Continuous Subcutaneous Insulin Infusion and Multiple Daily Injection Therapy Are Equally Effective in Type 2 Diabetes

A randomized, parallel-group, 24-week study

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OBJECTIVE — Compare the efficacy, safety, and patient satisfaction of continuous subcutaneous insulin infusion (CSII) therapy with multiple daily injection (MDI) therapy for patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — A total of 132 CSII-naive type 2 diabetic patients were randomly assigned (1:1) to CSII (using insulin aspart) or MDI therapy (bolus insulin aspart and basal NPH insulin) in a multicenter, open-label, randomized, parallel-group, 24-week study. Efficacy was assessed with HbA_{1c} and eight-point blood glucose (BG) profiles. Treatment satisfaction was determined with a self-administered questionnaire. Safety assessments included adverse events, hypoglycemic episodes, laboratory values, and physical examination findings.

RESULTS — HbA_{1c} values decreased similarly for both groups from baseline (8.2 ± 1.37% for CSII, 8.0 ± 1.08% for MDI) to end of study (7.6 ± 1.22% for CSII, 7.5 ± 1.22% for MDI). The CSII group showed a trend toward lower eight-point BG values at most time points (only significant 90 min after breakfast; 167 ± 48 vs. 192 ± 65 mg/dl for CSII and MDI, respectively; $P = 0.019$). A total of 93% of CSII-treated subjects preferred the pump to their previous injectable insulin regimen for reasons of convenience, flexibility, ease of use, and overall preference. Safety assessments were comparable for both treatment groups.

CONCLUSIONS — Insulin aspart in CSII therapy provided efficacy and safety comparable to MDI therapy for type 2 diabetes. Patients with type 2 diabetes can be trained as outpatients to use CSII and prefer CSII to injections, indicating that pump therapy should be considered when initiating intensive insulin therapy for type 2 diabetes.

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Patients with type 2 diabetes require insulin treatment when an appropriate combination of oral antidiabetic agents (OADs) and lifestyle changes fail to provide adequate glycemic control. Eventually, many individuals with type 2 diabetes, not unlike individuals with type 1 diabetes, require multiple daily injection (MDI) therapy to achieve optimal diabetes control.

Continuous subcutaneous insulin infusion (CSII) with external pumps is a viable alternative to MDI therapy for patients with type 1 diabetes who are capable, motivated, and trained to use insulin pumps (1–4). Decreased HbA_{1c} values, as well as a decreased incidence of severe hypoglycemia, have been demonstrated for type 1 diabetic patients treated with CSII therapy as compared with those treated with MDI therapy (2,5). These advantages of CSII, as well as improvements in pump technology, have led to increasing acceptance of CSII therapy for type 1 diabetes (6).

The benefits of CSII therapy may also be achieved by type 2 diabetic patients who require intensive insulin therapy but seek an alternative to MDI therapy. Two studies demonstrated that CSII was as safe and effective as MDI therapy for treating type 2 diabetes (7,8). Short-term use of CSII therapy aided glycemic control in

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Abbreviations: BG, blood glucose; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injection; OAD, oral antidiabetic agent.

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

type 2 diabetic patients who failed to maintain glycemic control with diet or OADs (9,10). CSII therapy seems to be a viable alternative to MDI therapy and may become an appropriate method to alleviate the challenge of initiating intensive insulin therapy for type 2 diabetes.

Although human insulin injection (Velosulin), insulin aspart, and insulin lispro are used in insulin pump therapy, only Velosulin and insulin aspart are approved by the Food and Drug Administration (11). Insulin aspart is well suited for use in pumps because it has uniform absorption characteristics (12), is physically compatible for use in pumps (13), and is as safe and effective as buffered regular insulin and insulin lispro in CSII therapy for type 1 diabetes (14). The objective of the present study was to show that pump-naive type 2 diabetic patients could be trained as outpatients to use CSII and then to compare the efficacy, safety, and patient satisfaction of CSII with that of MDI therapy.

RESEARCH DESIGN AND METHODS

— This was an open-label, randomized, parallel-group study conducted at 14 sites in the U.S. CSII-naive subjects with type 2 diabetes received insulin aspart for 24 weeks after being randomly assigned (1:1) to CSII by external pump or to MDI therapy. Subjects were randomized to the lowest available randomization number within each center to provide a treatment assignment for each center that was as balanced as possible. No criterion was used to stratify subject randomization. The study was performed in accordance with the Declaration of Helsinki and with the approval of local independent review boards. Written informed consent was obtained from all subjects.

