Continuous subcutaneous insulin infusion therapy is associated with reduced retinopathy progression compared with multiple daily injections of insulin

Title Page

Title

Continuous Subcutaneous Insulin Infusion Therapy Is Associated With Reduced Retinopathy Progression Compared With Multiple Daily Injections of Insulin

Authors

LJ Reid[1, 2], FW Gibb[1], H Colhoun[3], SH Wild[4], MWJ Strachan[1], K Madill[5], B Dhillon[5], S Forbes[1, 2]

Affiliations

1. Edinburgh Centre for Endocrinology and Diabetes, NHS Lothian, Edinburgh, UK

2. Queen's Medical Research Institute, BHF Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, UK

3. Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK

4. Usher Institute, University of Edinburgh, Edinburgh, UK

5. Princess Alexandra Eye Pavilion, NHS Lothian, Edinburgh, UK

Corresponding Author:

S Forbes;

Centre for Cardiovascular Science,

University of Edinburgh,

Queen's Medical Research Institute,

47 Little France Crescent,

Edinburgh,

EH16 4TJ

E-mail: Shareen.Forbes@ed.ac.uk

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Abstract

AIM

To compare diabetic retinopathy (DR) outcomes in people with type 1 diabetes following introduction of continuous subcutaneous insulin infusion (CSII) therapy compared to people receiving continuing therapy with multiple daily insulin injections (MDI).

RESEARCH DESIGN AND METHODS

Retrospective cohort study using the Scottish diabetes database for retinal screening outcomes and HbA1c changes in 204 adults commenced on CSII therapy between 2013-16, and 211 adults eligible for CSII during the same period but who continued on MDI therapy. DR progression (time to minimum one grade worsening in DR from baseline grading) was plotted for CSII and MDI cohorts using Kaplan-Meier curves, and outcomes compared using multivariate cox regression analysis adjusting for age, gender, baseline HbA1c, blood pressure, cholesterol, smoking status and socioeconomic quintile. Impact of baseline HbA1c and change in HbA1c on DR progression was assessed within CSII and MDI cohorts.

RESULTS

CSII participants were significantly younger, from less socially deprived areas and had lower HbA1c and higher diastolic BP at baseline. There was a larger reduction in HbA1c at one year in those on CSII versus MDI (-6mmol/mol (-0.6%) versus -2mmol/mol (-0.2%), $p<0.01$). DR progression occurred in a smaller proportion of adults following commencement of CSII versus continued MDI therapy over mean

2.3 year follow-up (26.5% versus 18.6%, *p*=0.0097). High baseline HbA1c (75mmol/mol (9%)) was associated with DR progression in MDI group (*p*=0.0049) but not CSII group (*p*=0.93). Change in HbA1c at follow up, irrespective of baseline glycaemic status, did not significantly affect DR progression in either group.

CONCLUSIONS

CSII was associated with reduced DR progression compared to continued MDI therapy, and may be protective against DR progression for those with high baseline HbA1c. Progression of DR over three years was not associated with a change in HbA1c.

Key Words: Clinical science, Clinical diabetes, Insulin therapy, Retinopathy, Microvascular complications

Research in Context

What is already known about this subject?

- Improved glycaemic control confers long term benefits for reduction in DR risk but may be associated with early DR worsening.
- Introduction of CSII therapy for management of Type 1 diabetes is associated with reductions in HbA1c compared to MDI.
- CSII is associated with reduced DR risk versus MDI in adolescents.

What is the key question?

- Is the introduction of CSII therapy associated with early DR worsening or long term benefits in DR progression versus continued MDI therapy in adults with Type 1 diabetes?

What are the new findings?

- No evidence of early DR worsening following the introduction of CSII therapy in those with no or mild baseline DR.
- Change in HbA1c is not associated with DR progression .
- Reduced DR progression in adults treated with CSII compared to MDI, particularly for those with highest baseline HbA1c.

How might this impact on clinical practice in the foreseeable future?

- This provides reassurance that, in adults with no or mild DR risk at baseline, there is no evidence of early DR worsening, with DR risk reduction following the introduction of CSII therapy. This will help facilitate patient-centred decision making regarding insulin treatment options and retinopathy screening intervals following treatment changes.

Tweet

Continuous Subcutaneous Insulin Infusion Therapy Is Associated With Reduced Retinopathy Progression Compared With Multiple Daily Injections of Insulin

Introduction

Diabetic retinopathy (DR) is one of the leading causes of blindness worldwide [1], and prevalence rises with age [2]. It has been well established, following the landmark Diabetes Control and Complications Trial (DCCT), that good glycaemic control confers long term benefits to reduce the risk of developing DR [3]. However, concerns remain that rapid improvements in glycaemia precipitate transient worsening of DR [4], and many guidelines recommend controlled improvements in glycaemic targets with increased monitoring for retinopathy in the initial stages when treatment is altered [5].

