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ORIGINAL ARTICLE

Predicting the Effectiveness of Insulin Pump Therapy on Glycemic Control in Clinical Practice: A Retrospective Study of Patients with Type 1 Diabetes from 10 Outpatient Diabetes Clinics in Sweden over 5 Years

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Abstract

Background: Multicenter long-term studies of predictors for the effectiveness of continuous subcutaneous insulin infusion (CSII) in clinical practice are lacking. We hypothesized that there are substantially greater reductions in hemoglobin A1c (HbA1c) in patients with poor glycemic control and that other predictors may also exist.
Subjects and Methods: We used data from 10 outpatient diabetic clinics in Sweden and studied CSII treatment over 5 years. Patients with HbA1c values available ≤ 6 months before starting CSII and at 5 years were included ($n = 272$, 82% of CSII patients) along with 2,437 contemporaneous controls on multiple daily insulin injections (MDI). Baseline variables evaluated were age, sex, diabetes duration, insulin dose, body mass index (BMI), HbA1c at baseline, and outpatient clinical care unit.
Results: At 5 years, significantly greater reductions in HbA1c by CSII compared with MDI were found for patients with higher baseline HbA1c ($P = 0.032$) and lower baseline BMI ($P = 0.013$). For baseline HbA1c levels of 7.0%, 8.0%, and 9.0% and a BMI of 25 kg/m^2, the reduction in HbA1c level by CSII was 0.08% (difference not significant), 0.16% (95% confidence interval, 0.03–0.29%), and 0.25% (95% confidence interval, 0.11–0.39%), respectively. Corresponding analyses for the change in HbA1c level from start to 1 and 2 years revealed a significant interaction of insulin pump therapy only with baseline HbA1c levels ($P < 0.001$ and $P = 0.030$, respectively). The interaction term between outpatient clinical care unit and CSII treatment was statistically significant for some care units, with some care units demonstrating a benefit from CSII and others demonstrating a detriment.
Conclusions: Patients with high HbA1c levels have a greater probability of improved HbA1c after initiating pump therapy, but effects remain relatively modest even for patients with poor control. Factors predicting successful insulin pump use need further study.

Introduction

Poor glycemic control in patients with type 1 diabetes is associated with a substantially increased risk of diabetes complications.[1–3] To obtain good glycemic control in this patient group, multiple daily insulin injections (MDI) or administration via an insulin pump, also termed continuous subcutaneous insulin infusion (CSII), is recommended.[4,5] Although patients with type 1 diabetes generally use either MDI or CSII today, many patients still exhibit poor glycemic

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control.[6–9] In two large national diabetes registries in Sweden and Scotland[6,7] and one study from Australia,[8] over 20% of type 1 diabetes patients had a hemoglobin A1c (HbA1c) level above 9.0%, and only 13–15% achieved HbA1c targets. In a study of youths with type 1 diabetes in the United States, only 23–27% met HbA1c targets by International Society for Pediatric and Adolescent Diabetes guidelines.[9]

Hence there remains a critical need to understand how to improve glycemic control in daily life among patients with type 1 diabetes. In clinical trials, switching treatment from MDI to CSII has been associated with improved HbA1c by approximately 0.3% (3 mmol/mol).[10] However, data from long-term multicenter evaluations of CSII in daily life are sparse. We recently evaluated the effects of CSII versus MDI from 10 hospital-based diabetes outpatient clinics over 5 years.[11] CSII was associated with approximately 0.4% lower HbA1c after 1–2 years, but the effect decreased significantly with time, to a relative reduction in HbA1c of 0.2% after 5 years, compared with patients continuing on MDI.[11]

From a population perspective where many patients with type 1 diabetes have very poor glycemic control, data from clinical trials and practice indicate that the average effects in reducing HbA1c by CSII may be relatively modest. However, analyses from clinical trials have also indicated that the effects of CSII in reducing HbA1c are greater in patients with poor glycemic control.[12–14] The aim of this study was to understand the magnitude of effects of CSII on reducing HbA1c levels for various patient groups in clinical practice (e.g., in those with poor versus good glycemic control). Specifically, we hypothesized that there are substantially greater reductions in HbA1c level in patients with poor glycemic control and that other predictors (e.g., at which diabetes clinics patients receive treatment) may also exist.

