

# Long-term treatment effects of insulin pump therapy

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## Abstract

This study was designed to examine potential long-term effects on glycaemic control and treatment satisfaction in people with type 1 diabetes who changed from multiple daily insulin injections (MDI) to insulin pump therapy (CSII, continuous subcutaneous insulin infusion).

Forty-six patients who changed from MDI to CSII were recruited at a Swedish medical clinic. They were followed one year prior to starting CSII and four years afterwards. Repeated measurements of HbA<sub>1c</sub> were performed during follow up. Treatment satisfaction was assessed using Bradley's Diabetes Treatment Satisfaction Questionnaire, status version.

After initiation of CSII, reductions of HbA<sub>1c</sub> were seen after the first year (0.66 units of percent [95% CI 0.46–0.91,  $p < 0.001$ ]) and after two to four years (0.65 [95% CI 0.38–0.95,  $p < 0.001$ ]). Moreover, treatment satisfaction increased significantly after six months (10.0 score units [95% CI 8.0–12.0,  $p < 0.001$ ]) and remained at the same level after three years (10.5 score units [95% CI 8.0–13.0,  $p < 0.001$ ]).

It was concluded that, compared to MDI, insulin pump therapy improves glycaemic control with sustained treatment satisfaction after up to four years. Our long-term data provide further support for CSII as an effective and well tolerated treatment regimen for patients with type 1 diabetes. Copyright © 2011 John Wiley & Sons.

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## Key words

type 1 diabetes mellitus; continuous subcutaneous insulin infusion; multiple daily insulin injections; glycaemic control; treatment satisfaction

## Introduction

Meta-analyses from randomised controlled studies have shown that continuous subcutaneous insulin infusion (CSII) provides better glycaemic control, in people with type 1 diabetes, compared to multiple daily insulin injections (MDI).<sup>1–3</sup> Even in the comparison between MDI with long-term insulin analogues, there seems to be an advantage with CSII.<sup>4</sup> A problem in these evaluations is the short follow-up period regarding glycaemic control. In a recently conducted meta-analysis, the follow up in the majority of the included studies was less than a year.<sup>2</sup>

Guidelines for diabetes treatment have been formulated by the World Health Organization and the International Diabetes Federation within the St Vincent Declaration. The general goals are to improve health, and promote a higher quality of life and a longer life for all people who have diabetes.<sup>5,6</sup> In line with the St Vincent Declaration, an earlier developed questionnaire that measures the individual's satisfaction with the treatment, Diabetes Treatment Satisfaction Questionnaire (DTSQ), was used as a complement to HbA<sub>1c</sub>

when diabetes studies were planned and carried out.<sup>7</sup> The questionnaire measures changes in satisfaction with the treatment of people with diabetes that are not necessarily reflected in a changed HbA<sub>1c</sub>.<sup>8</sup>

Long-term data are of particular importance given that type 1 diabetes requires lifelong treatment regimens. The following study contributes with a long follow-up and objective results from everyday clinical routines in a diabetic clinic in parallel with the individual's evaluation of treatment satisfaction.

Based on previous data, we hypothesised that a change from MDI to CSII would improve long-term glycaemic control and treatment satisfaction in patients with type 1 diabetes. Accordingly, the aim of this study was to examine the effects on glycaemic control and treatment satisfaction after a four-year follow up in people with type 1 diabetes who switched from MDI with insulin pens to insulin pump therapy, CSII.

## Materials and methods

### Population and sample

This study was conducted at the Medical Clinic of Falun Hospital,

Sweden, where approximately 700 adult patients with type 1 diabetes are regularly monitored. During the period May 1999 to February 2004, a total of 57 changed from MDI to CSII. In the same period, the Diabetes Treatment Satisfaction Questionnaire, status version, (DTSQs) was used as a routine quality control before commencing usage of the pump, after six months of treatment and again after three years (minimum three, maximum three and a half years) of treatment with CSII.

Ten of the 57 patients who started treatment with CSII did not answer the DTSQs at any point (two patients had serious visual impairment, and eight individuals declined). One patient died of a heart attack after one year with CSII. This case series study consists of the remaining 46 patients (22–64 years old, median 44), all followed individually one year before changing to CSII and four years afterwards. All study participants used NPH-insulin or zinc insulin in combination with a rapid-acting insulin analogue as basal and meal insulin before the change-over. Baseline characteristics are presented in Table 1.

