A Clinical Trial of Continuous Subcutaneous Insulin Infusion Versus Multiple Daily Injections in Older Adults With Type 2 Diabetes

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OBJECTIVE — To compare the efficacy and safety of continuous subcutaneous insulin infusion (CSII) and multiple daily injection (MDI) in older adults with insulin-treated type 2 diabetes and to assess treatment satisfaction and quality of life.

RESEARCH DESIGN AND METHODS — Adults ($n = 107$) ≥60 years of age (mean age 66 years) with insulin-treated type 2 diabetes (mean duration 16 years, BMI 32 kg/m^2, and HbA_{1C} [A1C] 8.2%) were randomized to CSII (using insulin lispro) or MDI (using insulin lispro and insulin glargine) in a two-center, 12-month, prospective, randomized, controlled clinical trial. Efficacy was assessed with A1C, safety by frequency of hypoglycemia, and treatment satisfaction and quality of life with the Diabetes Quality of Life Clinical Trial Questionnaire and the 36-item short-form health survey, version 2.

RESULTS — Forty-eight CSII subjects (91%) and 50 MDI subjects (93%) completed the study. Mean A1C fell by 1.7 ± 1.0% in the CSII group to 6.6% and by 1.6 ± 1.2% in the MDI group to 6.4%. The difference in A1C between treatment groups was not statistically significant ($P = 0.20$). Eighty-one percent of CSII subjects and 90% of MDI subjects experienced at least one episode of minor (self-treated) hypoglycemia ($P = 0.17$), and three CSII and six MDI subjects experienced severe hypoglycemia ($P = 0.49$). Rates of severe hypoglycemia were similarly low in the two groups (CSII 0.08 and MDI 0.23 events per person-year, $P = 0.61$). Weight gain did not differ between groups ($P = 0.70$). Treatment satisfaction improved significantly with both CSII and MDI ($P < 0.0001$), and the difference between groups was not statistically significant ($P = 0.58$).

CONCLUSIONS — In older subjects with insulin-treated type 2 diabetes, both CSII and MDI achieved excellent glycemic control with good safety and patient satisfaction.

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Abbreviations: CSII, continuous subcutaneous insulin infusion; DQOLCTQ, Diabetes Quality of Life Clinical Trial Questionnaire; MDI, multiple daily injection; SF-36 v2, 36-item short-form health survey, version 2.

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

In the U.S., >20% of adults >65 years of age have diabetes (1). The risk of micro- and macrovascular complications increases in elderly patients with diabetes and is associated with higher hemoglobin HbA_{1C} (A1C) and longer duration of diabetes (2). In middle-aged adults with type 2 diabetes, intensive glycemic management can delay or prevent the development of microvascular and neuropathic complications (3,4). While the benefits of glycemic management are less clearly established in older adults, both the American Diabetes Association and the American Geriatrics Society recommend that older adults with good functional status maintain A1C levels <7% (5,6). Despite these recommendations, surveys have shown that only one-third of diabetic patients 65–74 years of age had A1C levels <7%. Of those using insulin, only 27% had A1C levels <7%, whereas nearly half had A1Cs >8% (7).

While lifestyle changes and oral antidiabetes medications can improve glycemic control early in the course of type 2 diabetes, insulin is often required to reach A1C goals later in the course of disease. Intensive insulin therapy regimens employ either continuous subcutaneous insulin infusion (CSII) or multiple daily injections (MDIs) of insulin to mimic the normal physiology of insulin secretion (8). The efficacy and safety of these methods have not been evaluated in older type 2 diabetic patients. Studies comparing CSII and MDI in patients with type 1 diabetes have found either comparable outcomes or have favored CSII (9–12). In the only study comparing CSII and MDI in type 2 diabetic patients, comparable glycemic control was reported (13). None of these studies included significant numbers of patients >60 years of age. The purpose of this study was to compare the efficacy and safety of CSII and MDI in older adults with insulin-treated type 2 diabetes.