Subjects and Methods

Data source

Data were obtained from a medical patient record system, Diab-Base (Journalia AB, Östra Ämtervik, Sweden), which is used at 10 hospital-based diabetes clinics for adult outpatients (18 years or older) in Sweden.[11] Most clinics have used Diab-Base since approximately the year 2000. The system has previously been described in detail and used in several previous studies of diabetes treatments in patients with both types 1 and 2 diabetes.[11,15–19] In brief, Diab-Base includes information on risk factors, treatments, and complications that are recorded during clinical visits. The system is constructed so that all measurements on risk factors such as HbA1c, blood pressure, blood lipids, body mass index (BMI), type of diabetes, and insulin dose can be tracked electronically. It includes information on the date of CSII initiation. In the current study, data were collected until September 2009; we used a cohort identical to that from a recent study evaluating individuals treated with CSII over at least 5.5 years.[11]

Inclusion/exclusion

Inclusion and exclusion criteria for this cohort have previously been described in detail.[11] In brief, patients with type 1 diabetes, diabetes duration of >1 year, and CSII treatment for at least 5.5 years were included. HbA1c values had to be recorded within 6 months before the start of CSII and at 5 years ± 6 months. In total, 82% ($n = 272$) of patients treated with CSII for 5 years ± 6 months in Diab-Base had an HbA1c measurement in accordance with these criteria. The control group consisted of patients treated with MDI over an identical time period as patients treated with CSII. The control group was selected without resampling such that the highest possible number of unique control patients was matched to each patient from the CSII group with respect to CSII start date. Similar to the CSII patients, only patients with a diabetes duration >1 year and those with information on HbA1c level at 5 years ± 6 months were included. Patients with intermittent use of CSII were excluded. In total, 2,437 control patients were included in the current analyses.

Variable definitions

We studied whether the relative effect of CSII compared with MDI on HbA1c level at 1, 2, and 5 years differed with respect to various baseline characteristics. The following possible predictors for a greater or lower effect on HbA1c from CSII compared with MDI were analyzed: age, sex, diabetes duration, BMI, insulin dose (U/kg/day), baseline HbA1c level, and care unit. ''Care unit'' refers throughout the article to each of the 10 hospital-based diabetes outpatient clinics included in the study. Because diabetes clinics in Sweden used HbA1c methods calibrated to the high-performance liquid chromatography Mono-S method until September 2010, all HbA1c values were converted to the National Glycohemoglobin Standardization Program and International Federation for Clinical Chemistry standards.[20] Percentage units are used for the National Glycohemoglobin Standardization Program, and units of mmol/mol are used for the International Federation for Clinical Chemistry.

This study was approved by the ethical committee of the University of Gothenburg.

Statistical analyses

For categorical variables, data are presented as numbers (%). For continuous variables, mean (± SD) values are presented. For comparison between groups, Fisher's exact test was used for dichotomous variables, and Student's *t* test was used for continuous variables. For multivariable analyses, the MIXED procedure (analysis of covariance) in SAS (version 9.2) software (SAS Institute, Cary, NC) was used to determine the effect size for interaction variables between each baseline variable of interest and CSII treatment at the specified time points. The final model for each time point is adjusted for other baseline variables that significantly statistically differed between the groups and that have demonstrated an impact on the outcome. The results from these analyses are expressed in differences between the treatments in least square (LS) means with 95% confidence intervals (CIs) and *P* values. All tests were two-tailed, and statistical significance was considered to be achieved at $P \le 0.10$ for the interaction terms and $P \le 0.05$ for all other terms.

Results

Baseline characteristics are presented in Table 1. The baseline HbA1c levels were significantly higher in the CSII group, with a mean HbA1c of 8.39% (68.1 mmol/mol) compared with 8.07% (64.7 mmol/mol) ($P < 0.001$) in the