### Data collection method and measuring instrument

Glycaemic control was examined in terms of HbA<sub>1c</sub> and was analysed either at the hospital's accredited chemical laboratory with the Mono S method or at the diabetes clinic with a patient-based instrument, Bayer DCA 2000. Both methods were analysed on a capillary sample. There was no way in which to separate the two analytical methods; therefore, all values were used in the calculations. Every HbA<sub>1c</sub> result the year before switching to CSII and during the whole follow up of four years was included. Data on HbA<sub>1c</sub> were obtained from medical records and the clinic's quality database, Journalia Diab-Base®.

Treatment satisfaction was evaluated through DTSQs.<sup>8,9</sup> The questionnaire consists of eight diabetes-specific questions. Six questions measure different aspects of the treatment (treatment satisfaction) and two of the questions deal with perceived frequency of high and low

blood glucose levels, respectively. The questions are answered by circling a digit from 0–6. Six indicates the best possible alternative regarding treatment satisfaction, whereas zero is the best possible alternative concerning blood glucose levels. Therefore, the questions regarding blood glucose levels are reported separately.<sup>10</sup> This means that the questions about aspects of treatment can provide a maximum of 36 score units. The issue of frequency of either high or low blood glucose can generate a maximum of six score units each. A highly-rated figure means that high or low blood glucose levels are perceived to occur too often. DTSQs is translated and validated for Sweden.<sup>11</sup>

### Data analysis

The distribution of each person's average HbA<sub>1c</sub> values was taken during the year before the insulin pump (treatment with MDI). The values were compared with the distribution of each person's average values during the first year with CSII, as well as the allocation of each person's average HbA<sub>1c</sub> taken during the second to fourth year after beginning with CSII. Comparisons were performed with Wilcoxon's signed-ranked test for paired comparisons. In terms of the DTSQs, the individual score unit for each category (treatment satisfaction/unacceptably low or high blood glucose levels) was calculated. The differences in the distribution of the total scores before, after six months and after three years were analysed with Wilcoxon's signed-rank test for paired comparisons. A small number of individuals did not respond to one of the six questions about aspects of treatment. In these cases, the existing score was multiplied by 6/5. All statistical analyses were carried out with 'R' (a statistical computing language for data analysis and graphics).<sup>12</sup>

### Ethics

Request for ethic approval was submitted to the Regional Ethical Review Board in Uppsala and accepted in February 2009.

### Results

#### Glycaemic control

Glycaemic control improved significantly during the first year. HbA<sub>1c</sub>

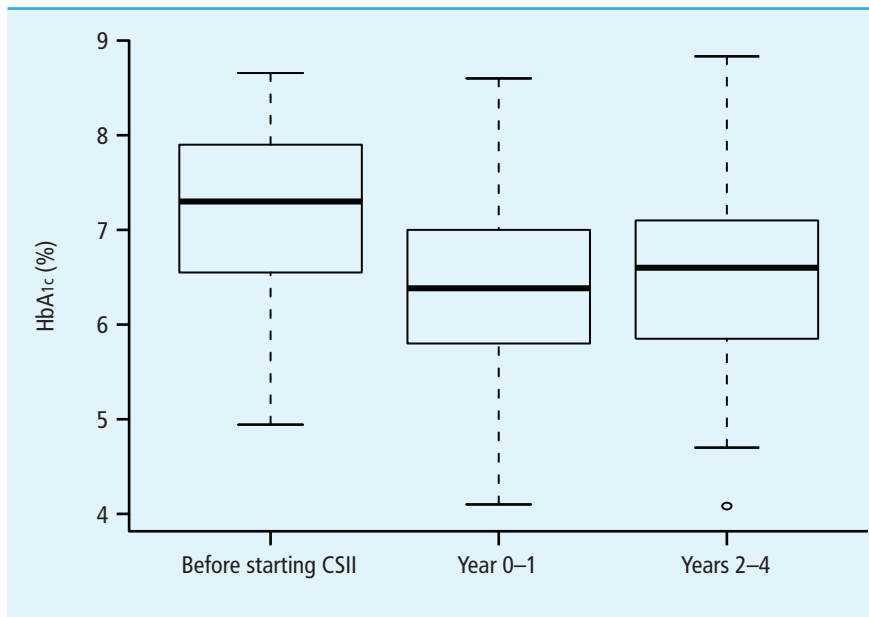
Variable	n	%
Male/female	17/29	37/63
Age (yrs)		
<30	10	22
30–39	9	20
40–49	12	26
50–59	12	26
≥60	3	6
Non-smoker/smoker	43/3	93/7
BMI (kg/m <sup>2</sup> )		
<20	0	0
20–25	25	54
26–30	15	33
>30	6	13
Diabetes duration (yrs)		
<10	11	24
10–20	15	33
>20	20	43
Microvascular complications		
Nephropathy	20	43
Retinopathy	35	76