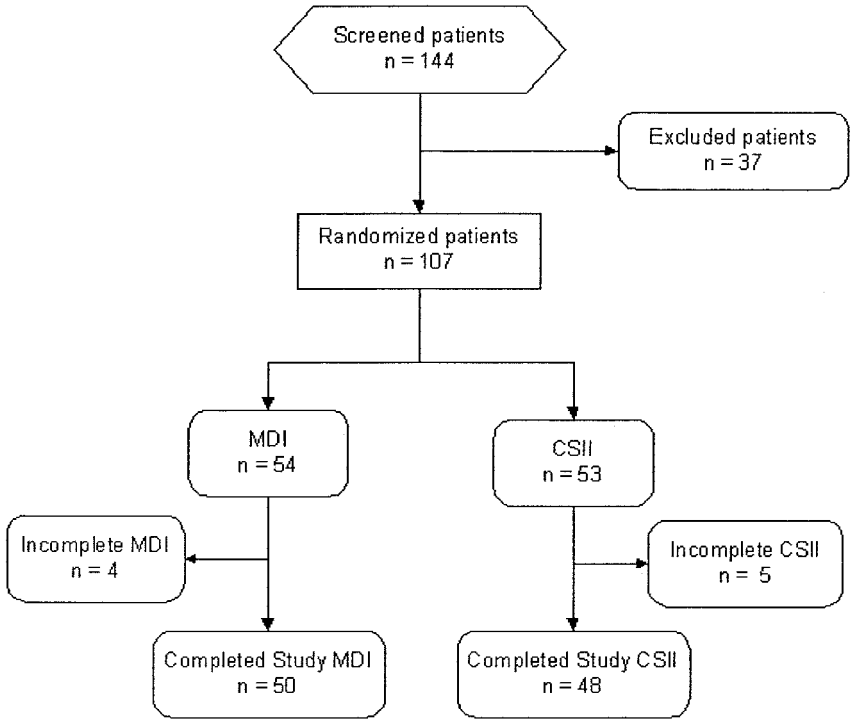

Figure 1—*Study recruitment and retention.*

RESEARCH DESIGN AND METHODS

— This was a two-center, prospective, randomized, controlled clinical trial. The study was reviewed and approved by the institutional review boards at both participating institutions, and all subjects provided written informed consent. A data safety monitoring board reviewed the progress of the study.

Subjects were eligible to participate if they were ≥60 years of age, had a clinical diagnosis of type 2 diabetes for at least 1 year, were taking at least one injection of insulin per day for the past month (with or without oral antidiabetes medications), and had an A1C ≥7.0%. Patients were excluded from the trial if they had a BMI >45 kg/m^2; severe impairment of cardiac, hepatic, or renal function; the presence of any physical, psychological, or cognitive impairments that would interfere with adherence to an intensive insulin therapy program; or more than two episodes of severe hypoglycemia in the past year or a history of hypoglycemia unawareness.

Figure 1 illustrates subject recruitment and retention. Subject eligibility was determined at a screening exam (−4 weeks). Eligible subjects were seen again in 2 weeks (−2 weeks) to discontinue oral antidiabetes medications and to meet with the study staff who instructed them about diet, self-monitoring of blood glucose, and record keeping. A blood glucose meter (Accuchek Advantage or Accuchek Complete; Roche Diagnostics, Indianapolis, IN), test strips, and lancets were provided to each subject. Subjects returned again in 2 weeks (0 week) for baseline laboratory measurements, randomization, and to be instructed in intensive therapy. A block randomization scheme was used at each site. Upon verification of eligibility, the study coordinator or investigator contacted the data-coordinating center for the randomization assignment.

Intensive therapy was implemented with preprandial insulin lispro (Humalog; Eli Lilly, Indianapolis, IN) and with basal insulin provided either as continuous lispro infusion for those randomized to CSII or as once-daily insulin glargine (Lantus; Aventis, Bridgewater, NJ) for those randomized to MDI. CSII subjects were treated with MiniMed 508 insulin infusion pumps (Medtronic MiniMed, Northridge, CA) and instructed to replace the insulin reservoirs and infusion sets at least every 72 h. Subjects randomized to MDI were treated with 3.0 ml Humalog Pens (Eli Lilly) with Microfine III pen needles (Becton Dickinson, Franklin Lakes, NJ) and with glargine using an insulin syringe (Becton Dickinson).