In order to optimise glycaemic targets, insulin is typically delivered either via multiple daily injections (MDI) of insulin or by continuous subcutaneous insulin infusion (CSII). A recent Cochrane review suggested that CSII is associated with a small but significant improvement in glycaemic control versus MDI therapy (0.3% absolute reduction in HbA1c) [6]. However, relatively few studies have evaluated whether treatment with CSII confers any benefits over MDI in reducing long term DR risk in an adult population, or whether there is any increased risk of early DR worsening following a change in treatment from MDI to CSII.

Early studies assessing DR progression following the introduction of CSII typically showed no improvement or deterioration of DR with CSII [7, 8]. However, study numbers were small, participants were selected for CSII due to poor glycaemic control on conventional therapy and suitable comparator groups were not used. In addition, early insulin pump systems used in many previous study populations were

more cumbersome as they did not have the ability to pre-programme variable basal rates and lacked safety alarms to notify users about infusion problems. A more recent study in adolescents suggests that CSII is associated with lower rates of retinopathy than MDI [9].

Our main aim in this study was to investigate retinopathy outcomes in adults with type 1 diabetes following the introduction of CSII therapy compared to those continued on therapy with MDI using a robust clinical database system.

Research Design and Methods

Study participants

Participants were identified from three diabetes centres within NHS Lothian, Scotland, using the Scottish Care Information (SCI-) Diabetes database, which links clinical information for all registered people with diabetes in Scotland using electronic care records in primary care, hospitals and pharmacies.

Diabetes records were reviewed for all participants with type 1 diabetes who were commenced on CSII therapy between 1st January 2013 and 1st December 2016 (*n*=293). Retinal data collected during annual retinopathy screening for these participants were reviewed from 1st January 2011 to 1st December 2018. Within NHS Lothian, a five-day structured education course on carbohydrate counting and diabetes management is recommended prior to referral for CSII therapy. To identify a control MDI group who had received a similar level of diabetes education to the

CSII group, people who completed this course at a similar time to the CSII participants, but who remained on MDI therapy, were recruited for comparison (*n*=279).

People were included if they were aged >16 years, had documented type 1 diabetes, defined as a clinical diagnosis of type 1 diabetes with no evidence in the historical record of >6 months between diagnosis and insulin requirement, and no history of use of oral hypoglycaemic drug treatment other than adjuvant metformin. All participants were on treatment with either CSII or MDI therapy and were participating in the Scottish diabetes retinopathy screening programme during the study period. People were excluded if the date of commencing CSII therapy or completion of diabetes education could not be verified, if baseline or follow up retinal images had not been taken, or those taken were deemed ungradable for both eyes, if they had been suspended from the retinal screening programme for assessment and potential treatment at ophthalmology clinics, or if they had the maximum severity retinopathy grading (R4) at baseline and could not therefore 'progress' to higher DR severity grade.

The study was approved by the South East Scotland Ethics Committee and NHS Lothian Caldicott Guardian, and was conducted according to the principles of the Declaration of Helsinki.

Study design

This was a retrospective cohort study using routine clinical and diabetes retinal screening data. Data were extracted from SCI-Diabetes, including up to date information on retinal screening records, HbA1c, mode of current insulin therapy, diabetes education history, anthropometric, metabolic and demographic data (weight, BMI, blood pressure, cholesterol, smoking history and an area-based measure of socio-economic deprivation).

Study time

Study entry (time = 0) for CSII group was the date of commencing CSII therapy. Mean lag time from completing the recommended structured diabetes education course to commencing CSII therapy was 945 days (median 841 days, IQR 333 – 1555 days). Study entry for the MDI group was calculated as 945 days from the date of completion of the diabetes education course to give an equivalent entry time to the CSII group using the mean lag time from education to CSII commencement. Secondary analyses calculating study entry as 841 days from the date of completion of the diabetes education course were also completed using the median lag time from education to CSII commencement, and results for this analysis can be found in the electronic supplementary material. Study exit for CSII and MDI groups was taken as the earliest occurring of any of the following; a retinal event occurring, emigration from Scotland, death, or the end of the study period on 1st December 2018.

Retinopathy Assessment

DR assessment was performed as part of the Scottish diabetes retinal screening programme. A single macula centred photograph is taken for each eye every 6 to 12 months and retinopathy grading assessed using the Scottish Diabetic Retinopathy Grading Scheme [10] by experienced SDRGS qualified graders. Severity of DR was classified as 0) No DR, 1) Mild background DR, 2) Moderate observable DR, 3) Referable DR, 4) Proliferative DR [10]. Repeatibility of image grading was not assessed, however this is the same data that is used to inform clinical decision making for further retinal assessment. Images were also assigned a maculopathy grading based on whether markers of macular oedema were present. For accurate assessment for the presence of macular oedema, 3D imaging, usually using ocular coherence tomography (OCT), is required as false positives are common from 2D fundus images. As such, this study focused on retinopathy gradings rather than maculopathy gradings.

