice daily for basal insulin coverage. Rapid-acting insulin analogs are administered as mealtime boluses to control postprandial glycemic excursions and have been shown to be more effective than regular human insulin (1,2). The long-acting insulin analog insulin glargine has prolonged pharmacodynamics that make it suitable for use as a basal insulin (3,4).

The growing use of CSII therapy is based on its proven efficacy, improvements in pump technology, and increased patient preference (5–10). Occasionally, patients utilizing CSII therapy may have to temporarily discontinue CSII use because of pump malfunction, skin problems, or physical activity (especially contact sports and water sports). During such periods, type 1 diabetic patients switching to MDI therapy could continue to use insulin aspart as the mealtime insulin and could use insulin glargine as the basal insulin.

Previous studies have shown that CSII is at least equivalent to, and often more effective than, MDI therapy (10–12). The use of an analog-only MDI regimen consisting of basal glargine and mealtime rapid-acting analog has been nicknamed "poor man's pump." However, its safety and efficacy compared with CSII has never been tested in a controlled, cross-over clinical trial setting. Consequently, we compared insulin aspart as the only approved rapid-acting analog for CSII with insulin aspart/glargine in MDI therapy. Because the principles applied to mealtime coverage were identical during both treatments, the study tests whether

the theoretically smooth profile of glargine will provide safety and efficacy comparable to the "customized" basal insulin delivery that can be programmed by an infusion pump during CSII.

RESEARCH DESIGN AND METHODS

— This was a multicenter, open-label, randomized, two-period, crossover, 10-week study in which CSII was compared with MDI therapy in two 5-week treatment periods. The study was conducted at 15 centers in the U.S., in accordance with the Declaration of Helsinki and good clinical practice guidelines (13). All subjects provided written informed consent. Analyses of blood samples for safety and efficacy parameters were performed by Medical Research Laboratories International (Highland Heights, KY).

Enrolled type 1 diabetic subjects were ≥18 years old, had BMI ≤40 kg/m^2, and had HbA_{1c} ≤9%. All were previously treated by CSII for at least 3 months before the screening visit. Subjects with impaired hepatic or renal function (alanine aminotransferase or creatinine values ≥2 times the upper limit of the normal reference range for the age-group), impaired cardiac function, hypoglycemia unawareness, or recurrent major hypoglycemia were excluded. Subjects performed self-measured blood glucose (SMBG) measurements and were knowledgeable in the methods of prandial insulin bolus dose adjustment based on preprandial glycemia and carbohydrate intake. Women of child-bearing age were excluded if they were pregnant, breast-feeding, or not practicing contraception. Subjects and investigators were blinded to treatment sequence up to the point of subject randomization.

For a 1-week period before randomization, subjects were switched from use of their prestudy CSII insulin to insulin aspart on a unit-by-unit basis. Subjects were instructed on insulin dose adjustment and on the use of the Induo device (LifeScan, Milpitas, CA). In general, the mealtime insulin coverage with aspart boluses during MDI and CSII treatments followed the same principles of dose adjustments based on carbohydrate counting and a preprandial blood glucose value. At randomization, subjects either remained on CSII with insulin aspart (NovoLog, Novo Nordisk Pharmaceuticals, Princeton, NJ) or were switched, on a unit-for-unit basis, to MDI therapy using a single basal bedtime injection of insulin glargine (Lantus, Aventis Pharmaceuticals), consistent with product labeling in the U.S. at that time, and mealtime boluses of insulin aspart delivered by the Induo device. Subjects assigned to CSII treatment during the study used their own prestudy insulin pumps.

In both groups, the basal insulin coverage could be modified through the scheduled phone communications with the subject during a 1-week dose-adjustment period with a goal of fasting and predinner glycemia in the range of 90–126 mg/dl (5–7 mmol/l). The investigator made final adjustments to the basal insulin dose at the visit scheduled for the end of the 1-week dose-adjustment period, after which the adjusted basal insulin rate/dose was maintained for the remaining 4 weeks of the treatment period. At the end of the 5-week treatment period, subjects crossed over to the alternate treatment therapy (e.g., CSII to MDI), with a 1-week basal dose adjustment period immediately followed by 4 weeks of treatment.