All subjects were instructed to monitor their blood glucose levels before meals and at bedtime and to check for any symptoms or signs of hypoglycemia. At least 1 day per month, subjects were also asked to monitor before and 90 min after each meal, at bedtime, and at 3:00 A.M. to evaluate postprandial glucose excursions, assess efficacy of mealtime insulin bolus doses, and monitor for nocturnal hypoglycemia.

In the 1-week period between randomization and treatment initiation, subjects monitored their diet, physical activity, and blood glucose levels. These data, as well as body weight, A1C, previous insulin dose, and use of oral antidiabetes medications, were used to estimate the initial total daily insulin dose. For CSII subjects, the initial basal rate (units per hour) was calculated as 50% of the total daily insulin dose divided by 24 h. Basal insulin for MDI subjects was calculated as 50% of the total daily insulin dose and administered as glargine before bedtime. In both groups, the remaining 50% was administered as preprandial lispro boluses (~15% of the total daily dose before breakfast, 15% before lunch, 15% before dinner, and 5% before snacks, if applicable). All participants were instructed to adjust their premeal boluses based on their premeal capillary glucose readings and, when necessary, their anticipated carbohydrate consumption.

Study staff maintained close, often daily, contact with subjects via telephone or e-mail during the 1st month of therapy and with clinic visits at week 1, 2, and 4. Insulin doses were adjusted to achieve target blood glucose levels of 80–120 mg/dl before meals, 100–150 mg/dl at bedtime, and A1C <5.6% (the upper limit of normal for the assay used) without incurring unacceptable hypoglycemia. In general, participants were called at least weekly while therapy was being actively adjusted. Otherwise, participants were called every 2 weeks. Individual nutritional instruction was provided as needed. Participants were seen in follow-up 2 months after randomization and at 2-month intervals for 12 months.

A1C was measured at the Diabetes Research Laboratory at the University of Texas Southwestern at Dallas using high-performance liquid chromatography. The A1C interassay coefficient of variability is

Table 1—*Characteristics of the study population*

	CSII	MDI
Subjects randomized (*n*)	53	54
Age (years)	66.6 ± 5.9	66.2 ± 4.5
Sex (male)	38 (72)	24 (44)
Race		
Caucasian	43 (81)	49 (91)
Black	4 (8)	2 (4)
Hispanic	4 (8)	2 (4)
Other	2 (4)	1 (2)
Duration of diabetes (years)	16.9 ± 9.0	15.4 ± 8.9
Prior diabetes treatment		
Insulin only	30 (57)	33 (61)
Insulin and oral agent(s)	23 (43)	21 (39)
Prior insulin treatment (years)	8.1 ± 8.3	8.2 ± 7.7
History of diabetes complications*		
Retinopathy	20 (42)	19 (36)
Nephropathy	9 (17)	7 (13)
Neuropathy	37 (72)	32 (59)
History of cardiovascular complications*		
Hypertension	38 (72)	41 (76)
Dyslipidemia	31 (58)	41 (76)
Cigarette smoking (current)	2 (4)	3 (6)
Angina/myocardial infarction/heart failure	24 (45)	17 (32)
BMI (kg/m^2)	32.5 ± 5.8	31.8 ± 5.8
A1C (%)	8.4 ± 1.1	8.1 ± 1.2

Data are means ± SD or *n* (%). *Self-reported.

<2% and intra-assay variability <0.3%. The Diabetes Laboratory is certified by the National Glycohemoglobin Standardization Program.