As retinopathy gradings were available for both eyes, the more severe grading was used as the baseline grading.

The DR screening assessment immediately prior to the study entry date was taken as the baseline grading (median 71 (IQR 18 - 243) days) prior to study entry date.

Retinopathy progression was defined as a minimum one grade worsening in either eye from the baseline grading.

Assessment of glycaemic control by HbA1c

For each participant, HbA1c data were extracted from the SCI-diabetes database. Timings of baseline and follow up HbA1c values relative to the time of study entry were variable. The HbA1c value immediately prior to the study entry date was taken as the baseline HbA1c (median 75 (IQR 27 - 172) days prior to study entry date). Subsequent follow up HbA1c readings for each individual were identified for each subsequent six-month period where available. Where multiple HbA1c readings had been taken within a six month period, the HbA1c value closest to, but not exceeding, the six month time point was used as the HbA1c value for that interval. Mean study HbA1c over three year follow up was estimated by calculating the mean HbA1c from the six-monthly values for each individual. The HbA1c at approximately one year post study entry was also recorded, with a range from 8 to 20 months from study entry accepted as the one-year HbA1c value in cases where 12 month values were not available. Study exit HbA1c was recorded as the last available HbA1c value recorded after 20 months from study entry.

Statistical Analyses

Baseline variables including age, sex, diabetes duration, baseline HbA1c, socioeconomic status (assessed using quintile of Scottish Index of Multiple Deprivation (SIMD) score [11]) and diastolic BP were summarized as median with interquartile range (IQR) for continuous data and as percentages for categorical data. In the CSII versus MDI groups, baseline demographic and metabolic data were compared using the unpaired t-test for continuous normally distributed data and Chi-

squared or Fisher's exact test for categorical data. Kaplan-Meier plots were used to assess time to an event corresponding to retinopathy progression, or exit from the study for another reason (death, emigration, end of study period) in CSII and MDI groups, with calculation of statistical differences between groups using the log-rank test. Univariate and multivariate Cox proportional hazards were performed using the following co-variates: CSII or MDI treatment Group, age, gender, diabetes duration, baseline HbA1c, systolic BP, diastolic BP, cholesterol, creatinine, SIMD, smoking status and baseline DR grading.

To assess the impact of baseline, mean study, one year and study exit HbA1c, participants were stratified using the following HbA1c values, (<58mmol/mol (<7.5%)), 58 - 75mmol/mol (7.5 - 9%) and >75mmol/mol (>9%)) and compared using Kaplan-Meier plots as above. Similarly, to assess the impact of the change in HbA1c at one year participants were stratified using the following values (>5mmol (>0.5%), -5 to 5mmol/mol (-0.5 to 0.5%) and < -5mmol/mol (-0.5%) change) and compared using Kaplan-Meier plots as above.

Statistical significance was assumed for $p<0.05$. Statistical analyses were completed using R, version 3.4.1.

Results

Study populations

Between 1st January 2013 and 1st December 2016, 293 people with type 1 diabetes who commenced CSII therapy were identified. Of these, 89 were excluded: 23 were aged <16 years at commencement of CSII, 23 had no available baseline and/or follow-up graded retinal screening results, 31 had been excluded from screening for further ophthalmology assessment or treatment, 3 had the maximum severity retinopathy grading at baseline and for a further 9 we were not able to verify if the dates for commencing CSII were correct. The remaining 204 were included in the analysis (Figure 1).

We identified 277 MDI controls who had completed structured diabetes education at a similar time to the CSII cohort but who did not proceed to CSII therapy largely due to patient preference. Of these, 66 were excluded: 34 had no available baseline and/or follow graded retinal screening results, 28 had been excluded from screening for further ophthalmology assessment or treatment, 1 had the maximum severity grading at baseline and for a further 3 we were not able to verify if the dates for diabetes education were correct. The remaining 211 were included in the analysis (Figure 1).

Baseline demographic and metabolic data is shown in Table 1. CSII participants were significantly younger, with earlier age of diabetes diagnosis, lower baseline HbA1c, higher diastolic BP and with lower proportions of people in more deprived socioeconomic quintiles. The majority of participants had either no DR or mild DR at

baseline. There were no significant differences in baseline DR gradings between CSII versus MDI cohorts.