Efficacy assessments

Overall glycemic control was assessed by fructosamine measurements taken at the beginning and end of each treatment period (normal fructosamine range: 0–285 μmol/l). HbA_{1c} values were measured at the beginning and end of the study (normal HbA_{1c} range: 4–6%). Overall glucose control and postprandial glycemic control were assessed by comparison of 8-point SMBG profiles (blood glucose readings before and 2 h after breakfast, lunch, and dinner and at 12:00 A.M. and 3:00 A.M.) performed at the end of each treatment period.

During the last week of each 5-week treatment period, subjects wore a continuous glucose monitoring system (CGMS) (MiniMed MMT-7102; Medtronic, Northridge, CA) for up to 72 h. Data were obtained from the CGMS using Solutions 7314 Sensor Data Export Utility software (Medtronic). MiniMed Glucose Sensors (MMT-7002; Medtronic) were used. Glucose sensor signals were acquired every 10 s, and the average over 5 min was saved in memory. Accuracy of glucose sensing was ensured by using CGMS data that had a correlation of at least 0.79 with standard blood glucose meter readings. Thirty-six subjects had to have their glucose sensor reimplanted to obtain usable CGMS data. The sensor failure rate was ~20%. Glucose exposures were compared between treatment groups and were based on the first 24 h of CGMS monitoring. The 24-h glycemic profiles were calculated from the area under the curve (AUC) for glucose values ≥80 mg/dl (4.4 mmol/l) and ≥140 mg/dl (7.8 mmol/l). CGMS profiles had to be at least 24 h in duration to be suitable for use in the AUC calculations. For the CGMS data analysis, glycemia of 80 mg/dl was the minimal value considered optimal. Accordingly, glycemic control was considered to be better/tighter when the glucose exposure of AUC ≥80 mg/dl was minimized in a treatment regimen.

Safety assessments

Safety assessments included adverse events, physical examination findings, and clinical laboratory evaluations. Adverse events were recorded throughout the study, and a general physical examination was conducted at the beginning and end of the study.

The frequency of hypoglycemic episodes was monitored. Minor hypoglycemic episodes were defined as any asymptomatic blood glucose measurement <50 mg/dl, or as episodes with symptoms consistent with hypoglycemia with confirmation by blood glucose measurement <50 mg/dl that were handled by the subject. Major hypoglycemic episodes were defined as episodes with severe central nervous system symptoms consistent with hypoglycemia that the patient was unable to treat himself/herself, which had either *1*) blood glucose <50 mg/dl or 2) reversal of symptoms after either food intake or glucagon/intravenous glucose administration. Symptomatic hypoglycemic episodes were symptoms that were considered to be related to hypoglycemia but not confirmed by blood glucose measurement <50 mg/dl.

Safety assessments included hematology (red blood cell, white blood cell, hematocrit, and hemoglobin) and blood chemistry parameters (creatinine, total protein, liver function tests, lactic dehydrogenase, sodium, and potassium).

Statistical analysis

Fructosamine and AUC glucose parameters based on 24-h glycemic profile from CGMS were analyzed using a standard ANCOVA model. CGMS profiles had to be at least 24 h in duration to be used in

Table 1—*Characteristics of enrolled population and rate of study completion*

	Treatment sequence		
	CSII to MDI	MDI to CSII	All subjects
n	50	50	100
Age (years)	41.7 ± 11.1	44.2 ± 11.0	43.0 ± 11.1
Sex (%)			
Male	19 (38)	18 (36)	37 (37)
Female	31 (62)	32 (64)	63 (63)
Race (%)			
Caucasian	48 (96)	48 (96)	96 (96)
Hispanic	2 (4)	1 (2)	3 (3)
Asian	0 (0)	1 (2)	1 (1)
BMI (kg/m^2)	27.1 ± 4.1	26.7 ± 4.0	26.9 ± 4.0
HbA_{1c} at screening (%)	7.5 ± 0.8	7.4 ± 0.8	7.5 ± 0.8
Duration of diabetes (years)	19.7 ± 11.3	23.9 ± 12.3	21.8 ± 11.9
Daily insulin dose (IU/kg)	0.54 ± 0.23 (n = 45)	0.54 ± 0.21 (n = 50)	0.54 ± 0.22 (n = 95)
Basal	0.27 ± 0.10	0.29 ± 0.14	0.28 ± 0.12
Bolus	0.29 ± 0.18	0.25 ± 0.11	0.27 ± 0.15
Daily basal pump rates (%)			
One basal rate	12 (24)	6 (12)	18 (18)
Two basal rates	6 (12)	7 (14)	13 (13)
Three basal rates	14 (28)	14 (28)	28 (28)
Four basal rates	18 (36)	23 (46)	41 (41)
Subjects completing study (%)	45 (90)	46 (92)	91 (91)
Withdrawals during treatment (%)	5 (10)	4 (8)	9 (9)
Adverse events (*n*)	0	0	0
Noncompliance (%)	2 (4)	3 (6)	5 (5)
Ineffective therapy (%)	1 (2)	1 (2)	2 (2)
Withdrew consent (%)	2 (4)	0	2 (2)