Subjects

Subjects had type 2 diabetes of ≥2 years' duration and treatment for ≥6 months with at least one insulin dose per day (regular insulin, lispro insulin, NPH, premixed insulin, Lente, or Ultralente), with or without an OAD. The study enrolled 127 men and women aged ≥35 years who, at baseline, had fasting C-peptide level >0.2 nmol/l, BMI ≤43 kg/m^2, and HbA_{1c} level ≥6% and ≤12%. Subjects with impaired hepatic, renal, or cardiac function or recurrent major hypoglycemia were excluded. Women of childbearing age were excluded if they were pregnant, breast-feeding, or not practicing contraception.

Treatments

Subjects received instruction on intensive insulin therapy by a registered nurse during two separate study visits during the 2-week training period before receiving study medication. Intensive insulin therapy was defined as mealtime administration of a fast-acting insulin at each meal with basal insulin coverage by a long-acting insulin administered once or twice daily. Subjects randomized to MDI therapy received instruction on the use of the NovoPen 3.0 (Novo Nordisk, Bagsvaerd, Denmark), and those randomized to CSII therapy received instruction on the use of MiniMed 507C insulin infusion pumps (Medtronic MiniMed, Northridge, CA) on two separate visits. Subjects discontinued OADs upon receiving the study medication.

The MDI group used NovoPen 3.0 with PenFill 3-ml cartridges containing insulin aspart (NovoLog) or Novolin N (Novo Nordisk) (100 units/ml) and NovoFine 30-G disposable needles. Insulin aspart was injected just before meals, with NPH administered as basal insulin. Subjects in the CSII group used insulin aspart (100 units/ml). CSII bolus doses were administered just before meals. CSII-treated subjects were instructed to replace the infusion sets and insulin at intervals not exceeding 48 h.

During the first 8 weeks after randomization (dose-adjustment period), the investigator reviewed the blood glucose (BG) meter readings with the subject to maximize insulin therapy to achieve the targeted fasting (prebreakfast) BG level between 4.4 and 6.7 mmol/l (80–120 mg/dl) without unacceptable hypoglycemia. The subjects continued on their adjusted dose regimen during weeks 8–24 (maintenance period) unless further dose adjustment was required.

Subjects recorded meter-measured BG values, insulin doses, symptoms of hypoglycemia with associated BG readings, and (for the CSII patients) time and date of infusion set changes and any occurrences of obstruction or leakage of the infusion system. Episodes of hyperglycemia (BG >19.4 mmol/l [350 mg/dl]) were derived from BG values reported in the subjects' diaries. All subjects were given a One-Touch meter (LifeScan, Milpitas, CA) to measure BG.

Efficacy assessments

Efficacy was assessed using HbA_{1c} values and eight-point BG profiles. The HbA_{1c} values at baseline and at weeks 8, 20, and 24 were determined by Quest Diagnostics (San Capistrano, CA) using an assay with linearity over the range of 4.3–20.4% and a range of 4.3–6.1% for nondiabetic subjects (15,16). The eight-point BG profiles (BG measurements before and 90 min after each of three meals, at bedtime, and at 2:00 A.M.) were recorded by the subject during the week before the randomization visit and before study visits at weeks 8, 16, 20, and 24. Total daily insulin doses (adjusted by baseline body weight) for the week before visit 12 and the last week of treatment were determined and separated into daily basal and bolus insulin doses.

Safety assessments

Safety assessments included adverse events, physical examination findings, and clinical laboratory evaluations. Hypoglycemia was defined as minor if the subject had symptoms of hypoglycemia (i.e., palpitations, tiredness, sweating, strong hunger, dizziness, tremor, etc.) confirmed by BG meter reading <2.8 mmol/l (50 mg/dl) and was able to deal with the episode without assistance. A major hypoglycemic episode was an event with a BG meter reading <2.8 mmol/l that was associated with severe central nervous system dysfunction that required the assistance of another person or required administration of parenteral glucose or glucagon.