HbA1c changes in CSII and MDI

The median number of six-monthly HbA1c values per person collected over a three year study interval was 5 (IQR 4-6). There was a small but statistically significant difference in baseline HbA1c (CSII 66 mmol/mol (8.2%) versus MDI 67 mmol/mol (8.3%), $p<0.01$). In the CSII group, there was a significant reduction in mean study HbA1c (62 mmol/mol (7.8%)), one year HbA1c (59 mmol/mol (7.5%)) and study exit HbA1c (61 mmol/mol (7.7%)) from baseline (all $p<0.001$). In contrast, there were no significant changes in mean study HbA1c, one-year HbA1c or study exit HbA1c (all 67 mmol/mol (8.3%)), from baseline in the MDI group. At all follow up time points, CSII participants had a significantly lower HbA1c than MDI participants ($p<0.001$), and a greater HbA1c reduction (one year: -6 mmol/mol (-0.6%) versus -2 mmol/mol (-0.2%), $p<0.01$; study exit: -4 mmol/mol (-0.4%) versus -2 mmol/mol (-0.2%), $p=0.12$). In both groups, univariate regression analysis showed higher baseline HbA1c was significantly associated with greater reductions in HbA1c at one year ($p<0.0001$).

The distribution of HbA1c in the CSII and MDI groups is shown in Table 2. There was a higher proportion of MDI versus CSII participants in the highest baseline HbA1c group (>75 mmol/mol (>9%)) but differences were not statistically significant (Table 2). Follow up HbA1c at one year increased by 5 mmol/mol (>0.5%) in 11.1% versus 18.1% and decreased by more than 5 mmol/mol (0.5%) in 51.9% versus 29.3% ($p<0.001$; Table 2). Changes at study exit showed a similar pattern between

MDI and CSII groups, though numbers of participants with available data for analysis was lower (p=0.03; Table 2).

Retinopathy events in CSII versus MDI

Kaplan-Meier curves describing time to a DR progression event for comparator groups are shown in Figure 2 (A-E). Mean follow up for the entire cohort was 839 days (2.3 years) with DR progression occurring in 38 participants (18.6%) in the CSII group versus 56 participants (26.5%) in the MDI group (Figure 2A, p=0.0097). Of these, unilateral retinal progression was identified in 21/58 (36.2%) people in the MDI group, versus 14/38 (36.8%) people in the CSII group, while the rest had bilateral retinal progression.

Pump participants had a reduced risk of DR progression on univariate (HR 0.58, p=0.01) and multivariate (HR 0.56, p=0.02) Cox proportional hazard analysis, adjusting for age, gender, diabetes duration, baseline HbA1c, BP, cholesterol, creatinine, SIMD, smoking status and baseline DR grading (Table 3).

Those with mild retinopathy at baseline were also at low risk of progression (HR 0.07), with the majority of events occurring in those with no baseline retinopathy (76/94, 80.9%). Older age was also associated with reduced risk of DR progression (HR 0.97), though longer diabetes duration (HR 1.03), increased creatinine (HR 1.01) and history of previous smoking (HR 1.89) were associated with increased DR progression risk on multivariate analysis.

Higher baseline HbA1c was associated with increased DR progression risk for the entire cohort on univariate and multivariate analyses (HR 1.03, $p<0.001$, Table 3). However this effect was driven by the MDI cohort, with baseline HbA1c having no significant impact on the frequency of DR progression occurring in the CSII cohort (Figure 2B, $p=0.93$), while in the MDI cohort HbA1c >75 mmol/mol (>9%) was associated with significantly higher proportion of participants with DR progression (28/69 participants, 40.6%) than those with HbA1c <58 mmol/mol (<7.5%) (6/44 participants, 13.6%) (Figure 2C, $p=0.0049$). The same outcomes were found when groups were stratified by mean study HbA1c, with no significant impact of high mean study HbA1c on DR progression noted in the CSII cohort ($p=0.26$), while high mean study HbA1c was associated with increased DR progression in the MDI cohort ($p=0.023$). HbA1c values at one year and study exit showed no significant impact on the frequency of DR progression in either cohort. Change in HbA1c at one year from baseline was not associated with DR progression in either cohort (CSII: Figure 2D ($p=0.19$), MDI: Figure 2E ($p=0.21$)).

Discussion

In this real-world study, using a robust clinical database and a nationalized single DR scoring system we observed that CSII therapy was associated with significantly lower DR progression over a three year follow up period in adults with type 1 diabetes who had completed structured diabetes education than those on MDI therapy who had completed an equivalent structured diabetes education programme (18.6% in CSII vs 26.5% in MDI, p=0.0097). In addition, there was no evidence of early DR worsening in those using CSII compared to MDI over the first 18 months. This is despite significantly larger reductions in HbA1c in the CSII group (6mmol/mol (0.5%) reduction) versus MDI group (1mmol/mol (0.1%) reduction) at one year post study entry (p<0.001). Findings were confirmed on multivariate analysis adjusting for multiple potential confounders.