Data are means ± SD or *n* (%). Treatment sequence refers to the order of insulin administration in the two treatment periods (i.e., CSII to MDI refers to CSII treatment during period 1 and MDI treatment during period 2).

the analysis. For analysis of end-of-period fructosamine values, the last observation carried forward approach was used.

RESULTS — Demographic variables of age, HbA_{1c}, and BMI were similar at baseline for subjects in both treatment sequences (Table 1). Prior insulin use was balanced between treatment sequences: in each sequence, 41, 7, and 2 subjects used insulin lispro, insulin aspart, and buffered regular insulin, respectively.

Efficacy

Overall, CSII therapy with insulin aspart provided improved glycemic control compared with MDI therapy with insulin aspart/glargine as measured by fructosamine values and 8-point SMBG profiles. The mean fructosamine value determined at the end of the CSII treatment for combined subjects was significantly lower than after treatment with MDI therapy (Table 2). The mean 8-point SMBG profiles for combined subjects at the end of the CSII or MDI treatment periods showed that the overall blood glucose profiles were not significantly different between treatments ($P = 0.074$). Although not different, the blood glucose values after breakfast (CSII 158 ± 63 mg/dl and MDI 182 ± 82 mg/dl), before dinner (128 ± 58 and 148 ± 71 mg/dl), and after dinner (144 ± 64 and 159 ± 77 mg/dl) tended to be lower for CSII therapy than MDI therapy. Results of the 8-point SMBG profiles were not affected by treatment sequence.

Subjects maintained overall glycemic control during the study. The mean HbA_{1c} values for subjects at the end of the 10-week study were similar between treatment sequences (CSII to MDI 7.3 ± 0.7% vs. MDI to CSII 7.1 ± 0.7%, $P > 0.05$) and demonstrated that subjects maintained overall glycemic control in both treatment sequences. The end-of-study HbA_{1c} value for combined subjects was significantly less than their baseline value (7.2 ± 0.7 vs. 7.5 ± 0.8%, respectively; $P < 0.01$).

Based on subjects with available CGMS data, the AUC glucose values ≥80 and ≥140 mg/dl were significantly reduced for subjects during CSII treatment (Table 2) compared with MDI treatment. The observation of reduced AUC glucose values for CSII treatment was not dependent on treatment sequence. During the CGMS monitoring period, CSII-treated subjects spent significantly more time in the glucose range ≥80 but ≤140 mg/dl than MDI-treated subjects, as demonstrated by the greater percentage of glycemic measurements in that range (43 vs. 33% of readings for the CSII vs. MDI subjects, respectively; $P < 0.0001$). CSII-treated subjects also spent significantly less time in the glucose range >140 mg/dl than MDI-treated subjects (41 vs. 50% of readings for the CSII vs. MDI subjects, respectively; $P < 0.0001$). The percentage of glycemic readings <80 mg/dl was similar for both treatments (17% of all readings).

The mean blood glucose profiles from the CGMS readings during the 1st complete day of monitoring (12:00 A.M. to 12:00 A.M.) are presented in Fig. 1. The generally lower blood glucose values during evening, nighttime, and morning for the CSII group represent those time periods that contribute to the lower overall AUC glucose values determined for the CSII group from the CGMS profiles.

Subjects in both treatment sequences reported using total daily insulin doses during CSII and MDI treatments that were similar to their baseline total daily insulin dose (Table 2). For both treatment regimens, the total daily insulin dose for combined subjects was divided nearly equally between basal and bolus doses (22.4 ± 9.6/21.3 ± 12.7 vs. 23.6 ± 10.9/22.5 ± 11.1 units for basal/bolus doses in CSII vs. MDI groups, respectively).

