DR JOHN A MCKNIGHT (Orcid ID : 0000-0002-8214-7625)

DR ANDREAS OCHS (Orcid ID : 0000-0002-1926-8029)

DR FRASER GIBB (Orcid ID : 0000-0002-5576-6463)

PROFESSOR HELEN M COLHOUN (Orcid ID : 0000-0002-8345-3288)

The effect of DAFNE education, continuous subcutaneous insulin infusion, or both in a population with type 1 diabetes in Scotland

J. A. McKnight[1,2], A. Ochs[3], C. Mair[2], O. McKnight[4], R. Wright[5], F. Gibb[6], S. G. Cunningham[7], M. Strachan[1], S. Ritchie[1], S. J. McGurnaghan[3] and H. M. Colhoun[3,8]

[1]Edinburgh Centre for Diabetes and Endocrinology, Metabolic Unit, Western General Hospital, Edinburgh, UK

[2]Centre for Population Health Sciences, University of Edinburgh, Edinburgh, UK

[3]Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK

[4]Forth Valley Royal Hospital, NHS Forth Valley, Scotland

[5]Department of Diabetes, St John's Hospital, Livingston, UK

[6]Edinburgh Centre for Diabetes and Endocrinology, New Royal Infirmary of Edinburgh, Edinburgh, UK

[7]Division of Population Health and Genomics, University of Dundee, Dundee, UK

[8] Department of Public Health, NHS Fife, Kirkcaldy, UK

Correspondence to: John A. McKnight. E-mail: john.mcknight@nhs.net

What's new?

- Both DAFNE (Dose Adjustment For Normal Eating) education and continuous subcutaneous insulin infusion lower the levels of HbA_{1c} in people with type 1 diabetes. The size and duration of effect are not well documented.
- HbA_{1c} decreases with either intervention and the effect lasts at least 5 years. Those with high HbA_{1c} to start with have a very large decrease in HbA_{1c}. Continuous subcutaneous insulin infusion is effective in lowering HbA_{1c} with or without previous DAFNE education.
- DAFNE education and continuous subcutaneous insulin infusion are good options for people with high HbA_{1c}. DAFNE education should not be a prerequisite before continuous subcutaneous insulin infusion.

Abstract

Aim To investigate the effect of DAFNEand continuous subcutaneous insulin infusion in clinical practice.

Methods Within NHS Lothian, continuous subcutaneous insulin infusion started in 2004 and DAFNE education began in 2006. We extracted anonymized data from the national database for all those aged > 18 years with type 1 diabetes having a Dose Adjustment For Normal Eating course or continuous subcutaneous insulin infusion start date (n = 4617).

Results In total, 956 persons received DAFNEeducation, and 505 had received an insulin pump, 208 of whom had DAFNE education followed by insulin pump. Mean (SD) HbA_{1c} before DAFNE education was 68 (15) mmol/mol (8.4% [1.4%]) and 66 (13) mmol/mol (8.2% [1.2%]) before continuous subcutaneous insulin infusion. In the year following DAFNE education, the mean fall in within-person HbA_{1c} was 3.8 mmol/mol (95% CI 4.0 to 3.4; 0.3% [0.4% to 0.3%]). Those with the poorest control ($HbA_{1c} \geq 85$ mmol/mol [9.9%]) experienced the largest decline (15.7 mmol/mol [1.4%]). Those in the lowest HbA_{1c} band at initiation (< 53 mmol/mmol [7.0%]) experienced a rise.

In the year following continuous subcutaneous insulin infusion initiation there was a mean fall in within-person HbA_{1c} of 6.6 mmol/mol (6.8 to 6.4; 0.6% [0.6% to 0.6%]). In those with the poorest control ($HbA_{1c} \geq 85$ mmol/mol [9.9%]), the mean fall in HbA_{1c} was 22.2 mmol/mol (23 to 21; 2.0% [2.1% to 1.9%]). Continuous subcutaneous insulin infusion effectiveness was not different with or without DAFNE education. The effects of both interventions were sustained over 5 years.

Conclusions Both DAFNE education and insulin pump therapy had the greatest effect on HbA_{1c} in those with higher baseline values. There was little difference to attained HbA_{1c} when Dose Adjustment For Normal Eating education was introduced before insulin pump therapy.