Those with longer duration of diabetes were found to be at higher risk of DR progression which was expected as this is a well established risk factor for DR [1]. Surprisingly older age was associated with a small but significant reduction in risk of DR progression in our cohort. This was driven by MDI participants, with no significant effect of age on DR progression when CSII participants were analysed in isolation. The addition of drug therapies such as statins and antihypertensive in older participants may have contributed to DR risk reduction, however we were unable to assess this in our cohort.

Studies of DR progression in adults are lacking in real world settings. However, our findings are consistent with a longitudinal study of adolescents (aged 12-20 years)

treated with either CSII or MDI therapy over a period of 15 years [9]. They showed a significantly lower risk of developing retinopathy in those treated with CSII versus MDI (OR 0.66), though the majority of assessments (79%) were from participants who were only reviewed once during the study period. Proportions of people developing retinopathy were slightly lower than in our cohort (17% in CSII, 22% in MDI), however this is likely to be consistent with a patient cohort of younger age and shorter diabetes duration than in our study. A further study assessed retinal changes in 31 adults following initiation of CSII using a range of imaging modalities, including OCT, and showed stable retinal characteristics over one year with no evidence of early DR worsening [12].

High baseline HbA1c (75mmol/mol (>9%)) was associated with increased DR progression in the MDI group. In contrast, DR progression in the CSII group was not found to be associated with baseline HbA1c. In the MDI group there were no significant reductions in follow up HbA1c values when compared to baseline levels. However, in the CSII group, follow up HbA1c values were significantly reduced from baseline, and were lower than HbA1c levels assessed at the same timepoints in the MDI group. Absolute change in HbA1c at one year from baseline was not significantly associated with DR progression for either group.

We hypothesise that factors intrinsic to CSII therapy are protective against DR progression in those with high baseline HbA1c while those with high baseline HbA1c on MDI remain at increased DR risk. Many of the MDI participants did not achieve a substantial reduction in HbA1c on follow up and therefore had continued exposure to high glycaemic levels which may have contributed to increased DR risk. This is

supported by the fact that high mean study HbA1c was significantly associated with DR progression in the MDI group, though this was not true in the CSII group.

While exposure to high glycaemic levels is a well established risk factor for DR, recurrent disabling hypoglycaemia may also increase DR risk [13]. Though recurrent disabling hypoglycaemia is a possible indication for consideration of CSII therapy, it was not possible for this to be accurately assessed within our cohorts and levels of hypoglycaemia within the groups may have differed. It is therefore possible that some of those perceived to have good glycaemic control, reflected by a lower baseline HbA1c, were exposed to higher levels of hypoglycaemia prior to the study period, which could have contributed to increased DR risk. CSII therapy has been shown to reduce frequency of hypoglycaemia [14] which may also have conferred a benefit in terms of DR risk, even in those with no HbA1c reduction.

Other factors related to better control of diabetes (including glycaemic variability, discussed further below) may have also contributed to the reduction in DR observed in the CSII group.

It is important to note that, within our retinopathy screening programme in Scotland, when people are commenced on CSII therapy recommendations are in place with regards to modifications to early HbA1c targets where appropriate, particularly for those with high baseline HbA1c levels, and improved surveillance for retinopathy [5]. As such, the reductions in HbA1c, although significant in our study, may have been achieved more gradually in the CSII group, and may have facilitated improved retinopathy outcomes.

Glycaemic control as measured by HbA1c has been shown to be important in reducing DR progression as evidenced from the DCCT study [15]. However, other studies do not demonstrate an association between baseline HbA1c, or change in HbA1c, and DR progression following initiation of CSII therapy [16]. Evidence from the DCCT also showed that HbA1c changes did not fully explain the risk of DR progression in type 1 diabetes, and that other features of glucose control, such as the extent of postprandial glucose excursions or counterregulatory responses to hypoglycaemia, which are not easily reflected by a summary measure such as HbA1c, may have an impact on the risk of developing complications [15]. DCCT analyses assessing time in range (TIR) from seven point fingerstick data showed this had a strong association with the development of microvascular complications including retinopathy [17], though earlier DCCT analyses suggest within-day glycaemic variability (GV) and mean amplitude of glucose excursions (MAGE) were not predictive of DR [18].

More widespread availability of continuous glucose monitoring (CGM) systems in recent years has led to expanding interest in the role of glycaemic markers other than HbA1c, including TIR, GV and MAGE, with recommendations now in place for their use in routine diabetes management [19].