Table 1. Baseline Characteristics

Variable	*CSII* (n = *272*)	*MDI* (n = *2,437*)	P *value*
Sex			
Male	119 (43.8%)	1391 (57.1%)	
Female	153 (56.3%)	1046 (42.9%)	< 0.001
Age (years)	38.6 (11.3) (*n* = 267)	45.6 (14.4) (*n* = 2,437)	< 0.001
HbA1c	*n* = 272	*n* = 2,437	< 0.001
NGSP (%)	8.39 (1.30)	8.07 (1.27)	
IFCC (mmol/mol)	68.1 (14.2)	64.7 (13.9)	
BMI (kg/m^2)	24.8 (3.4) (*n* = 266)	25.0 (3.8) (*n* = 2,392)	0.38
Insulin dose (U/kg/day)	0.632 (0.372) (*n* = 271)	0.671 (0.226) (*n* = 2,427)	0.09
Diabetes duration (months)	15.1 (11.2) (*n* = 272)	20.1 (13.2) (*n* = 2,437)	< 0.001
Care Unit 1	5.9%	6.1%	1.0
Care Unit 2	2.6%	7.1%	0.003
Care Unit 3	15.8%	27.6%	< 0.001
Care Unit 4	21.3%	7.6%	< 0.001
Care Unit 5	4.4%	6.1%	0.32
Care Unit 6	10.3%	17.5%	0.002
Care Unit 7	19.1%	15.0%	0.09
Care Unit 8	5.9%	6.6%	0.78
Care Unit 9	13.2%	3.5%	< 0.001
Care Unit 10	1.5%	2.9%	0.24

BMI, body mass index; CSII, continuous subcutaneous insulin infusion; HbA1c, hemoglobin A1c; IFCC, International Federation for Clinical Chemistry; MDI, multiple daily insulin injections; NGSP, National Glycohemoglobin Standardization Program.

MDI group. Individuals treated with CSII were younger than patients treated with MDI, with the mean age in the groups being 38.6 and 45.6 years ($P < 0.001$), respectively. More individuals were women in the CSII group (56% vs. 43%; $P < 0.001$), and diabetes duration was shorter, with a mean duration of 15.1 versus 20.1 years ($P < 0.001$), respectively. Mean BMI was 24.8 and 25.0 kg/m^2 for patients treated with CSII and MDI, respectively, and mean insulin doses were similar for the two groups (0.63 vs. 0.67 units/kg/day, respectively). There were significantly more individuals treated with CSII in Care Units 4 and 9 and significantly more individuals treated with MDI in Care Units 2, 3 and 6, compared with the distribution of CSII and MDI treatment in all other care units.

Predictive analysis of change in HbA1c levels over time

In the predictive analysis of change in HbA1c from baseline to 5 years, significant interactions between insulin pump therapy and both baseline HbA1c levels ($P = 0.032$) and BMI ($P = 0.013$) were apparent. Estimates revealed that the greater the baseline HbA1c level, the greater the decrease in HbA1c. Similarly, the lower the baseline BMI, the greater the decrease in HbA1c observed over 5 years (Fig. 1). For a baseline HbA1c level of 7.0%, the differences in LS means between the groups were 0.18%, 0.08%, and 0.01% (all differences not significant) for baseline BMI values of 22, 25, and 27 kg/m^2, respectively. The difference in LS means for the approximate mean values of HbA1c and BMI of 8.0% and 25.0 kg/m^2, respectively, was 0.16% (95% CI, 0.03–0.29%) between the CSII and MDI groups, with a greater decrease in HbA1c levels occurring for the CSII group. For baseline HbA1c level of 9.0%, the LS mean differences between the groups with respect to HbA1c change were 0.35% (95% CI, 0.18–0.52%), 0.25% (95% CI, 0.11–0.39%), and 0.18% (95% CI, 0.02–0.34%) for baseline BMI values of 22, 25, and 27 kg/m^2, respectively, with all improvements favoring CSII. No statistically significant interaction with age, sex, insulin dose, or diabetes duration could be confirmed in the prediction analysis for change in HbA1c from baseline to 5 years.

Corresponding analyses were also performed for change in HbA1c from baseline to 1 and 2 years, respectively. Analyses only revealed a statistically significant interaction between insulin pump therapy and baseline HbA1c levels, respectively ($P < 0.001$ and $P = 0.030$, respectively). In the analysis of change in HbA1c from baseline to 1 year, the differences in LS means between the CSII and MDI group were 0.16% (95% CI, 0.01–0.32%), 0.35% (95% CI, 0.24–0.46%), and 0.53% (95% CI, 0.42–0.65%) for baseline HbA1c levels of 7.0%, 8.0%, and 9.0%, respectively, with each difference favoring CSII therapy. Similarly, these values were 0.29% (95% CI, 0.11–0.47%), 0.39% (95% CI, 0.27–0.52%), and 0.50% (95% CI, 0.36–0.63%), respectively, in the analysis of change in HbA1c from baseline to 2 years.