Subjects randomized to the CSII therapy group were trained to recognize clogs and blockages of the pump or infusion set. Subjects recorded such events, along with any interruptions in pump use (≥1 h in duration) in their diaries.

Patient satisfaction questionnaire

Subjects in both treatment groups completed a patient satisfaction questionnaire at baseline and at weeks 16 and 24 to assess the convenience, ease of use, overall satisfaction, and preference of pre-study and study treatments (17). The questionnaires used were components of the PHASE V Technologies Outcomes Information System (Wellesley Hills, MA), which included a diabetes treatment satisfaction module and a quality-of-life summary scale (18,19). At the end of the study, subjects randomized to the CSII

Table 1—*Baseline demographic characteristics and subject enrollment and attrition*

	CSII	MDI
Number of subjects treated	66	61
Age (years)	55.1 ± 10.2	56.0 ± 8.18
Sex (men/women)	42 (64)/24 (36)	35 (57)/26 (43)
BMI (kg/m^2)	32.2 ± 4.2	32.2 ± 5.1
Race: caucasian/black/other	53 (80)/8 (12)/5 (8)	50 (82)/8 (13)/3 (5)
HbA_{1c} (%)	8.2 ± 1.4	8.0 ± 1.1
Duration of diabetes (years)	13.8 ± 7.9	11.9 ± 6.4
Prior history of diabetes complications		
Neuropathy	23 (35)	24 (39)
Retinopathy	14 (21)	13 (21)
Nephropathy	4 (6)	1 (2)
Prior insulin treatment (years)	5.9 ± 5.0	4.6 ± 5.1
Previous treatment*		
Insulin in combination with OAD	27 (41)	22 (36)
Insulin only	38 (59)	39 (64)
Insulin requirements at enrollment (units/kg)	0.75 ± 0.46	0.69 ± 0.39
Withdrawals during treatment	6 (9)	6 (10)
Noncompliance	1 (2)	2 (3)
Withdrawals consent	5 (8)	1 (2)
Ineffective therapy	0	1 (2)
Adverse event	0	2 (3)†
Completed study	60 (91)	55 (90)

Data are means ± SD or *n* (%). *One subject in CSII group had missing data on prestudy insulin use; †one subject had maculopapular rash, and one subject had osteomyelitis and skin ulceration.

group answered an additional module specific to insulin pump therapy relating to preference, convenience, and ease of use of pumps in CSII compared with their prestudy insulin treatment. The patient satisfaction study design, data collection, and analyses were conducted by separate investigators from the Harvard School of Public Health (Boston, MA) and PHASE V Technologies. The brief summary of the data and the material presented here were adapted from previous work with permission (20,21).

Evidence for reliability and responsiveness of the PHASE V Outcomes System Diabetes Treatment Satisfaction Questionnaire scales was established in a pooled analysis of multiple independent, randomized clinical trials. Internal consistency coefficients (Cronbach α) based on 8,058 questionnaires administered to 1,535 subjects with diabetes were ≥0.80 for all scales with three or more items. Responsiveness was established with diet and exercise, oral hypoglycemic agents, and insulin therapy, either as monotherapy or as combination therapy, across a total of 723 person-years of treatment (R.R. Turner, personal communication). The full report on the validation of the questionnaire and the patient satisfaction data are pending publication.

Statistical analysis

A total of 51 subjects were needed in each group to ensure 80% of power to claim an HbA_{1c} difference of 0.4%. Between-treatment comparisons for efficacy end points, except daily insulin dose, were made using an ANCOVA model with treatment and center as fixed effects and the corresponding baseline measurement as the covariate. The last observation carried forward approach was used in the statistical analyses. Results are stated as means ± SD.

RESULTS

Subjects

A total of 205 subjects gave written informed consent and were screened for the study from April 1999 through March 2000. Of those screened, 132 were randomized to treatment; 75 subjects failed the inclusion/exclusion criteria (screening failures). Five subjects (three from the CSII group and two from the MDI group) withdrew from the study during the 2-week training period on intensive insulin therapy and, therefore, received no study medication. Accordingly, efficacy and safety data are based only on those subjects receiving treatment (66 in the CSII group and 61 in the MDI group).