Safety

The numbers of adverse events and subjects reporting those events were similar between treatment therapies. One subject reported moderate diabetic ketoacidosis during CSII treatment; the event was resolved on the same day. There were no reports of diabetic ketoacidosis in the MDI group.

Hypoglycemic episodes were experienced by 92% of the subjects during CSII

Table 2—*Glycemic parameters at the end of each treatment period*

Glycemic parameter Treatment sequence	*n*	Baseline	Treatment *n*	CSII	*n*	MDI	Difference (CSII − MDI)	*P*
Mean fructosamine (μmol/l)								
CSII to MDI	50	351 ± 44	48	352 ± 46	49	360 ± 49		
MDI to CSII	49	345 ± 48	50	334 ± 48	48	349 ± 50		
Combined subjects		NA	98*	343 ± 47	97	355 ± 50	−11.8 [−13.4 to −4.63]	0.0001†
Mean AUC glucose ≥80 mg/dl (mb · h · dl^{-1})‡								
CSII to MDI		NA	37	1,150 ± 758	34	1,605 ± 1018		
MDI to CSII		NA	33	1,403 ± 713	37	1,718 ± 1,069		
Combined subjects		NA	70	1,270 ± 742	71	1,664 ± 1039	−394 [−654 to −196]	0.0005†
Mean AUC glucose ≥140 mg/dl (mg · h · dl^{-1})‡								
CSII to MDI		NA	37	381 ± 397	34	774 ± 721		
MDI to CSII		NA	33	557 ± 496	37	779 ± 778		
Combined subjects		NA	70	464 ± 452	71	777 ± 746	−313 [−489 to −150]	0.0004†
Daily insulin dose (units)§								
CSII to MDI	45	42.3 ± 17.9	50	42.1 ± 19.2	46	46.0 ± 18.2		
MDI to CSII	50	41.6 ± 16.1	48	39.6 ± 17.5	50	46.2 ± 20.5		
Combined subjects	95	41.9 ± 16.9	98	40.9 ± 18.4	96	46.1 ± 19.4		0.08

Data are means ± SD or difference [95% CI]. *Numbers of subjects are greater than those who completed the trial because fructosamine was determined at an end-of-study visit; the last observation carried forward approach was used for fructosamine; †statistical inference was made for combined values only; treatment, sequence, and center were included as fixed effect, subject as random effect in the model; ‡AUC glucose was based on the first 24 h of CGMS monitoring; §treatment insulin dose values were measured after the 1-week dose adjustment period for each treatment period.

treatment and by 91% of the subjects during MDI therapy (Table 3). Fifty-three percent of all hypoglycemic episodes during both treatments were symptomatic hypoglycemic episodes (not confirmed with blood glucose <50 mg/dl). The rates of daily minor hypoglycemic episodes were not different between treatments. However, the rate of nocturnal minor hypoglycemic episodes was significantly less for subjects treated with CSII than for subjects treated with MDI therapy. In contrast, the rate of daytime minor hypoglycemic episodes was significantly greater for subjects treated with CSII than for subjects treated with MDI therapy (Table 3). Seven major hypoglycemic episodes occurred during the study: two CSII-treated subjects had a single episode, two MDI-treated subjects had two episodes each, and one MDI-treated patient had a single episode. No subjects had a major hypoglycemic episode during both treatments.

No end-of-study differences in blood chemistry or hematology laboratory values were noted for the study population. Mean values for vital signs and weight at the end of the study were similar to baseline values.

CONCLUSIONS — The 5-week crossover treatment periods in this clinical trial were not of sufficient duration to use HbA_{1c} as a primary efficacy end point. However, the significantly lower fructosamine values and significantly reduced AUC glucose values during CSII therapy indicate that CSII therapy with insulin aspart provides better glycemic control than MDI therapy with insulin aspart/insulin glargine.

The 24-h CGMS blood glucose profiles demonstrate that CSII therapy provided improved glycemic control during the nighttime and morning hours (Fig. 1), time periods that contributed substantially to lowering the AUC glucose parameters >80 and >140 mg/dl for the CSII group.