Outcomes

Efficacy was assessed using A1C measured at the baseline and at the 1-, 2-, 4-, 6-, 8-, 10-,and 12-month visits. Hypoglycemia, weight, and infusion site and injection site problems were assessed at scheduled study visits. The frequency of minor hypoglycemia was recorded for the week before each scheduled visit, and all severe and catastrophic hypoglycemic episodes were documented. Minor hypoglycemia was defined as capillary glucose <65 mg/dl that the patient was able to treat himself/herself or, if glucose was not measured, symptoms of hypoglycemia that resolved with administration of oral carbohydrates. Severe hypoglycemia was defined as a capillary glucose <50 mg/dl associated with confusion, loss of consciousness, or seizures, or, in the absence of a glucose determination, confusion, loss of consciousness, or seizures that resolved with the administration of oral carbohydrate, glucagon, or intravenous glucose by another person. Catastrophic hypoglycemia was defined as severe hypoglycemia that resulted in life-threatening injury to the patient or another person, hospitalization, and/or death.

The Diabetes Quality of Life Clinical Trial Questionnaire (DQOLCTQ) was administered to subjects before randomization, 4 weeks after randomization, and at the 6- and 12-month visits. This validated questionnaire includes both generic and disease-specific areas and was used to measure treatment satisfaction, treatment flexibility, frequency and bothersomeness of symptoms, social stigma, diabetes satisfaction, diabetes impact, social worry, and diabetes worry (14). Physical and mental health composite scores for the 36-item short-form health survey, version 2 (SF-36 v2) were used to measure quality of life (15).

Power calculations and statistical analyses

We initially sought to recruit 180 subjects, 90 in each treatment arm. Based on 180 subjects, the study had power to detect a difference in A1C of 0.5% between groups using a two-tailed Students' *t* test (α = 0.05% and power = 0.90). Interim analysis by the data safety monitoring board prompted a recommendation to halt recruitment due to an observed difference of 0.2% between treatment groups that was unlikely to become significant even if the study was continued to the end.

Results are presented as means ± SD. An intention-to-treat analysis employing repeated-measures ANOVA, adjusted for sex and baseline A1C, was used to test the change in mean A1C over time. Difference in proportions were compared using Fisher's exact test (two tailed), and numbers of events, adjusted for exposure time, were compared using Poisson regression. The prerandomization DQOLCTQ scores were subtracted from those at the subsequent visits to create Δ scores. Repeated-measures ANOVA was used to assess differences. When the test of equality of the differences between visits was significant, pairwise comparisons of visits were performed. A *P* value <0.05 was interpreted as statistically significant.

RESULTS — A total of 144 subjects were screened for the study, and 107 were randomized (Fig. 1). Baseline characteristics of randomized subjects are shown in Table 1. More men were randomized to CSII than to MDI. Ninety-eight subjects (92%) completed the study. Eight subjects, four from each treatment group, withdrew from the study, and one subject (CSII) died at 8 months due to cancer. Two CSII subjects withdrew before initiation of therapy, two others withdrew after 2 weeks and 4 months of therapy. Two MDI subjects withdrew after 2 months of therapy, one after 8 months, and one after 10 months of therapy.

Figure 2 shows A1C levels by treatment group and time. Because baseline A1C values tended to be higher in the CSII group, we used repeated-measures ANOVA and adjusted for baseline A1C to test the change in mean A1C over time. The mean difference in A1C between treatment groups was not significant (P = 0.19). In both treatment groups, A1C improved significantly over time (P < 0.0001). There was no interaction between treatment group and time (P = 0.27). Sex, BMI, and study site were also tested as covariates but were not significantly associated with A1C values. At study end, mean A1C was 6.6 ± 0.8% in the CSII group and 6.4 ± 0.8% in the