Table 1. Baseline characteristics, n=46

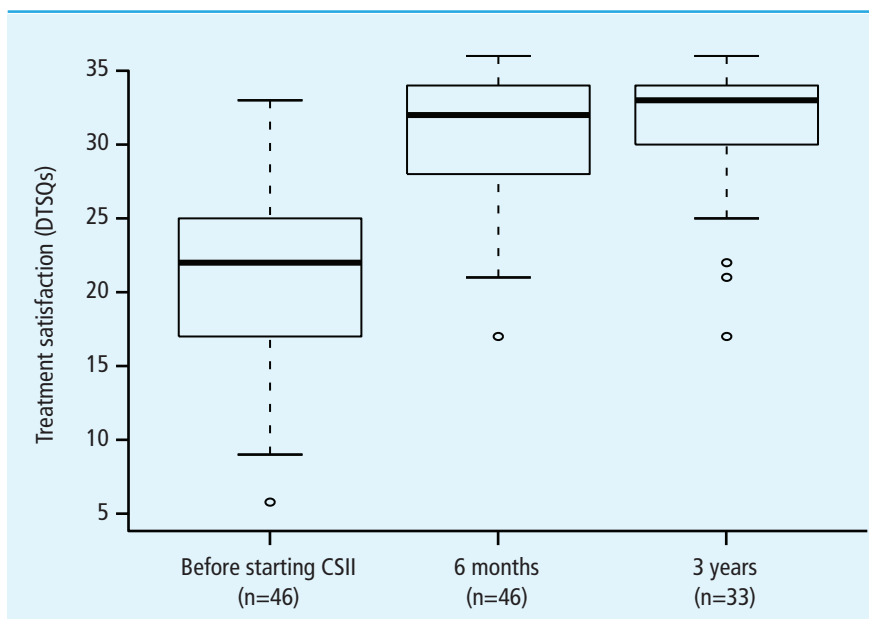
decreased (0.66 units of percent [95% CI 0.46–0.91, p<0.001]) and in years two to four (0.65 units of percent [95% CI 0.38–0.95, p<0.001]) in comparison to the year prior to commencing with the pump (Figure 1). An indication of increasing HbA<sub>1c</sub> was noted between the first year and years two to four, but was not statistically significant (-0.09 units of percent [95% CI -0.34–0.17, p=0.27]).

#### Diabetes treatment satisfaction

Before starting with CSII, the breakdown of the DTSQs scores varied between 4 and 33 and the median value was 22. After six months, the corresponding range was 17–36 and the median 32. After three years, the scores were also 17–36 but the median value had increased to 33 (Figure 2). In other words, the degree of treatment satisfaction increased significantly after six months of treatment with CSII (10.0 score units [95% CI 8.0–12.0, p<0.001]). After three years, the median degree was a little higher (10.5 score units [95% CI 8.0–13.0, p<0.001]). Between six months and three years, there were no statistically



**Figure 1.** Distribution of HbA<sub>1c</sub> values: prior to starting CSII during the first year and in years 2–4 after the change to insulin pump therapy (n=46). (Thick line = median value; boxed area = first quartile and third quartile; dotted line = range; o = outlying value)



**Figure 2.** Distribution of score for treatment satisfaction prior to starting with CSII, after 6 months and after 3 years with insulin pump therapy (0 = very dissatisfied, 36 = very satisfied)

significant changes (1.0 score units [95% CI -1.0–3.0,  $p=0.1$ ]). The number of answered questionnaires after three years was slightly lower (n=33) compared to the number of answered questionnaires before the start of treatment with CSII and after six months (n=46).