CSII allows the nighttime basal insulin rate to be fine-tuned; thus, it may provide a distinct advantage over MDI therapy by being better able to control the dawn phenomenon and possibly curtail the exacerbation of postprandial hyperglycemia at breakfast. The reduced postprandial rise after dinner with CSII, despite standardized dinnertime bolus insulin dosing, might be explained by better adjustment of the basal rate by CSII therapy in the late postprandial period or by the waning effect of insulin glargine at dinnertime during MDI therapy. In a study switching type 1 diabetic patients from twice-daily NPH insulin during MDI to once-daily glargine during MDI, one-quarter of the subjects required further switching to twice-daily glargine injections to achieve acceptable glycemic control (14). The switch to twice-daily glargine was prompted by an increase in HbA_{1c} or persistent elevation of the predinner blood glucose, despite efforts to titrate both bolus insulin and glargine insulin. In the present trial, the tested drug products were used according to their existing U.S. labeling. At the time of the study, glargine was indicated for single-dose bedtime injections. We chose not to explore off-label use during the trial. The 1-week titration phase may also have been too short for optimization of glargine in the MDI regimen.

The improvement in glycemic control for the CSII group did not come at the expense of an increase in insulin dose (Table 2). However, the trend was for a slightly lower total daily insulin dose in the CSII group regardless of treatment sequence, although the difference was not significant.