<Typesetter: Format the reference citations throughout the text in the DME journal style, thanks.>

Introduction

The challenges of managing type 1 diabetes are well known. People with this condition require insulin for survival and there is a need to achieve glycaemic control that reduces the risk of long-term microvascular and macrovascular complications [1,2]. Many people with diabetes in the UK, and indeed throughout the world, have higher levels of HbA_{1c} than is recommended [3,4]. The use of structured education packages [5] and technologies such as continuous subcutaneous insulin infusion (CSII) provide opportunities to improve self-management of diabetes and outcomes. The recent Relative Effectiveness of Pumps Over Structured Education (REPOSE) study described the relative effectiveness of CSII compared with MDI, both with structured education in a 2-year cluster randomized trial [6].

Currently within NHS Lothian there are 4617 people with type 1 diabetes aged > 18 years. A CSII service was started in NHS Lothian in 2004, and the DAFNE (Dose Adjustment For Normal Eating) education programme was introduced in 2006. We aimed to examine the long-term effects of the DAFNE course and CSII therapy on HbA_{1c} in our local population.

Methods

Core data relating to the diabetes care of > 99% of people with diabetes in the Lothian region are held on the national diabetes database, SCI Diabetes. We extracted anonymized data from this database for all those individuals recorded as having a start date for a DAFNE course (n = 956) and those in receipt of an insulin pump (n = 505), either with (n = 208) or without prior DAFNE (n = 297). From the electronic health records, we extracted all the available HbA_{1c} data covering time periods both retrospective and prospective to the intervention for these individuals. For each 12-month period before and after the intervention, the median value of multiple measures in that 12-month period was used for each individual.

Initial tabulations were made showing the average within-person difference in HbA$_{1c}$ across time both retrospective and prospective to the intervention date. Both median and interquartile range (IQR) and mean and 95% confidence interval (95% CI) of the within-person difference for each 12-month block before and after the interventions were summarized across all persons. Tabulations and figures were also generated showing these data by strata of age, initial HbA$_{1c}$ level, sex and diabetes duration. In these tabulations, those who had DAFNE then pump had their HbA$_{1c}$ data used for evaluating DAFNE right-censored upon the date of pump receipt. For those receiving an insulin pump, analyses were further stratified by those with and without prior DAFNE.

We chose to describe the response in five different initial HbA$_{1c}$ groups. We were going to describe the HbA$_{1c}$ change based on the HbA$_{1c}$ groups as reported in the previous international comparison [3], but then we added two further extremes of HbA$_{1c}$ control to give a more detailed analysis of response for our population.

To confirm whether any apparently significant changes in HbA$_{1c}$ upon receipt of the intervention (i.e. those with a CI for the change not overlapping zero) were statistically significant, we fitted an additive mixed regression model with a random effect for the individual and a first order autoregressive correlation structure to account for temporal dependencies in these data within individuals. Time was scaled relative to the intervention. All models included age at diagnosis of diabetes, current age group, sex and initial HbA$_{1c}$ band. Significant periods of change were identified as previously described [7]. All analyses used the R statistical package.

Ethical approval

This was an audit/observational study. We obtained Caldicott Guardian permission to review the anonymized data and did not require Ethics committee approval.

Results

In total, 956 persons had ever received DAFNE, 505 had ever received an insulin pump, of whom 208 had DAFNE followed by pump. As summarized in Table 1, the median time period of observation in the diabetes registry prior to DAFNE was 10–11 years, 4 years post-DAFNE and post-pump, and was slightly longer at 6 years for those receiving DAFNE then going on to a receive a pump. The median number of HbA$_{1c}$ values per 12-month period was 1.5 measures per person across this time period.

<INSERT TABLE 1>

DAFNE

Figure 1a shows the median and IQR of the within-person difference in HbA$_{1c}$ across time compared with the values in the 12 months prior to the DAFNE initiation date. The mean (95% CI) change across time and the median (IQR) are summarized for all persons combined and by sex in Table 2. The data are shown in detail by other strata of interest in Tables S1 and S5.