### Frequency of unacceptably high or low blood glucose levels

The median value for perceived unacceptably high blood glucose

levels was 4 score units before starting CSII and 2 after six months and three years, respectively. The change from before using the insulin pump to the measurement after six months (1.00 score units [95% CI 0.00–2.00]) as well as the change in measurement after three years (2.00 score units [95% CI 1.50–2.50]) were both statistically significant;  $p<0.001$ . No changes were seen between six months and three years (0.00 [95% CI -1.00–1.00]), (Figure 3).

Unacceptably low blood glucose levels were also reduced in extent. Before using CSII, the median value was 3 score units and after six months 2. The change was statistically significant (2.00 score units [95% CI 1.50–2.50,  $p=0.01$ ]). After three years with CSII, the median value was still 2 score units, but the range in the responses had been reduced to between 0–4 score units compared to between 0–5 after six months. This change was also statistically significant (2.00 score units [95% CI 1.50–2.50,  $p<0.001$ ]) compared to prior to using the insulin pump. No changes were seen between six months and three years (0.00 [95% CI -1.00–0.50]), (Figure 4).

These questions also had slightly fewer questionnaire replies after three years (n=33) compared with the number of questionnaire respondents before and after six months (n=46).

## Discussion

### Principal findings

In the present study, patients with type 1 diabetes, who switched from MDI to CSII, showed improved glycaemic control, as measured by lower HbA<sub>1c</sub> after up to four years' follow up. Importantly, enhanced diabetes treatment satisfaction was also seen in these patients after the change in treatment regimen. In addition, there were fewer experiences of unacceptably high and low levels of blood glucose as evaluated by the DTSQs questionnaire.

### Comparisons with the literature

In 1993, the first scientific results showing reduced risk of microangiopathy with an intensified insulin regimen were published.<sup>13,14</sup> In the Diabetes Control and Complications Trial, this intensified regimen consisted of approximately 40% CSII-users. Within the earliest studies demonstrating the improvement with CSII, NPH insulin was used as basal insulin in the groups treated with MDI. When long-term insulin analogues were introduced, they appeared to be equal to CSII when measured according to HbA<sub>1c</sub> values;<sup>15,16</sup> however, the meta-analysis by Jeitler showed an advantage with CSII.<sup>2</sup>

Since the early 1980s, a number of studies have evaluated the effect of CSII compared with MDI. Continued lower HbA<sub>1c</sub> levels have been confirmed in several studies.<sup>2,3,17–20</sup> One problem with these studies is the short follow up. However, a recently published study<sup>21</sup> has evaluated the effects of CSII on HbA<sub>1c</sub> after seven years and reached the same conclusion as our own. It must be stressed that in the future we will need more randomised controlled trials that measure the long-term effects of CSII on HbA<sub>1c</sub> given the fact that diabetes is a lifelong disease.

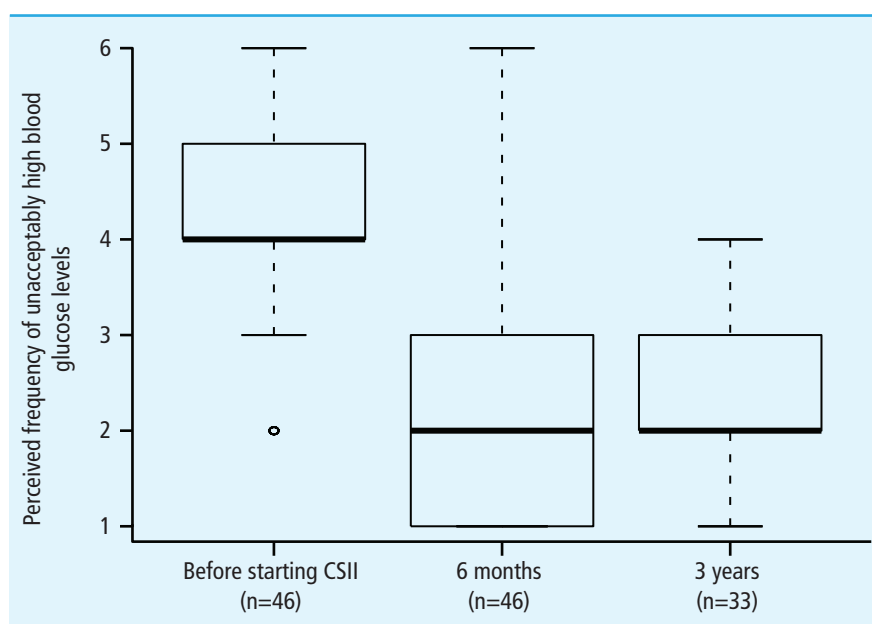
Evaluation of new drugs and treatment for diabetes mellitus requires both objective data (e.g. glycaemic control) and patient reported outcome data estimated by the individuals, as practised in the large US Diabetes Control and Complications Trial.<sup>22</sup>