Effect of care units on change in HbA1c over time

In order to determine the degree to which the benefits of CSII varied by clinical care unit, we also evaluated the impact of CSII on change in mean glycemic control at 5 years after stratifying by care unit. At some sites (e.g., Care Unit 4), CSII was associated with a greater reduction in HbA1c at 5 years across all BMI and baseline HbA1c strata (LS mean difference of 0.48% [95% CI, 0.17–0.80%]) (Fig. 2A). At other sites, patients on CSII and MDI therapy experienced similar changes in glycemic control at 5 years (e.g., Care Unit 9) (Fig. 2B). At still other sites, patients on CSII experienced consistently higher HbA1c at 5 years compared with patients on MDI (e.g., Care Unit 2), with a LS mean difference of −0.49% (95% CI, −1.24% to 0.25%) (Fig. 2C).

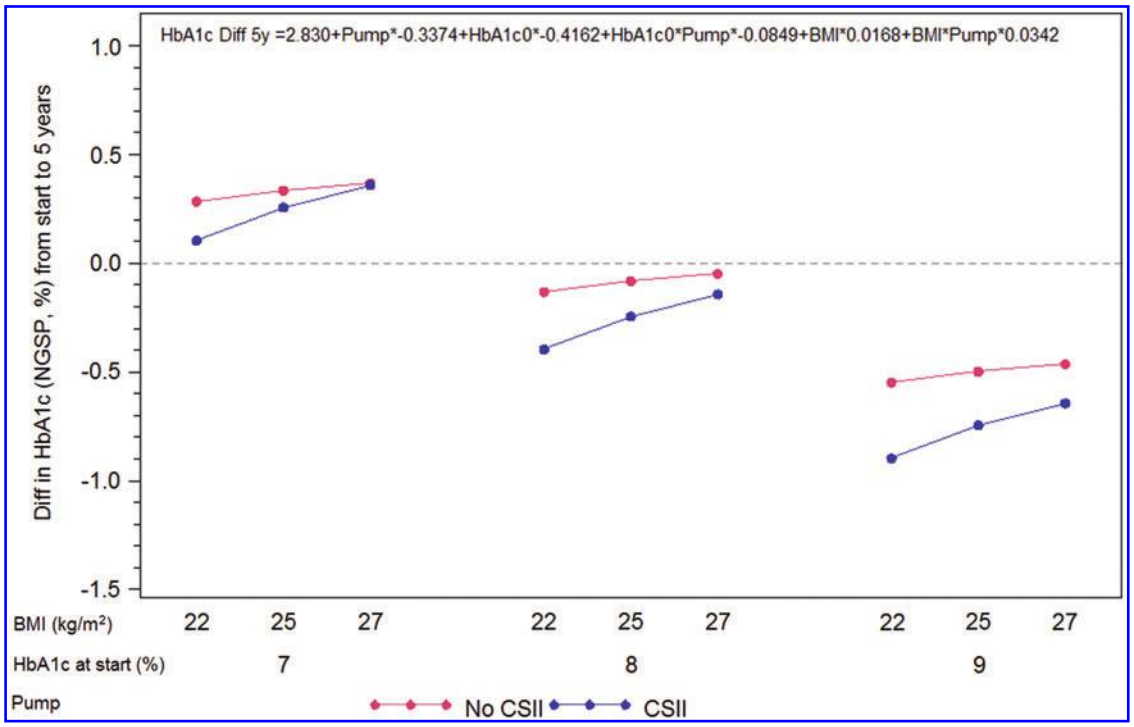


FIG. 1. Least square means for change in hemoglobin A1c (HbA1c) (National Glycohemoglobin Standardization Program [NGSP], in %) from baseline to 5 years in patients on continuous subcutaneous insulin infusion (CSII) versus multiple daily insulin injections (No CSII), presented for selected baseline HbA1c and body mass index (BMI) values. Diff, difference. Color images available online at www.liebertonline.com/dia