For DAFNE, it can be seen that HbA$_{1c}$ in the 12 months preceding DAFNE initiation was not significantly different to the values at the time of initiation of DAFNE. Earlier values were slightly higher than at initiation. Then, in the year following DAFNE, the mean fall in within-person HbA$_{1c}$ was 3.8 mmol/mol (95% CI 4.0 to 3.4; 0.3% [0.4% to 0.3%]) compared with HbA$_{1c}$ in the year prior to DAFNE. Overall, this decrease was broadly sustained over time. The decrease with DAFNE was slightly greater in women than men (Table 2). There were clear differences in the magnitude of the HbA$_{1c}$ change with DAFNE, depending on the HbA$_{1c}$ level upon initiation of DAFNE (Fig. 2a, Table S1); those with the poorest control (HbA$_{1c}$ ≥ 85 mmol/mol [9.9%]) experienced the largest decline, with a mean within-person change in HbA$_{1c}$ of 15.7 mmol/mol (1.4%), and indeed those in the lowest HbA$_{1c}$ band at initiation (< 53 mmol/mmol [7.0%]) experienced an increase. Difference in change in HbA$_{1c}$ with DAFNE did not show a large variation by either age band or duration (Tables S1 and S6), other than in those aged > 65 years and in those with duration < 10 years, who experienced slightly less change.

<INSERT FIGURE 1>

<INSERT FIGURE 2>

<INSERT TABLE 2>

CSII

Figure 1 shows the median and IQR of the within-person difference in HbA$_{1c}$ across time compared with the values in the 12 months prior to the CSII initiation date, separated by whether there was (Fig. 1b) or was not (Fig. 1c) prior DAFNE. The mean (95% CI) change across time and the median (IQR) are summarized for all CSII recipients, combined and by sex in Table 2. The data are shown in detail by other strata of interest in Table S2. Data for CSII recipients, separated into those with and without prior DAFNE, are summarized in Tables S3 and S7.

For CSII, it can be seen that HbA$_{1c}$ in the 12 months preceding CSII initiation was not significantly different to the values at the time of initiation of CSII. Earlier values were slightly higher than at initiation. Then, in the year following CSII initiation, there was a large mean decrease in within-person HbA$_{1c}$ of 6.6 mmol/mol (6.8 to 6.4) (0.6%). This decrease was sustained over time. The mean fall in HbA$_{1c}$ with CSII in the year following initiation was 5.2 mmol/mol (5.5 to 4.9) (0.5%) in men and 7.4 mmol/mol (7.7 to 7.2) (0.7%) in women (Table 2). CSII was effective regardless of whether there was or was not prior DAFNE (Fig. 1b,c, Table S3). There were clear differences in the magnitude and direction of HbA$_{1c}$ change with CSII depending on the HbA$_{1c}$ level at initiation, as shown in Fig. 2b and Table S2. In those with the poorest control (HbA$_{1c}$ ≥ 85 mmol/mol [9.9%]), the mean fall in HbA$_{1c}$ in the year following receipt of CSII was 22.2 mmol/mol (23

to 21.4) (2.0% [2.1% to 1.9%]), whereas in those with HbA_{1c} < 53 mmol/mol (7.0%) at initiation, values remained about the same. Difference in change in HbA_{1c} with CSII did not show a large variation by age band and were slightly less in those receiving CSII within 5 years of onset of diabetes.

Adjusted for multiple comparisons within individuals, the changes in HbA_{1c} with both DAFNE and CSII in the 4 years following receipt of these interventions were highly significant (all P < 0.0001). The regression model showed that the fall in HbA_{1c} remained significant when adjusted for other variables. Although in those CSII recipients without prior DAFNE the change in HbA_{1c} with CSII was slightly greater than in those with prior DAFNE (Fig. 1b,c), this was not a significant difference in effect when adjusted for other covariates.

Discussion

These observational data have shown that, overall, the provision of a DAFNE course or CSII (with associated education) decreases HbA_{1c}. The effect is due mainly to a decrease in those with higher HbA_{1c} values before either intervention. In those with HbA_{1c} in a more acceptable range, these interventions have little effect upon overall HbA_{1c}, and in some individuals with low values of HbA_{1c} at initiation there is a slight rise in HbA_{1c} with DAFNE. This is not surprising, as the purpose of the interventions in those with tight glycaemic control is to decrease hypoglycaemia and improve quality of life, as demonstrated by the Irish DAFNE Study Group [8], rather than to change overall HbA_{1c}. Further research will explore the impact on these clinical events when data accrue.