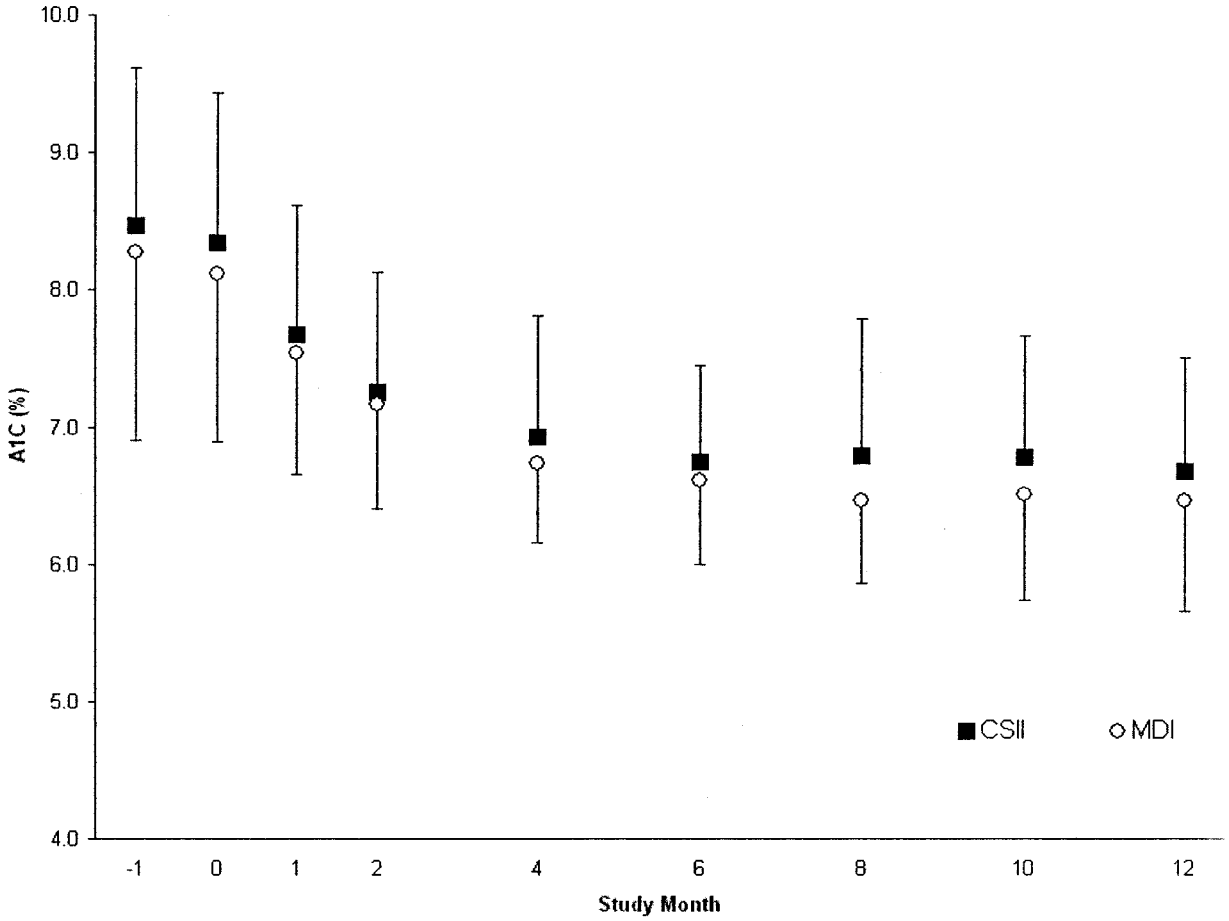

Figure 2—*Mean A1C by treatment group and time. Data are means ± SD.*

MDI group ($P = 0.19$). The mean change in A1C from baseline to study end was −1.7 ± 1.0% in the CSII group and −1.6 ± 1.2% in the MDI group. At study end, 75% of subjects in the CSII group and 84% of those in the MDI group achieved A1C levels <7.0% ($P = 0.30$).

At the end of the study, total daily insulin requirements were similar for the two treatment groups. The mean total daily insulin requirement was 108 ± 63 units for CSII subjects and 108 ± 62 units for MDI subjects ($P = 0.998$). There were no differences between groups in mean daily basal insulin doses (CSII 54 ± 32 units, MDI 51 ± 28 units, $P = 0.63$) or in mean daily bolus insulin doses (CSII 55 ± 40 units, MDI 57 ± 40 units, $P = 0.83$).