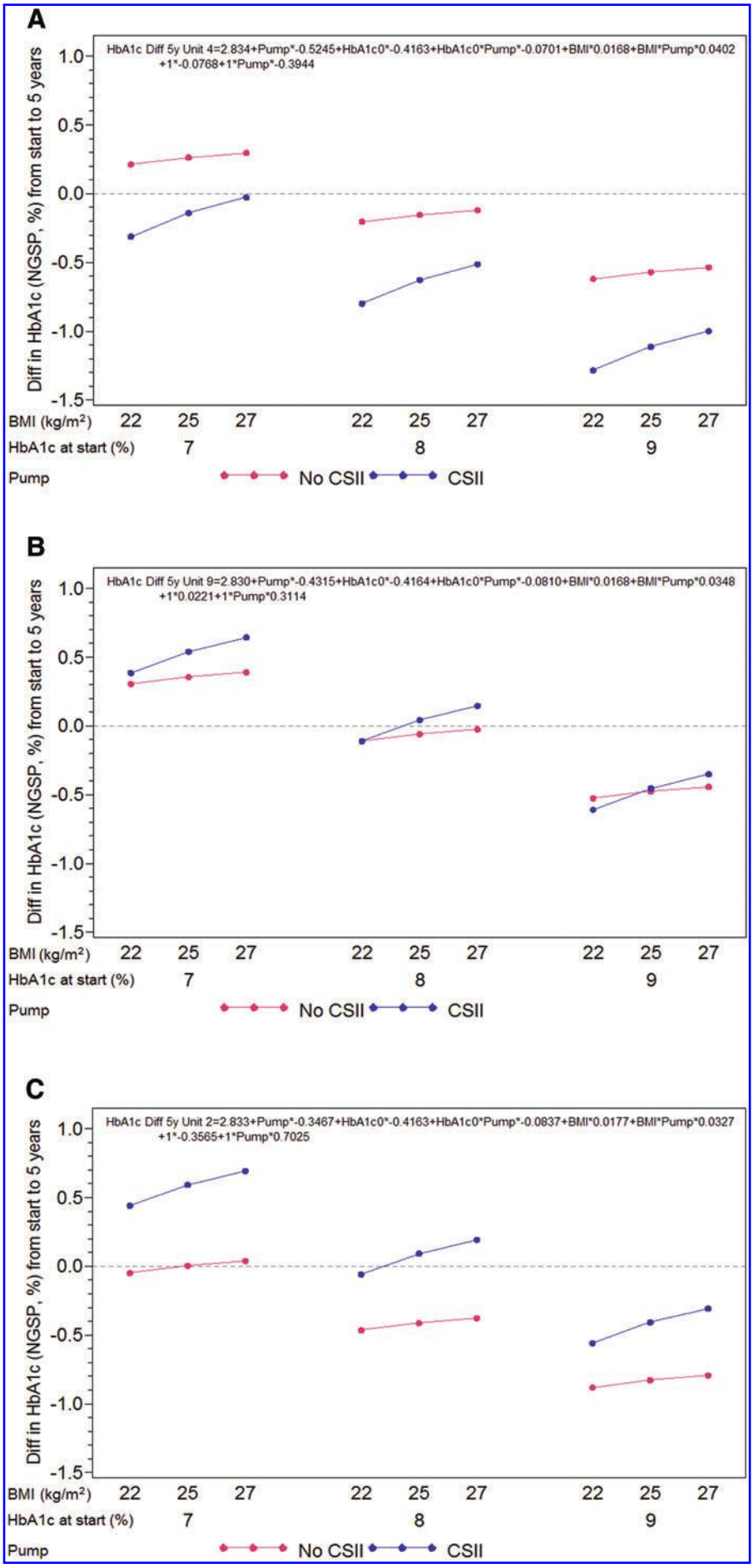
Discussion

In this multicenter study evaluating predictors for the effect of CSII in clinical practice and with long-term follow-up, higher baseline HbA1c was associated with a greater reduction in HbA1c on CSII therapy. This was found at 1, 2, and 5 years after initiation of CSII. Lower BMI was associated with a greater effect of CSII on HbA1c at 5 years, but not at 1 and 2 years. Although a greater effect of CSII on HbA1c was found at 5 years in patients with higher baseline HbA1c, the predicted effect was still relatively modest even for patients with poor glycemic control (e.g., a reduction of 0.25% in patients with baseline HbA1c of 9.0% and a BMI of 25 kg/m^2). In patients with baseline HbA1c of 7.0%, no significant reduction in HbA1c was found. At some clinical care units, CSII therapy resulted in lower HbA1c after 5 years relative to MDI therapy among patients with good glycemic control, whereas at others, no beneficial effect was seen irrespective of HbA1c level. At some care units, patients continuing with MDI achieved better glycemic control than those treated with CSII.