We have also demonstrated that the effect of CSII or DAFNE is maintained for at least 5 years after the intervention. We have demonstrated that, within the service provided by NHS Lothian, introducing CSII without a prior DAFNE course is at least as effective as with a prior DAFNE course. Thus, our data suggest that in those warranting CSII, this should not be delayed if DAFNE is not available.

It is interesting to note that HbA_{1c} changed in the few months before initiating DAFNE and before CSII therapy in those who had not previously received DAFNE training. This is likely to reflect the preparation process for starting DAFNE and CSII in Lothian. The CSII preparation involves a detailed review and education about carbohydrate counting and dose adjustment.

Our results are similar to those of the original DAFNE publication [5], which noted a mean HbA_{1c} decrease of 5 mmol/mol (0.5%) when compared after 1 year. In our analysis, the decrease following DAFNE was 3 mmol/mol (0.3%) in the first year after DAFNE, and this was maintained for 5 years. There are a number of possible explanations for any minor difference recorded. Many of our population had already been exposed to some carbohydrate counting training, and the mean HbA_{1c} at the time of intervention was 68 mmol/mol (8.4%), significantly lower than the 79 mmol/mol (9.4%) in the original DAFNE study. In a 1-year follow-up of 639 people who completed DAFNE training, HbA_{1c} decreased from 69 to 66 mmol/mol (8.5% to 8.2%) [9]. We found a similar, prolonged decrease in HbA_{1c}, but have also demonstrated a different response from those who start with a higher or lower HbA_{1c}. Our longer follow-up demonstrating an ongoing effect on a large cohort of people who have completed DAFNE is also important and adds to a previous smaller report relating to 141 people followed up for 44 months (10).

Our results also contrast with and add to the information from the recent REPOSE study [6]. In their cluster randomized controlled trial, decreases in HbA_{1c} at 2 years of 4.5 mmol/mol (0.4%) following DAFNE and of 9.3 mmol/mol (0.8%) following CSII were reported. We have been able to analyse our results for 4 years before and 5 years following the intervention, demonstrating a sustained effect that appears to be smaller than that noted in the REPOSE trial. Again, this is partly explained by our lower HbA_{1c} value at the time of the intervention (75 to 78 mmol/mol [9.0% to 9.3%] in REPOSE, 68 to 70 mmol/mol [8.4% to 8.6%] in our study). Our population was also different to the REPOSE study population, as the policy in NHS Lothian is to give CSII to those who fulfil the National Institute for Health and Care Excellence criteria for CSII, whereas those individuals were excluded from the REPOSE study.

In addition, we have shown that adding CSII to those who have not taken part in a DAFNE course is at least as effective in lowering HbA_{1c} as initiation in those who have received DAFNE. It is important to note, however, that knowledge and application of carbohydrate counting is assessed and addressed for each individual as part of the CSII referral and initiation process within NHS Lothian, and that people would not be considered for a pump without the appropriate skills. We have, however, also demonstrated that adding CSII to those who have already received DAFNE provides further added benefit in lowering HbA_{1c}.

A strength of this analysis is the use of routine clinical data, collected as part of clinical care, for the whole population in our area over a 10-year period. Our study population is sufficiently large to enable a detailed analysis and we do not believe there has been any selection bias as those studied were identified on our comprehensive, population-wide database. Previous studies have involved far fewer individuals. We have also provided information on a group of individuals selected as wanting these interventions, a better reflection of the effects in real clinical practice.

During the time period of this analysis there has been a change of overall glycaemic control in the whole population with type 1 diabetes in Lothian. Our regression analysis has, however, enabled us to ensure that the changes in HbA_{1c} within initiation of DAFNE and CSII were not attributable to any ongoing background downward trend in HbA_{1c}. Indeed, apart from the period immediately preceding and immediately after the intervention, HbA_{1c} control was stable both before and after the interventions in this group.