Forty-three subjects (81%) in the CSII group reported at least one episode of minor hypoglycemia compared with 49 subjects (90%) in the MDI group ($P = 0.17$). Between treatment months 2 and 12, there were 258 minor hypoglycemic events reported during 240 observations in the CSII group (1.08 events per week) and 286 minor hypoglycemic events reported during 234 observations in the MDI group (1.22 events per week) ($P = 0.33$). Three CSII subjects and six MDI subjects experienced at least one episode of severe hypoglycemia ($P = 0.49$). There were four severe hypoglycemic events during 49.87 person-years of follow-up in the CSII group (0.08 events per person-year) and 12 severe events during 51.43 person-years of follow-up in the MDI group (0.23 events per person-year) ($P = 0.61$). One MDI subject experienced four severe hypoglycemic events. One episode of severe hypoglycemia in one MDI subject was classified as catastrophic. The episode was associated with a motor vehicle crash, and the subject was hospitalized. The subject recovered completely, and no other individuals were injured.

Weight increased by 2.1 kg in the CSII group ($P < 0.01$) and 2.6 kg in the MDI group ($P < 0.01$). The difference in weight gain between the two treatment groups was not significant ($P = 0.70$).

Infusion and injection site problems were reported in both treatment groups (Table 2). Five infusion site infections requiring antibiotic treatment were reported in CSII subjects. Irritation and inflammation were more common in CSII subjects, and bleeding and bruising were more common in MDI subjects. There was no difference in the number of subjects experiencing site problems ($P = 0.41$).

There were 72 technical or mechanical problems related to the method of insulin delivery reported by 39 CSII subjects and 28 such problems reported by 22 MDI subjects (Table 2). Because the types of technical and mechanical problems differed between treatment groups, we did not perform statistical testing. Twenty-eight percent of problems reported among CSII subjects and 18% of those reported by MDI subjects occurred within the first 2 months of treatment.

Table 2—*Injection or infusion site problems and treatment-specific technical or mechanical problems reported by subjects*

	CSII (n = 51)		MDI (n = 54)		
	Events	Subjects	Events	Subjects	*P*
Injection and infusion site problems*					
Infection	5	5 (10)	0	0 (0)	0.20
Irritation/inflammation	85	36 (69)	15	10 (19)	<0.01
Bleeding/bruising	50	26 (50)	180	47 (87)	<0.01
Any site problem	122	42 (82)	188	48 (89)	0.41
Technical and mechanical problems					
Device malfunction (infusion pump or insulin pen)	20	17 (33)	9	7 (13)	
Improper or inadequate insulin delivery	10	10 (20)	3	2 (4)	
Difficulty with pump setup or operation	25	15 (28)	—	—	
Concern about pen accuracy	—	—	2	2 (4)	
Difficult to depress pen plunger	—	—	5	4 (7)	
Difficult to see units on pen	—	—	4	4 (7)	
Problem type not specified	16	14 (27)	5	5 (9)	
Any technical or mechanical problem	72	39 (76)	28	22 (41)	

Data are *n* (%). Events reported at time of routine study visits. All visits subsequent to treatment initiation are included. *P* values are for difference in numbers of subjects reporting problems. **P* values were calculated for injection/infusion site problems only. Treatment specificity of technical and mechanical problems precluded direct comparison of groups.

DQOLCTQ treatment satisfaction scores improved over time for both treatment groups (CSII from 52 to 81, MDI from 50 to 78) ($P < 0.01$) but was not different between groups ($P = 0.58$). The DQOLCTQ diabetes impact score improved by 2 points over time in both treatment groups ($P < 0.01$) and did not differ between groups ($P = 0.19$). Worry scores improved by 3 points over time in both treatment groups ($P = 0.02$) and did not differ between groups ($P = 0.62$). Diabetes worry, social worry, treatment flexibility, and social stigma did not change over the course of the study and there were no differences between groups.

The SF-36 v2 physical composite score increased slightly between baseline and study end (CSII from 40.5 to 41.1, MDI from 40.6 to 41.0). The SF-36 v2 mental composite score decreased slightly between baseline and study end (CSII from 51.0 to 50.0, MDI from 53.0 to 50.5). The changes over time in both physical and mental composite scores were not statistically significant within groups or between groups.