Long-term controlled clinical trials lasting 5 years and long-term multicenter evaluations of the effect of CSII in daily life are sparse. Some long-term clinical follow-up data exist, but these analyses have been characterized by limitations such as lack of a control group or inclusion of data from only a single center.[21–23] Evaluations of HbA1c without a control group can be misleading because many other factors may have influenced HbA1c levels during the study period, such as new strategies in diabetes care, changes in disease duration, and variance in the precision of laboratory methods by staff or otherwise.[24,25] Moreover, evaluations at a single site may not be representative of general effects in clinical practice, especially if performed at the investigator's own center.[24] Long-term follow-up is crucial because effects of any intervention are likely to be initially greater due to more frequent visits, increased attention from caregivers, and increased patient enthusiasm in the face of a ''novel'' intervention. This was indeed the case for CSII treatment in this cohort, in which the effect on HbA1c decreased over time.[11]

In the current study, even if the upper bound of the 95% CI is true, the effects on HbA1c in patients with poor control would not be that large from a population perspective—0.39% in patients with an HbA1c level of 9.0%, compared with treatment targets of ≤7.0% for HbA1c. Large proportions of patients today still have such poor glycemic control. On the other hand, the lower bound of the 95% CI was 0.11%, implying that the true effect may be less than the reduction of 0.25% estimated in patients with an HbA1c level of 9.0%. Therefore, an important implication from the current study is that other treatments or changes in diabetes care are urgently

FIG. 2. Least square means for change in hemoglobin A1c (HbA1c) (National Glycohemoglobin Standardization Program [NGSP], in %) from baseline to 5 years in patients on continuous subcutaneous insulin infusion (CSII) versus multiple daily insulin injections (No CSII), presented for selected baseline HbA1c and body mass index (BMI), in individual care units in which **(A)** CSII was superior to no CSII (site 4), **(B)** CSII was similar to no CSII (site 9), or **(C)** CSII was inferior to no CSII (site 2). Diff, difference. Color images available online at www.liebertonline.com/dia


A
HbA1c Diff 5y Unit 4=2.834+Pump*-0.5245+HbA1c0*-0.4163+HbA1c0*Pump*-0.0701+BMI*0.0168+BMI*Pump*0.0402 +1*-0.0768+1*Pump*-0.3944
Diff in HbA1c (NGSP, %) from start to 5 years
1.0
0.5
0.0
-0.5
-1.0
-1.5
BMI (kg/m²) 22 25 27 22 25 27 22 25 27
HbA1c at start (%) 7 8 9
Pump No CSII CSII
B
HbA1c Diff 5y Unit 9=2.830+Pump*-0.4315+HbA1c0*-0.4164+HbA1c0*Pump*-0.0810+BMI*0.0168+BMI*Pump*0.0348 +1*0.0221+1*Pump*0.3114
Diff in HbA1c (NGSP, %) from start to 5 years
1.0
0.5
0.0
-0.5
-1.0
-1.5
BMI (kg/m²) 22 25 27 22 25 27 22 25 27
HbA1c at start (%) 7 8 9
Pump No CSII CSII
C
HbA1c Diff 5y Unit 2=2.833+Pump*-0.3467+HbA1c0*-0.4163+HbA1c0*Pump*-0.0837+BMI*0.0177+BMI*Pump*0.0327 +1*-0.3565+1*Pump*0.7025
Diff in HbA1c (NGSP, %) from start to 5 years
1.0
0.5
0.0
-0.5
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-1.5
BMI (kg/m²) 22 25 27 22 25 27 22 25 27
HbA1c at start (%) 7 8 9
Pump No CSII CSII

needed to supplement implementation of CSII in order to help patients with type 1 diabetes reach treatment targets for glycemic control. Another implication is that patients with current good glycemic control or whose HbA1c level is close to targets for treatment have small or no further improvements in glycemic control. In patients with an HbA1c level of $<8.0\%$, the predicted reduction in HbA1c was 0.16% and declined with lower baseline HbA1c, with no significant effects at an HbA1c level of 7.0%. However, it should be noted that both previous studies and experience from clinical practice support the premise that many patients achieve a better quality of life with CSII than MDI, which also needs to be taken into account when deciding on type of therapy.[10,26,27] Variation in blood glucose concentration, which may be stressful and possibly harmful for patients, could potentially be reduced[28] as is the case for frequency and severity of hypoglycemic episodes.[27,29,30]