There is growing evidence from CGM that these markers are associated with DR in type 2 diabetes [20-22], however less is known about their role in type 1 diabetes [23]. We and others have reported that islet transplantation in recipients with type 1 diabetes is associated with diminished GV and reductions in HbA1c in association

with diminished progression of DR [24-26]. Further studies assessing the impact of GV on DR progression are needed.

CSII is associated with higher initial costs due to the expense of the pump, necessary consumables and pump education [27]. However, in longer-term cost benefit analyses studies indicate that such costs are offset by improved glycaemic control, enhanced quality of life markers and reductions in diabetes complications, and demonstrate that CSII is in fact a cost-effective treatment in Type 1 diabetes [27, 28]. Many cost-benefit models highlight the reduced morbidity and mortality related costs secondary to reductions in problematic hypoglycaemia associated with CSII therapy [27], however projected cost savings related to diminished micro- and macrovascular complications are also evident with an 18.3% lifetime reduction in severe visual loss with CSII versus MDI therapy [28].

The strengths of this study are that it is a relatively large study providing real world data on DR progression in type 1 diabetes in an adult cohort following initiation of CSII therapy. Furthermore, DR assessment was performed within a single retinopathy screening programme. It provides reassurance that, in people with no DR or mild DR at baseline, there is no evidence of increased risk of DR progression following initiation of CSII, and there is long term benefit particularly in those with the highest HbA1c compared to continued MDI therapy.

The study has several limitations. As a retrospective real-world study, timings of retinal imaging and HbA1c collection were not uniform for participants over the study period. In addition, participants were not randomized to receive either CSII or MDI

therapy resulting in potential confounding and allocation bias. Indeed, at baseline the CSII group was significantly younger with earlier age of diabetes onset, lower baseline HbA1c, lower diastolic BP and lived in less socio-economically deprived areas than the MDI group. Multivariate analyses were performed to minimise the impact of these differences. Study entry time for the MDI group, who did not have any specific intervention, was based on the lag time from receiving structured education to commencing on CSII therapy. Although there was some variability in this lag time, when data were reassessed using an alternative study entry time based on the median lag time (841 days) rather than mean lag time (945 days) outcomes were unchanged, with results still showing significantly fewer retinal events in the CSII group versus the MDI group (see electronic supplementary material). Retinal data was sourced from the diabetes retinopathy screening programme, therefore people who had no retinal screening results could not be assessed (7.8% CSII, 12.3% MDI). This could represent a population of non-attenders who are not fully engaging with aspects of their diabetes management, and as such may be at higher risk of developing DR. In addition, few participants with advanced retinal disease, who are known to be at the highest interval risk of DR [29], were assessed as these people leave the screening programme to enter into a management pathway under the care of ophthalmologists, though numbers excluded due to receiving ophthalmology care were similar in both groups (10.6% CSII, 10.1% MDI). Reporting of retinopathy outcomes using SDRG assessment is not the gold standard, therefore we may have missed more subtle retinal changes that could have been picked up by using Early Treatment Diabetic Retinopathy Study (ETDRS) screening, however as SDRG is designed to detect clinically significant changes we feel findings are still clinically relevant. These problems relating to the use of

screening data will have affected both groups, and therefore their impact on the study analysis was felt to be relatively small. Glycaemic analysis was limited to HbA1c data. Though this remains the gold standard for glycaemic assessment, further studies using CGM will help fully characterize the range of glycaemic factors involved in DR progression. Finally, this study was conducted in a predominantly white population across three diabetes centres from a single Scottish region, where a national DR screening service is offered for all people affected by diabetes. Therefore, results may not be generalizable to all people with type 1 diabetes from other ethnic groups, or where access to DR screening is limited.

Conclusion

This observational study has demonstrated reduced DR progression in a real-world population with type 1 diabetes commenced on CSII versus those who continued on MDI, with no evidence of early DR worsening. Although reductions in HbA1c were seen due to CSII therapy, this was not associated with the reduction in DR progression and as such other glycaemic factors associated with CSII therapy may play a role. Further prospective studies using CGMS may help establish if reductions in glycaemic excursions are causal in reducing the progression of DR and other microvascular diabetes complications.