Age, HbA_{1c}, BMI, and occurrence of diabetes-associated complications were similar at baseline for both treatment groups (Table 1). Both treatment groups had a 90% completion rate. Subjects in both treatment groups had similar mean daily insulin requirements before entering the study (Table 1). After the dose-adjustment period, the week 12 median total daily insulin doses as well as total daily basal and bolus doses were similar for both treatment groups (CSII 0.6, 0.3, and 0.4 units/kg; MDI 0.7, 0.3 and 0.4 units/kg, respectively). By week 24, both treatment groups had total daily insulin doses that increased slightly (by 0.1 units/kg; NS) from week 12 values.

Efficacy

At the end of the study, both treatment groups attained significant improvements from baseline ($P < 0.05$) in HbA_{1c} values (CSII 7.6 ± 1.22%; MDI 7.5 ± 1.17%). Change-from-baseline decreases in HbA_{1c} values tended to be slightly greater for the CSII group than the MDI group throughout the study (end-of-study decreases −0.62 ± 1.11% and −0.46 ± 0.89% for CSII and MDI, respectively; treatment difference not significant).

Both treatment groups had similar eight-point BG profiles at baseline and experienced improvements in eight-point BG profiles at the end of the study (Fig. 1). Statistically significant differences between the BG profiles of the two treatments were sporadic during the study, but BG was consistently lower for the CSII group 90 min after breakfast (end-of-study postbreakfast BG values: CSII 9.2 ± 2.6 mmol/l [167 ± 47.5 mg/dl]; MDI 10.7 ± 3.6 mmol/l [192 ± 65.0 mg/dl]; $P = 0.019$).

Mean weights of subjects in each treatment group were similar at baseline (CSII 96.4 ± 17.0 kg; MDI 96.9 ± 17.9 kg) and increased slightly for both treatment groups by the end of the study (CSII 98.1 ± 18.1 kg; MDI 97.6 ± 19.2 kg) but did not differ significantly by treatment group.

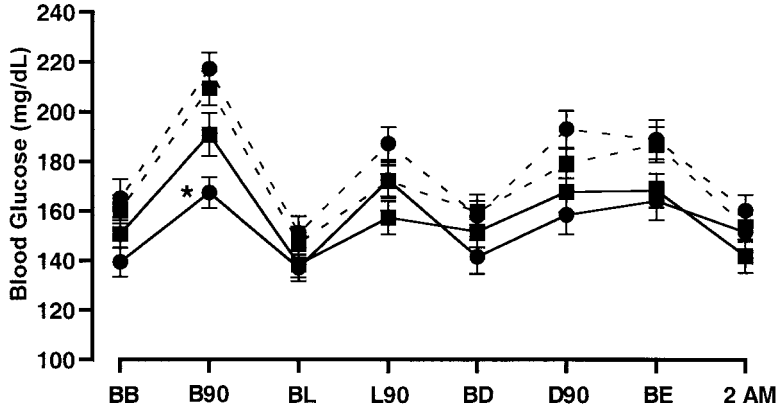

Figure 1—*Baseline and end-of-study eight-point BG profiles (mean ± SEM) for the intent-to-treat population. Dashed lines represent baseline profiles; solid lines represent end-of-study profiles.* ●*, means for CSII;* ■*, means for MDI therapy. Number of patients at each time point: CSII, 56–63; MDI, 54–59.* *P = *0.02. BB, before breakfast; B90, 90 min after breakfast; BL, before lunch; L90, 90 min after lunch; BD, before dinner; D90, 90 min after dinner; BE, at bedtime.*

Hypoglycemia

Hypoglycemic episodes were reported during the study by a similar percentage of subjects in each treatment group: 34 of 63 subjects (54%) in the CSII group, 36 of 61 subjects (59%) in the MDI group. The mean rates of hypoglycemic episodes were also similar (0.8 ± 1.6 and 1.2 ± 3.1 episodes per subject per 30 days for the CSII and MDI groups, respectively). No hypoglycemic episodes required glucagon, intravenous glucose, or assistance of another person. Nocturnal hypoglycemic episodes (midnight to 6:00 A.M.) during the maintenance period were reported by a similarly low percentage of subjects in each treatment group: 10 of 62 subjects (16%) in the CSII group and 13 of 59 subjects (22%) in the MDI group.