There is no existing consensus about how to measure patient reported outcome data.<sup>23</sup> Quality of life is often mentioned and this can be described as a multi-dimensional term that involves the individual's subjective experiences of physical, emotional and social wellbeing. Two people with the same objective health status can therefore have significantly varying subjective health status.<sup>24</sup>

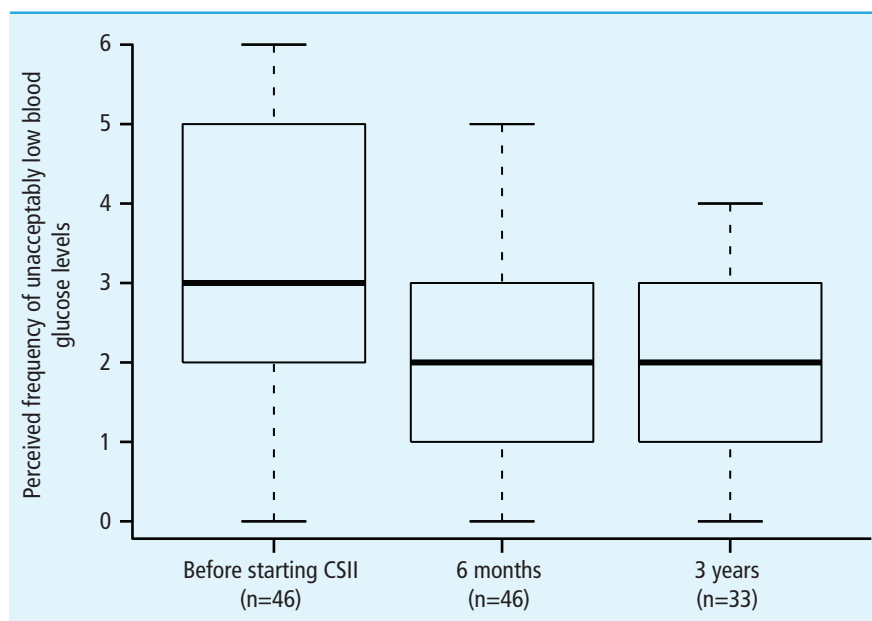
There are several instruments measuring self-perceived outcome. In the present study, patient reported outcome data are evaluated with Bradley's satisfaction with diabetes treatment measure, as recommended by the World Health Organization and the International Diabetes Federation.<sup>5,6</sup> A problem with using different measurements is the difficulty in comparing the results, although it is possible to observe significant improvement on different measures. In the future, it would be desirable to have an international consensus on which questionnaire(s) are best suited to measure subjective patient reported outcomes in diabetes studies.

### Potential mechanisms

In our opinion, the main reason for the improved glycaemic control depends on two important variables. First, CSII offers the opportunity of a



**Figure 3.** Distribution of score of perceived frequency of unacceptably high blood glucose levels (0 = not at any point, 6 = most of the time) before starting with CSII, after 6 months and after 3 years with insulin pump therapy



**Figure 4.** Distribution of score of perceived frequency of unacceptably low blood glucose levels (0 = not at any point, 6 = most of the time) before starting with CSII, after 6 months and after 3 years with insulin pump therapy

more flexible means of insulin delivery than MDI. Flexible basal rates can minimise the risk of nocturnal hypoglycaemia and increase the possibility of achieving normal fasting glucose levels. Even the bolus doses enable different variations such as normal, prolonged or double (i.e. a normal + prolonged bolus) or via the advanced carbohydrate calculator. These opportunities make it possible to improve postprandial

plasma glucose values. Secondly, although the participants did not receive structured education when switching from MDI to CSII, the usual care regarding the skills needed to handle the pump naturally had an impact on them.