A limitation of our study is that we have only investigated the effect of our interventions upon HbA_{1c}. We have not measured quality of life indicators, and do not believe that our information relating to hypoglycaemia is sufficiently accurate to be included in this analysis. It must therefore be recognized that we are failing to report on two very important aspects of diabetes care.

Despite these limitations, we conclude that both interventions are effective in lowering HbA_{1c}. The effects are greater in those with a higher HbA_{1c}, and in our experience it is not necessary to have received a DAFNE course before introducing CSII. These data provide further information to influence guidelines and health policy.

Funding sources

None.

References

1. Diabetes Control and Complications Trial Research Group, Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O *et al*. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; **329:** 977–986.

2. Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular outcomes in type 1 diabetes: the DCCT/EDIC study 30-year follow-up. *Diabetes Care* 2016; **39:** 686–693.

3. McKnight JA, Wild SH, Lamb MJE, Cooper MN, Jones TW, Davis EA *et al*. Glycaemic control of type 1 diabetes in clinical practice early in the 21st century: an international comparison. *Diabet Med* 2015; **32:** 1036–1050.

4. Amiel SA, Pursey N, Higgins B, Dawoud D, Guideline Development Group. Diagnosis and management of type 1 diabetes in adults: summary of updated NICE guidance. *BMJ* 2015; **351:** h4188.

5. DAFNE Study Group. Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial. *BMJ* 2002; **325:** 746.

6. Pollard DJ, Brennan A, Dixon S, Waugh N, Elliott J, Heller S *et al*. Cost-effectiveness of insulin pumps compared with multiple daily injections both provided with structured education for adults with type 1 diabetes: a health economic analysis of the Relative Effectiveness of Pumps over Structured Education (REPOSE) randomised controlled trial. *BMJ Open*. 2018; **8:** e016766.

7. Mair C, Wulaningsih W, Jeyam A, McGurnaghan S, Blackbourn L, Kennon B *et al*. Glycaemic control trends in people with type 1 diabetes in Scotland 2004–2016. *Diabetologia* 2019; **62:** 1375–1384.

8. Dinneen SF, O'Hara MC, Byrne M, Smith D, Courtney CH, McGurk C *et al*. Group follow-up compared to individual clinic visits after structured education for type 1 diabetes: a cluster randomised controlled trial. *Diabetes Res Clin Pract* 2013; **100:** 29–38.

9. Hopkins D, Lawrence I, Mansell P, Thompson G, Amiel S, Campbell M *et al*. Improved biomedical and psychological outcomes 1 year after structured education in flexible insulin therapy for people with type 1 diabetes: the U.K. DAFNE experience. *Diabetes Care* 2012; **35:** 1638–1642.

10. Speight J, Amiel SA, Bradley C, Heller S, Oliver L, Roberts S *et al*. Long-term biomedical and psychosocial outcomes following DAFNE (Dose Adjustment For Normal Eating) structured education to promote intensive insulin therapy in adults with sub-optimally controlled Type 1 diabetes. *Diabetes Res Clin Pract*. 2010; 89: 22–29.

Table 1 Characteristics of each group

	Ever DAFNE	Ever CSII	DAFNE then CSII
N (%)	956 (76.3)	505 (40.3)	208 (16.6)
Women, n (%)	523 (54.7)	307 (60.8)	121 (58.2)
Age of onset, median (IQR)	20.1 (11.9, 30.8)	14.8 (9.0, 24.9)	16.4 (10.2, 26.9)
Diabetes duration at pump initiation, median (IQR)		19.8 (11.3, 28.3)	21.1 (12.5, 27.3)
Diabetes duration at DAFNE initiation, median (IQR)	15.9 (7.4, 24.9)		18.3 (9.7, 25.0)
Initial HbA$_{1c}$ (mmol/mol), median (IQR)	68 (60, 78)	66 (60, 75)	68 (60, 77)
Initial HbA$_{1c}$ (%), median (IQR)	8.4 (7.6, 9.3)	8.2 (7.6, 9.0)	8.3 (7.6, 9.2)
Initial HbA$_{1c}$ band 1, n (%)	103 (11.4)	23 (11.1)	23 (11.1)
Initial HbA$_{1c}$ band 2, n (%)	95 (10.6)	20 (9.6)	20 (9.6)
Initial HbA$_{1c}$ band 3, n (%)	413 (45.9)	128 (61.5)	128 (61.5)
Initial HbA$_{1c}$ band 4, n (%)	160 (17.8)	23 (11.1)	23 (11.1)
Initial HbA$_{1c}$ band 5, n (%)	129 (14.3)	14 (6.7)	14 (6.7)
Pump start year, (minimum, maximum)		2004, 2017	2009, 2017
DAFNE start year, (minimum, maximum)	2002, 2018		2006, 2016
Time before CSII, median (IQR)		11.5 (15.1, 7.1)	10.6 (14.1, 7.3)
Time before DAFNE, median (IQR)	10.5 (15.1, 5.6)		10.6 (14.1, 7.3)
Time after CSII, median (IQR)		4.3 (2.9, 6.3)	4.3 (2.2, 5.1)
Time after DAFNE, median (IQR)	4.4 (2, 7)		6.2 (4.4, 8.1)