Safety

Overall, adverse events were reported by 77 and 70% of the subjects in the CSII and MDI groups, respectively. Two MDI-treated subjects withdrew from the trial because of adverse events (maculopapular rash, osteomyelitis, and skin ulceration). In general, the frequencies of the most commonly occurring adverse events were similar between treatment groups and included upper respiratory tract infections, accidental injury, back pain, and sinusitis. An exception included hyperglycemia, which was the second most commonly reported adverse event for the MDI treatment group. A total of 11 MDI-treated subjects (18%) reported 26 episodes of hyperglycemia compared with three CSII-treated subjects (5%) reporting six episodes. No injection site reactions (redness or soreness) were reported by MDI-treated subjects compared with 15 episodes reported by eight CSII-treated subjects (12%).

There were no clinically significant differences between treatments with respect to changes in vital signs, physical parameters, electrocardiograms, or clinical laboratory findings.

Pump compatibility

Pump compatibility of insulin aspart was judged by the incidence of clogs or blockages of the pump or infusion sets. A total of 20 CSII-treated subjects (30%) experienced no clogs or blockages during the 24-week treatment period. A total of 54 subjects (82%) experienced six or fewer clogs or blockages during the study (corresponding to no more than one clog or blockage per 4 weeks per subject). Subjects were able to respond appropriately to clogs and blockages such that only one reported event coincided with a hyperglycemic episode.

Patient satisfaction questionnaire

The CSII group had significantly greater improvement ($P < 0.001$) in overall treatment satisfaction (59.4 ± 2.1 at baseline to 79.2 ± 1.8 at end of study; mean ± SE) compared with the MDI group using pen injection devices (63.6 ± 1.9 at baseline to 70.3 ± 2.3 at end of study). The change from baseline in satisfaction subscales (e.g., convenience, flexibility, etc.) also corroborated the improved overall satisfaction of subjects in the CSII group compared with the MDI group (Fig. 2). The questionnaire on CSII use, given to only those subjects in the CSII group demonstrated that at least 93% of the responding pump-treated subjects preferred the pump to their previous injectable insulin regimen for reasons of convenience, flexibility, ease of use, and overall preference. Responses to this questionnaire were obtained from 59 of 66 of CSII-treated subjects (89%).

CONCLUSIONS — This study reports the first data on the use of any insulin analog in CSII in patients with type 2 diabetes. This 24-week clinical trial compares CSII and MDI therapies in type 2 diabetes while using insulin aspart in both treatment groups. Previous studies of subjects with type 1 diabetes treated with insulin aspart have demonstrated its suitability in infusion pumps (13,14). Use of insulin aspart in CSII had a safety and efficacy profile that was comparable to buffered regular insulin and insulin lispro (14).

In this clinical trial, subjects with type 2 diabetes previously treated with limited insulin therapy had significant improvements in HbA_{1c} values when switched to intensive insulin treatment using CSII or MDI therapy. The decreases in HbA_{1c} values may have been even greater if OADs had been continued in the study. Improvements from baseline in eight-point BG profiles were consistent with the decreases in HbA_{1c} values for both groups.

The high rate of completion in both groups (90%) attests to the acceptability by patients with type 2 diabetes to initiate intensive insulin therapy using either CSII or MDI. It is noteworthy that subjects assigned to the CSII group were able to initiate intensive insulin therapy on an outpatient basis. Although both treatment groups had comparable glycemic control, the significant improvements in satisfaction scores by subjects in the CSII treatment group suggest that some patients with type 2 diabetes would benefit by using CSII to initiate intensive insulin therapy.

Patient acceptability and long-term compliance of either therapy was not determined beyond the 24 weeks of this study. However, the significantly higher satisfaction scores for convenience, ease of use, and overall satisfaction by the CSII-treated patients suggests that they will have greater treatment acceptance