### Interpretation of analyses of treatment satisfaction

The Diabetes Treatment Satisfaction Questionnaire exists in two versions:

DTSQs (status version) and DTSQc (change version). The reason behind this is that the original version is often affected by a 'ceiling effect' – that is, a satisfied individual was unable to show an improvement in satisfaction if the measurement was repeated.<sup>25</sup> DTSQs were used in a prior study without showing any ceiling effect. The individuals had, after switching to insulin pump therapy, the opportunity to evaluate their treatment satisfaction as improved.<sup>26</sup> In the present study, we used DTSQs throughout the whole studied period, as DTSQc was not available from the very beginning.

Nor in this study, in our opinion, was a ceiling effect noted after three years, though the median was 33 out of a possible 36. Only three of the 33 participants attending throughout the whole study period scored the maximum of 36. It appears that treatment satisfaction is at the same level as that at six months after the change to CSII. Whatever the case, it did not become worse.

A sensitivity analysis shows that the result of DTSQs would have been identical regardless of the exclusion of the 3/46 who chose not to answer all of the questions, or of multiplying the existing score by 6/5.

### Strengths and limitations

The strengths of the present study include the longitudinal data with repeated assessment of glycaemic control and treatment satisfaction, the long follow up and the representative clinical study sample. Moreover, DTSQs is a widely utilised questionnaire with high reliability and validity.<sup>7,25,27,28</sup> The advantage of a health questionnaire is that it can reflect the subjective experience in a quantitative way in the form of a numeric value. The disadvantage is that the questions can be misunderstood, the answer choices may not correspond to the respondent's opinions, and analysis cannot be undertaken of any comments which the respondent might wish to write alongside given questions. In-depth interviews are an approach to take further advantage of an individual's perception and experience of a life situation, the meaning of subjective health and satisfaction with the treatment.

### Key points

- Given the fact that diabetes mellitus is a lifelong disease, long-term follow up is required. Evaluation needs both objective data such as glycaemic control and patient reported subjective outcome data
- This study shows that insulin pump therapy improves glycaemic control with sustained perceived treatment satisfaction compared to multiple daily insulin injections
- A significant change, shown as decreased HbA<sub>1c</sub> and enhanced diabetes treatment satisfaction, was seen after six months with insulin pump therapy. In addition, the changes remained at the same levels after up to four years
- The switch from MDI to CSII resulted in fewer experiences of unacceptably high and low levels of blood glucose as evaluated by the DTSQs questionnaire

There are, however, several limitations to our study that need to be acknowledged.

First, the best way in which to evaluate an intervention is through a randomised controlled trial. This study does not meet this criterion as a control group and random selection are lacking. Thus, in the present study, it is possible that our results are explained by concomitant changes in diabetes care (for example, changing the diabetes specialist nurse which was the case for most of the participants in this study) or various factors relating to the individual. The increased attention from health care providers with more frequent re-visit rates may also influence the outcome. The same concerns have been discussed in other observational studies.<sup>29,30</sup> Nonetheless, the fact that our results were similar concerning glycaemic control as compared to results from a previous small-scale randomised controlled trial, which included adult patients with type 1 diabetes but with shorter follow-up,<sup>2</sup> suggests that our results are valid.

Second, the early follow up in the first year with insulin pump can be influenced by the 'Hawthorne effect'<sup>31</sup> but, since the results remain during the long-term follow up, this effect is most likely to be negligible. An explanation of the large

difference in treatment satisfaction between injection treatment prior to CSII and the early follow up on CSII might be that the participants were not very satisfied with their MDI treatment, especially since they knew they would shortly switch to CSII.

Third, two different methods were used to assess HbA<sub>1c</sub> in capillary blood samples. However, both methods are accurate. HbA<sub>1c</sub> values from the patient-based instrument system (Bayer DCA 2000) have an average method error of less than -0.10% compared with the laboratory method.<sup>32</sup> We would like to point out that this would also be the case in clinical practice where glycaemic control is monitored year after year, often using different methods.

Finally, the modest number of participants in our study sample should be acknowledged. Nevertheless, our study sample was sufficiently large to identify as significant the improvements in glycaemic control and treatment satisfaction seen in the present study.

### Possible future research

Further large-scale, randomised intervention studies with long-term follow up are warranted to validate our findings; and additional qualitative studies are needed in order to obtain an in-depth view of the patients' long-term experiences of living with continuous subcutaneous insulin infusion.

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### Declaration of interests

There are no conflicts of interest declared.

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References are available in *Practical Diabetes* online at [www.practicaldiabetes.com](http://www.practicaldiabetes.com).

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