CSII, continuous subcutaneous insulin infusion; DAFNE, Dose Adjustment For Normal Eating

Band 1 < 53 mmol/mol (< 7.0%); band 2: 53 to 57 mmol/mol (7.0% to 7.4%); band 3: 58 to 74 mmol/mol (7.5% to 8.9%); band 4: 75 to 84 mmol/mol (9.0% to 9.9%); band 5 $\geq$ 85 mmol/mol ($\geq$ 10%)

Table 2 Difference in HbA1$_C$ (mmol/mol) with respect to intervention initiation date (results in % units are shown in Table S4)

Difference with respect to DAFNE initiation date overall									
Years since DAFNE	-4	-3	-2	-1	0	1	2	3	4
n median (IQR)* mean (95% CI)**	2,058 0.4 [0.1, 0.7] -0.5 (-6.0 to 6.0)	2,225 1.5 [1.2, 1.7] 0.0 (-4.5 to 6.0)	2,775 1.1 [0.9, 1.2] 0.0 (-2.0 to 3.0)	4,004 -0.2 [-0.3, -0.1] 0.0 (-1.0 to 1.0)	3,163 -3.8 [-4.0, -3.6] -3.0 (-8.5 to 2.0)	2,340 -3.7 [-4.0, -3.4] -2.5 (-10.5 to 3.5)	1,754 -3.2 [-3.5, -2.8] -2.5 (-10.0 to 5.0)	1,502 -3.6 [-4.0, -3.2] -3.0 (-12.0 to 5.0)	1,233 -4.6 [-5.1, -4.2] -3.0 (-13.5 to 5.0)
Difference with respect to DAFNE initiation date by sex									
Women	1,149 0.4 [-0.1, 0.8] -0.5 (-7.0 to 6.5)	1,251 1.4 [1.1, 1.8] 0.5 (-5.0 to 6.0)	1,541 1.0 [0.8, 1.3] 0.0 (-2.0 to 2.5)	2,222 -0.2 [-0.3, -0.1] 0.0 (-1.0 to 0.5)	1,792 -4.4 [-4.7, -4.1] -3.5 (-9.0 to 1.6)	1,358 -5.2 [-5.6, -4.8] -3.5 (-12.0 to 3.0)	1,026 -4.0 [-4.5, -3.5] -3.5 (-10.5 to 4.0)	882 -3.7 [-4.3, -3.2] -3.0 (-13.0 to 5.0)	745 -4.5 [-5.1, -3.9] -3.0 (-14.0 to 5.0)
Men	909 0.4 [0.0, 0.8] -0.5 (-5.0 to 5.0)	974 1.5 [1.2, 1.9] 0.0 (-4.0 to 6.0)	1,234 1.1 [0.9, 1.3] 0.0 (-1.5 to 3.0)	1,782 -0.2 [-0.3, -0.1] 0.0 (-1.5 to 1.0)	1,371 -3.1 [-3.4, -2.8] -3.0 (-7.5 to 3.0)	982 -1.7 [-2.1, -1.3] -1.0 (-6.5 to 5.0)	728 -2.0 [-2.5, -1.5] -1.5 (-9.2 to 5.0)	620 -3.4 [-4.0, -2.9] -3.0 (-9.5 to 4.5)	488 -4.9 [-5.6, -4.2] -2.5 (-13.0 to 4.0)
Difference with respect to CSII initiation date overall									
Years since CII	-4	-3	-2	-1	0	1	2	3	4
n median (IQR)* mean (95% CI)**	1,102 0.7 [0.3, 1.1] 1.0 (-5.5 to 6.3)	1,534 1.5 [1.2, 1.8] 1.5 (-4.0 to 6.0)	1,843 1.5 [1.4, 1.7] 0.2 (-1.3 to 2.8)	2,521 -0.4 [-0.4, -0.3] 0.0 (-1.8 to 1.0)	2,715 -6.6 [-6.8, -6.4] -5.5 (-10.8 to -0.5)	2,583 -7.3 [-7.5, -7.1] -6.7 (-12.0 to -1.0)	2,116 -5.8 [-6.1, -5.6] -5.1 (-12.0 to 0.3)	1,699 -7.2 [-7.5, -6.9] -5.5 (-14.3 to 0.5)	1,278 -6.1 [-6.4, -5.8] -5.3 (-12.2 to 0.3)