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Data Availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Contribution Statement

LJR, FWG, HC, SW, BD and SF contributed to study design. LJR, FWG, MS, KM, SW and SF facilitated acquisition of data. LJR collected and analysed data. LJR and SF wrote the manuscript. All authors reviewed and edited the manuscript. SF is the study guarantor. The authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

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Tables

Table 1: Baseline demographics and metabolic characteristics

Characteristic	CSII (*n*=204)	MDI (*n*=211)	*p* value
Age at Diagnosis (years)	15 (10 - 26)	21 (12 – 33)	<0.001
Age at Study Entry (years)	38 (29 – 48)	43 (31 – 53)	<0.001
Diabetes Duration (years)	18 (11 – 25)	16 (8 – 27)	0.63
Gender M:F (%M)	76:128 (37.3%)	90:121 (42.7%)	0.31
Weight (kg)	78.9 (67.6 – 90.3)	79.5 (67.6 – 91.5)	0.84
BMI (kg/m^2)	26.9 (24.0 – 31.2)	27.1 (24.2 – 30.4)	0.97
HbA1c (mmol/mol)	66 (58 – 74)	67 (60 – 80)	<0.05
HbA1c (%)	8.2 (7.5 – 8.9)	8.3 (7.6 – 9.5)	<0.05
SIMD	4 (3 – 5)	3 (2 – 5)	<0.05
Cholesterol (mmol/L)	4.7 (4.2 – 5.2)	4.8 (4.2 – 5.4)	0.14
Creatinine (µmol/L)	73 (67 – 83)	74 (68 – 84)	0.26
Systolic BP (mm/Hg)	128 (118 – 140)	128 (120 – 138)	0.95
Diastolic BP (mm/Hg)	78 (73 – 84)	77 (71 – 83)	<0.001
Smoking Status			0.20
Non-Smoker	141 (69%)	131 (62%)	
Ex-Smoker	48 (24%)	55 (26%)	
Current Smoker	15 (7%)	25 (12%)	
Baseline DR Grading			0.10
R0	93 (45.6%)	100 (47.4%)	
R1	109 (53.4%)	101 (47.9%)	
R2	0	2 (0.9%)	
R3	2 (1.0%)	8 (3.8%)	
R4	Excluded	Excluded	

Data are median (IQR) or number (%) unless otherwise indicated. P values calculated using unpaired t-test for continuous numerical data and Chi-squared or Fisher's exact test for categorical data. Baseline grading indicates the overall baseline retinopathy grading for each individual. As retinal data was available for both eyes, the more severe retinal grading outcome for that individual was used as the baseline. SIMD: Scottish Index Multiple Deprivation, DR Diabetic retinopathy

Table 2: Stratified HbA1c analysis in CSII and MDI groups

	CSII (*n*=204)	MDI (*n*=211)	*p* value
Baseline HbA1c /total n with data	/193	/209	0.06
<58mmol/mol (<7.5%) *n*(%)	42 (21.8)	44 (21.1)	
58-75mmol/mol (7.5-9%) *n*(%)	107 (55.4)	96 (45.9)	
>75mmol/mol (>9%) *n*(%)	44 (22.8)	69 (33)	
Change in HbA1c at One Year /total n with data	/189	/188	<0.001
>-5mmol/mol (>-0.5%) *n*(%)	98 (51.9)	55 (29.3)	
-5 to 5 mmol/mol (-0.5 to 0.5%) *n*(%)	70 (37.0)	99 (52.7)	
>5mmol/mol (>0.5%) *n*(%)	21 (11.1)	34 (18.1)	
Change in HbA1c at Study Exit /total n with data	/142	/124	0.03
>-5mmol/mol (>-0.5%) *n*(%)	63 (44.4)	36 (29.0)	
-5 to 5 mmol/mol (-0.5 to 0.5%) *n*(%)	58 (40.8)	61 (49.2)	
>5mmol/mol (>0.5%) *n*(%)	21 (14.8)	27 (21.2)	

Table showing numbers of all participants stratified to subgroups for baseline HbA1c and change in HbA1c at one year and study exit. P value comparing subgroups for all CSII and MDI or matched CSII and MDI cohorts calculated using Chi-squared.

Table 3: Hazard ratios for co-variates on univariate and multivariate cox proportional hazard analysis