CONCLUSIONS — The American Diabetes Association and the American Geriatrics Society have recommended that healthy older adults with good functional status maintain A1C <7.0% (5,6). We studied the efficacy, safety, and satisfaction associated with intensive insulin therapy using CSII or MDI in adults ≥60 years of age over 1 year. Both treatment groups had significant decreases in mean A1C to levels <7.0% and were able to maintain A1C levels <7.0% with good safety and high treatment satisfaction. There was no difference in efficacy between CSII and MDI and no difference in efficacy by baseline A1C, sex, BMI, or study site.

CSII and MDI have previously been shown to be equally effective in younger patients with type 2 diabetes. However, the previous trial used basal NPH insulin and did not achieve A1C levels <7.0% (13). Of the four randomized controlled clinical trials of CSII and MDI in patients with type 1 diabetes, one showed a clear advantage to CSII, two showed a slight advantage to CSII, and one showed no difference (9–12). When data from the latter three studies were combined in a meta-analysis, the overall treatment effect (CSII–MDI) was 0.35% ($P = 0.08$). A higher baseline A1C was associated with greater efficacy of CSII (16).

Hypoglycemia is the major complication of intensive insulin therapy and is an important barrier to intensive therapy in older adults. Risk factors associated with insulin-induced hypoglycemia in the elderly include insulin administration errors, missed meals, renal insufficiency, liver disease, and defective counterregulation (17–20). In our study, there was no significant difference in the numbers of subjects experiencing hypoglycemia or the number of hypoglycemic events in the CSII and MDI groups. Although there was a trend toward a higher number of severe hypoglycemic events in the MDI group, this was largely related to one subject who experienced four events.

The rates of minor and severe hypoglycemia in our study were higher than those in the previous study of CSII and MDI in type 2 diabetes (13). That study reported no severe events over a shorter time frame. This may be due to the older age of our population or to the lower levels of A1C achieved in our study. Our rates of both minor and severe hypoglycemia were similar to those reported in subjects with type 1 diabetes treated with CSII and MDI (9–11). A trend toward more severe events in the MDI group was not consistently demonstrated in those studies.

Weight gain occurred in both groups but did not differ between groups. The number of difficulties associated with pump therapy in our study was more than reported in the previous study of pump use in type 2 diabetes (13). This difference may have been because of better ascertainment or potentially because our subjects were less technologically savvy. The number of site problems was similar in the two groups.

Treatment satisfaction, diabetes impact, and diabetes satisfaction scores improved over time for both the CSII and MDI groups. Treatment satisfaction includes measures of the adequacy of diabetes control, satisfaction with insulin treatment, and willingness to continue

the present insulin regimen. The largest increase in treatment satisfaction occurred in the first 4 weeks of treatment, despite the fact that a higher percentage of technical difficulties occurred in the first 2 months.

Our study was limited in that more men were randomized to CSII and CSII subjects tended to have higher baseline A1C values. To address these issues, we assessed treatment effects using repeated-measures ANOVA that adjusted for sex and baseline A1C.

We have shown that intensive insulin therapy for older adults with type 2 diabetes can achieve A1C levels <7.0%, the goal recommended for highly functioning geriatric patients (5,6). CSII and MDI were equally effective in achieving this goal. The number of hypoglycemic events assessed as minor or severe was not excessive, despite the lower A1C levels achieved in our study compared with previous studies of intensive insulin therapy. Weight gain was similar in the two groups. Patients' satisfaction with treatment and diabetes satisfaction improved in both treatment groups and did not differ between treatment groups. This study suggests that for highly functioning insulin-treated type 2 diabetic patients ≥60 years of age, intensive treatment with either MDI or CSII is feasible and safe. Because MDI achieved results comparable to CSII and because MDI is less expensive than CSII (21), MDI may be preferred as an initial regimen for older patients with type 2 diabetes requiring intensive insulin therapy.

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