Moreover, our results indicate that other factors than those studied may be of importance in achieving a beneficial effect of CSII on HbA1c because the effect of CSII varied considerably from beneficial to negative between care units. Such factors may include socioeconomic status, diabetes care provider, provider/patient ratio, educator/patient ratio, dose, content, or delivery method of diabetes education, and technological literacy. Unfortunately, the current data were not complete with regard to study variables such as socioeconomic status or which educational approaches were used; these variables will be of great importance to include in future prospective studies.

To improve HbA1c levels in patients with type 1 diabetes, continuous glucose monitoring (CGM) may be one important adjunct treatment option in either the setting of CSII or MDI therapy.[31] In a previous clinical study, we found greater reductions in HbA1c level when introducing CGM in clinical practice than those observed here by CSII alone,[15] but this finding needs further examination in larger patient populations and over longer follow-up. Improved support for compliance with self-monitoring of blood glucose and insulin bolus delivery at meals, which have each shown strong associations to HbA1c level,[32,33] may also help. It is also possible that greater effectiveness of CSII for improving HbA1c could be achieved by more optimal education and support in clinical practice. Future research should evaluate novel factors that predict optimal outcomes of long-term CSII therapy, as well as factors that contribute to the observed site-to-site variation in the relative efficacy of CSII compared with MDI. Future research should also explore interventions designed to augment the efficacy of CSII in clinical practice.

Robust information on hypoglycemic events was not available. Even when this variable was available in electronic medical records, a large proportion of patients lacked complete information. In addition, even if information on hypoglycemic events were available, it would have been difficult to interpret because many patients do not measure glucose values as recommended during symptoms of hypoglycemia. Objective measures during symptoms are the basis for the definition of hypoglycemia used in many studies.[34] Introducing robust protocols for recording hypoglycemic events in clinical care might result in better self-reporting of hypoglycemic events by extending patients' SMBG testing to periods of suspected hypoglycemia and might result in patients being more active in their therapy.

One strength of the present study is that the data source, Diab-Base, tracks all HbA1c values along with dates for initiation of CSII together with other clinically relevant variables. Therefore it is possible to estimate the effects of CSII on HbA1c from many care units over long time periods. Another strength is that among all possible patients treated with CSII over 5 years during the study period, 82% had information on HbA1c before starting CSII and at 5 years. Thus the selected population was representative of care units. However, our finding of a greater effect of CSII on HbA1c in patients with low BMI should be interpreted with caution because this association was not found at 1 and 2 years, where the effects of CSII on HbA1c generally were greater. Therefore, this finding should be regarded as hypothesis-generating and requiring confirmation in future studies. It should be noted that the current results were obtained in adult patients in Sweden and may not be representative for a pediatric population or for other countries, where CSII training or diabetes care generally may differ. However, it is noteworthy that patients in Sweden who are treated with CSII receive rigorous education when starting CSII, and they are generally offered future group educational opportunities besides regular clinical visits to repeat and extend their knowledge of insulin pump functions. Finally, it is important to note that the last patients were followed up in 2009, when CGM was first introduced to a very small extent in clinical practice. Hence, the current results cannot show effects on HbA1c by combining CSII and CGM, which are likely greater than for CSII treatment alone.[35]

In conclusion, this study shows that changing therapy to CSII from MDI in clinical practice may improve glycemic control in patients with impaired or poor glycemic control. However, from a population perspective the effects on HbA1c are relatively modest; investigators should continue to search for treatments and strategies to achieve good glycemic control in a larger proportion of patients with type 1 diabetes. Alternative or complementary treatments or care strategies in diabetes should focus on substantially lowering the large risks for diabetes complications that many patients with type 1 diabetes experience. For instance, wider use of CGM in clinical practice may be essential to improve overall glycemic control. Other novel therapies, including ones that raise insulin sensitivity or lower serum uric acid levels,[36,37] appear promising, but those require further study in current and future clinical trials. Finally, the current findings need to be confirmed in other geographical areas using a similar design over longer time periods and in multiple care units.

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Author Disclosure Statement

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