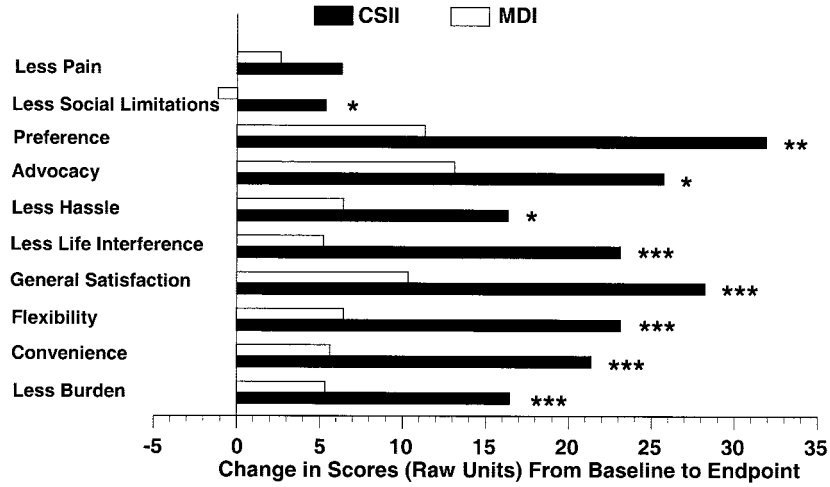

Figure 2— *Change-from-baseline improvements in patient satisfaction subscores at the end of the study. Improvements were compared between treatment groups, controlling for patient age. Responses to baseline questionnaires are based on prestudy insulin treatment. Change-from-baseline scores are available for 52 subjects (79%) in the CSII group and 52 subjects (85%) in the MDI group. Scoring of satisfaction categories ranged from 0 to 100 for least to most satisfaction, respectively.* *P $<$ *0.025;* **P $<$ *0.01;* ***P $<$ *0.001.*

than MDI-treated patients and could consequently be more compliant over time.

In this study, the CSII group had a safety profile that was similar to the MDI group. The CSII group had 15 episodes of injection site reactions (redness or soreness) reported by eight subjects. All episodes were mild, resolved spontaneously, and did not result in the withdrawal of any subject from the study. The causative relationship of injection site reactions to insulin aspart was not likely because insulin aspart was also used in the MDI group, which reported no incidents.

The lower incidence of hyperglycemia for the CSII group (3 subjects, 6 events) compared with the MDI group (11 subjects, 26 events) may signal an advantage of insulin delivery by an infusion pump. Although the slightly higher incidence of hyperglycemia in the MDI group cannot be attributed solely to lack of compliance (missed injections) or possible once-daily NPH dosing by some MDI-treated subjects, it is noteworthy that CSII patients who are continuously wearing their infusion pumps have easier access to insulin and, thus, may be more compliant with treatment.

The rates of hypoglycemia in both treatment groups were low and consistent for patients with type 2 diabetes. All episodes of hypoglycemia were mild and easily managed by the study subject. Hypoglycemia was not an impediment to the subjects' achieving the treatment glycemic goals. Significantly lower rates of hypoglycemia have been reported by patients with type 2 diabetes who had implantable insulin pumps (~0.6 episodes per month) compared with MDI therapy (~1.8 episodes per month) (8). However, the rate of episodes by CSII subjects in this study (0.8 ± 1.6 episodes per 30 days) was comparable to the rate achieved by the implantable insulin pump treatment group.

Subjects in this study reported an incidence of clogs and blockages similar to subjects with CSII-treated type 1 diabetes in a study comparing CSII use of insulin aspart, buffered regular insulin, and insulin lispro (14). Subjects in this trial were properly educated to monitor their BG levels and to recognize and correct the clogs and blockages, such that only one subject experienced a clog/blockage that coincided with a hyperglycemic episode.

Intensive insulin therapy for type 2 diabetes requires careful attention to insulin dosing, particularly during initiation of therapy. In the present study, the median insulin doses, both basal and bolus, were similar between treatment groups at baseline and increased only slightly for both groups by the end of the study. Therefore, subjects with type 2 diabetes were able to initiate and maintain intensive insulin therapy with CSII by using insulin doses similar to those used by the MDI group.

In conclusion, insulin aspart was a highly effective and compatible insulin for CSII using an external pump and was as safe and effective as MDI therapy for patients with type 2 diabetes initiating intensive insulin therapy. This study showed that patients can be trained to use pumps on an outpatient basis and that they greatly prefer CSII to insulin injections. The significantly greater satisfaction scores reported by CSII-treated subjects suggest that CSII may be the preferred method of intensive insulin therapy for capable patients with type 2 diabetes who desire optimal glycemic control.

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