Difference with respect to CSII initiation date by sex									
Women	695 -0.1 [-0.6, 0.4] 1.0 (-7.0 to 6.0)	1,012 1.4 [1.0, 1.8] 2.0 (-4.0 to 5.5)	1,142 1.3 [1.2, 1.5] 0.1 (-1.5 to 2.8)	1,474 -0.3 [-0.4, -0.2] 0.0 (-1.7 to 1.4)	1,709 -7.4 [-7.7, -7.2] -6.5 (-11.5 to -1.5)	1,659 -8.0 [-8.3, -7.7] -7.0 (-13.2 to -1.7)	1,379 -6.3 [-6.6, -6.0] -5.0 (-13.0 to 0.3)	1,128 -8.1 [-8.5, -7.7] -5.7 (-16.0 to 0.5)	881 -6.8 [-7.3, -6.4] -6.0 (-13.5 to -0.2)
Men	407 2.1 [1.6, 2.6] 1.0 (-3.5 to 7.0)	522 1.8 [1.4, 2.2] 1.0 (-4.0 to 6.5)	701 1.8 [1.6, 2.1] 0.8 (-1.0 to 3.0)	1,047 -0.4 [-0.5, -0.3] -0.5 (-2.0 to 0.5)	1,006 -5.2 [-5.5, -4.9] -4.0 (-10.0 to 1.4)	924 -6.1 [-6.4, -5.8] -5.0 (-11.0 to -0.5)	737 -5.0 [-5.4, -4.7] -5.2 (-9.7 to 0.0)	571 -5.5 [-5.9, -5.1] -5.0 (-11.2 to 0.0)	397 -4.5 [-4.9, -4.1] -4.0 (-8.5 to 0.3)

CSII, continuous subcutaneous insulin infusion; DAFNE, Dose Adjustment For Normal Eating

HbA$_{1c}$ values in International Federation of Clinical Chemistry mmol/mol units

*IQR, interquartile range in square brackets

**95% CI, 95% confidence interval in brackets

FIGURE 1 Median difference in HbA_{1c} over time compared with HbA_{1c} at date of intervention

FIGURE 2 Median difference in HbA_{1c} over time compared with HbA_{1c} at date of intervention by HbA_{1c} band at date of intervention

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 Difference in $HbA1_C$ over time with respect to DAFNE initiation date.

Table S2 Difference in $HbA1_C$ across time with respect to CSII initiation date by strata.

Table S3 Difference in $HbA1_C$ across time with respect to CSII initiation date stratified by DAFNE.

Table S4 Difference in $HbA1_C$ with respect to intervention initiation date ($HbA1_C$ in percentage units).

Table S5 Difference in $HbA1_C$ over time with respect to DAFNE initiation date ($HbA1_C$ percentage units).

Table S6 Difference in $HbA1_C$ across time with respect to CSII initiation date by strata ($HbA1_C$ in percentage units).

Table S7 Difference in $HbA1_C$ across time with respect to CSII initiation date stratified by DAFNE ($HbA1_C$ in percentage units).

<TYPESETTER: Ensure that the Supporting Information, which follows on from here, is not published with the main text.>