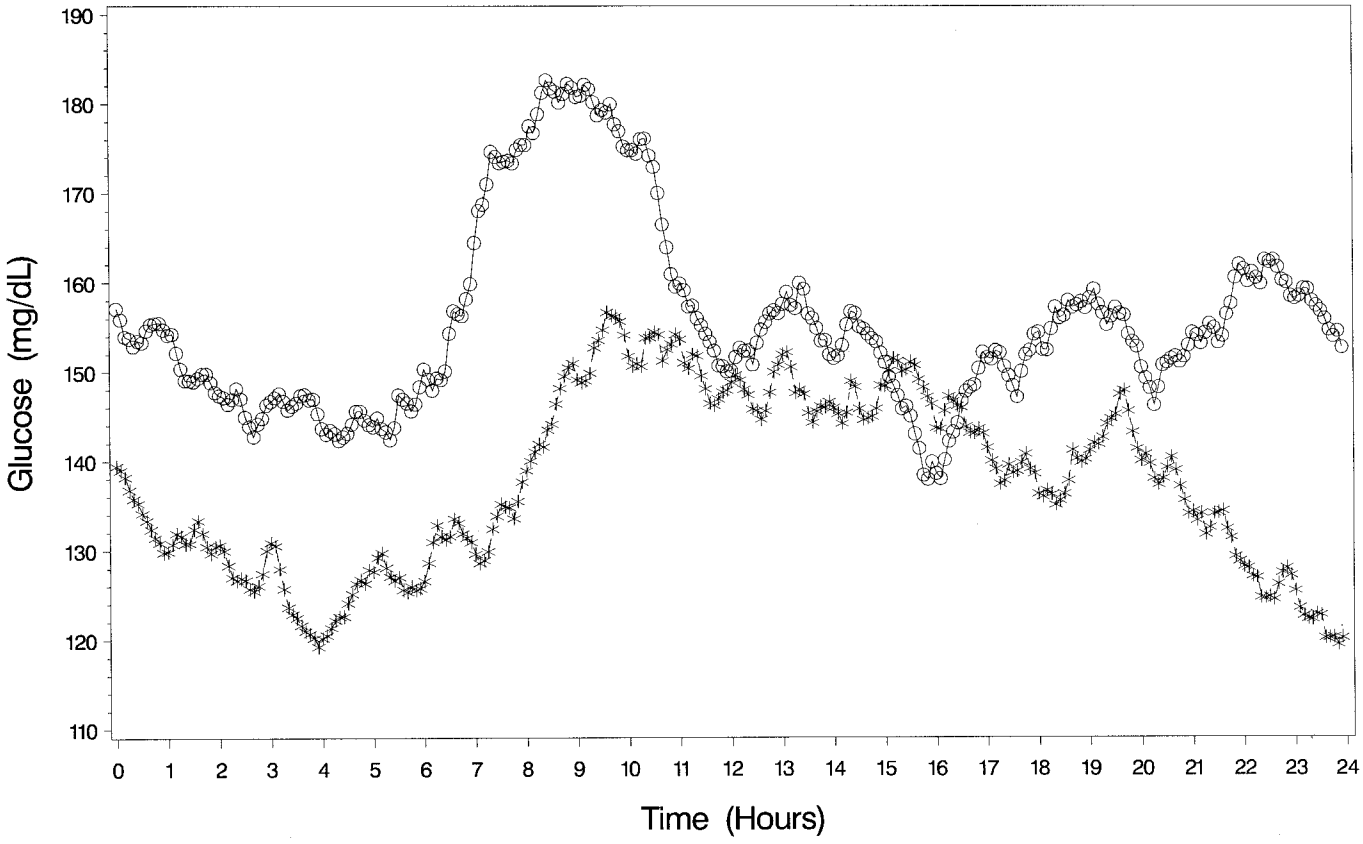

Figure 1—*Mean blood glucose profiles from continuous glucose monitoring. The 24-h profile (12:00 A.M. to 12:00 A.M.) is the mean blood glucose profile for the 1st complete day for combined subjects during the last week of each treatment. Only the 1st 24-h (12:00 A.M. to 12:00 A.M.) profile was presented because the alignment of CGMS profiles into proper time shift limited the available data for a profile containing the 2nd 24 h. Each time point represents the mean of all available data that had a correlation of at least 0.79 with standard blood glucose readings. Number of subjects per time point for each profile: CSII (*), 50–57; MDI (○), 54–57.*

Subjects were able to switch between CSII and MDI therapy without increasing the overall rate of minor hypoglycemic episodes (6.2 vs. 5.7 episodes per subject during the 5-week treatment period, respectively). The significantly lower risk of reported nocturnal hypoglycemia for CSII with insulin aspart is a noteworthy advantage over MDI using aspart/glargine. Avoiding nocturnal hypoglycemia is particularly important because it occurs when a patient may be unable to deal with the episode quickly and effectively. The decreased risk of nocturnal hypoglycemia during CSII treatment was offset by an increase in the risk of daytime minor hypoglycemia, although the rate was relatively low during both treatments (5.6 vs. 3.9 episodes per subject during the 5-week treatment period for CSII vs. MDI therapies, respectively).

When subjects temporarily interrupted CSII therapy using insulin aspart and used MDI therapy with insulin aspart/insulin glargine, the observed differences in glycemic control and risk of hypoglycemia events were small but statistically significant. Accordingly, switching therapy from CSII with insulin aspart to MDI with insulin aspart/insulin glargine was a clinically viable choice for

Table 3 —*Hypoglycemia reported at the end of each treatment period*

	CSII			MDI			
	Subjects	Episodes	Rate*	Subjects	Episodes	Rate*	*P*†
Symptomatic, minor, and major hypoglycemia							
Daily hypoglycemia	90 (92)	956	10.6	89 (91)	825	9.3	0.0041
Daytime hypoglycemia	87 (89)	736	8.5	87 (89)	541	6.2	<0.001
Nocturnal hypoglycemia	71 (72)	216	3.0	70 (73)	280	4.0	0.0024
Minor hypoglycemia							
Daily hypoglycemia	72 (74)	447	6.2	68 (69)	387	5.7	0.2099
Daytime hypoglycemia	59 (60)	333	5.6	59 (60)	232	3.9	<0.001
Nocturnal hypoglycemia	51 (52)	110	2.2	49 (50)	155	3.2	0.0020
Symptomatic hypoglycemia							
Daily hypoglycemia	73 (75)	507	6.9	71 (72)	434	6.1	0.0506
Daytime hypoglycemia	70 (71)	403	5.8	64 (65)	305	4.8	0.0124
Nocturnal hypoglycemia	41 (42)	104	2.5	47 (48)	125	2.7	0.7211

Data are *n* (%) or *n* unless otherwise indicated. Nocturnal episodes occurred between midnight and 8:00 A.M.; daytime episodes occurred between 8:00 A.M. and midnight. *Rate is based on the number of episodes by subjects having episodes during the 5-week treatment period; †calculated for the rate of hypoglycemia using Poisson regression.

temporary glycemic management of type 1 diabetes.

In conclusion, this clinical trial of relatively short duration indicates that CSII was a more optimal therapy than MDI, resulting in lower glycemic exposure without an increased risk of hypoglycemia.

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