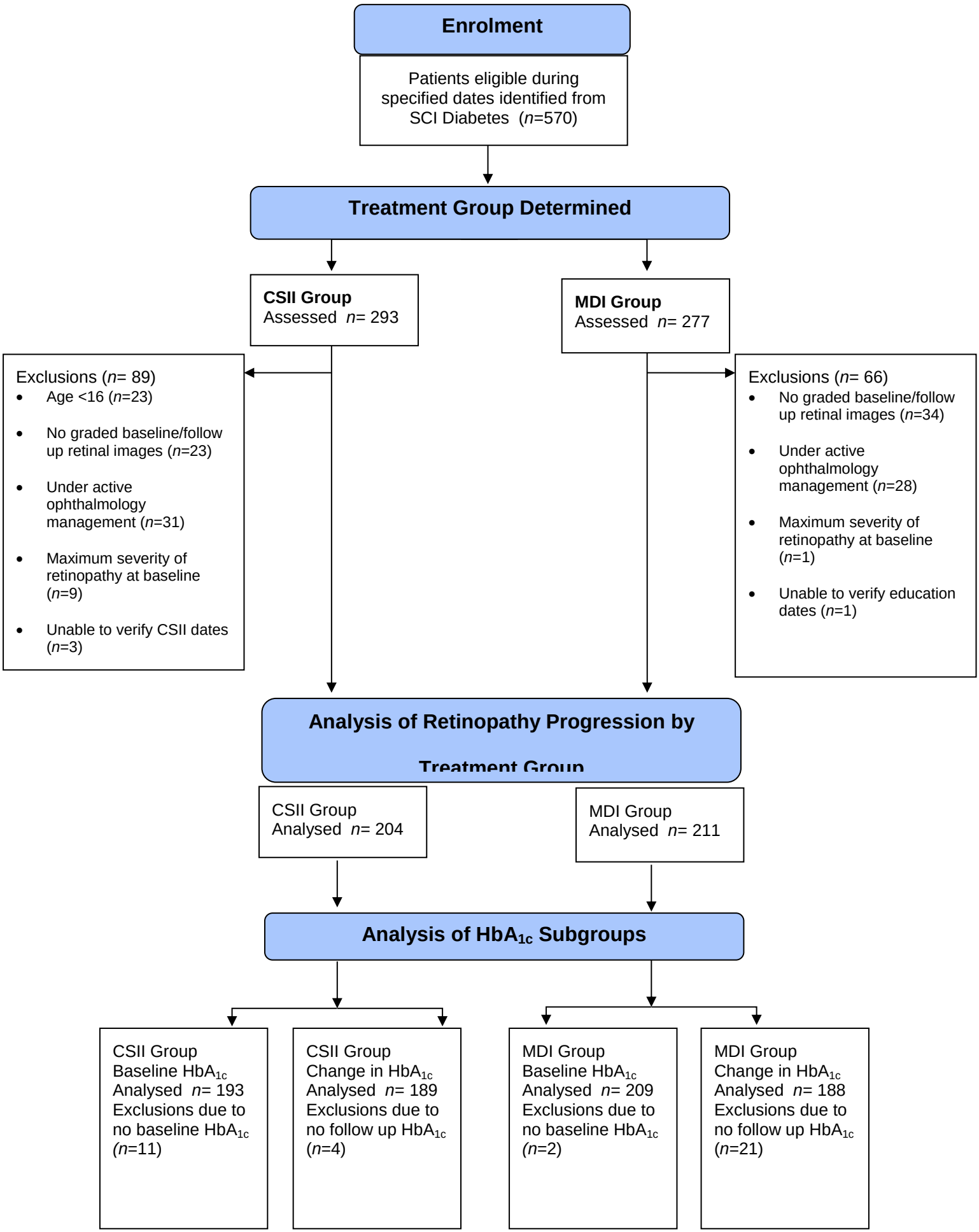
Co-Variate	Univariate Analysis			Multivariate Analysis		
	HR	**(95% CI)**	***p*.value**	**HR**	**(95% CI)**	***p*.value**
Pump Group	0.58	0.39 – 0.88	0.01	0.56	0.34 - 0.91	0.02
Age at Study Entry	0.98	0.96 – 0.99	0.99	0.97	0.96 - 0.99	<0.01
Male Gender	0.84	0.55 – 1.29	0.43	0.69	0.40 - 1.19	0.18
Diabetes Duration	1.00	0.98 – 1.01	0.65	1.03	1.02 - 1.05	<0.001
Baseline HbA1c	1.03	1.01 – 1.03	<0.001	1.03	1.01 - 1.04	<0.001
Systolic	1.00	0.98 – 1.01	0.68	1.00	0.98 - 1.02	0.92
Diastolic	0.99	0.97 – 1.02	0.61	1.01	0.99 - 1.04	0.36
Cholesterol	0.97	0.78 – 1.22	0.82	0.94	0.73 - 1.21	0.62
Creatinine	1.00	0.99 – 1.01	0.87	1.01	1.00 - 1.02	0.01
SIMD	0.89	0.77 – 1.03	0.13	0.94	0.79 - 1.12	0.51
Smoking status						
Non-smoker	1.00 (REF)			1.00 (REF)		
Ex-smoker	1.54	0.98 – 2.41	0.06	1.89	1.13 - 3.17	0.02
Current smoker	1.60	0.84 – 3.08	0.15	0.94	0.43 - 2.07	0.88
Baseline DR Grading						
R0	1.00 (REF)			1.00 (REF)		
R1	0.11	0.06 – 0.20	<0.001	0.07	0.03 - 0.13	<0.001
R2	5.43	1.32 – 22..32	0.02	2.90	0.62 - 13.6	0.18
R3	1.04	0.38 – 2..84	0.94	0.28	0.09 - 0.86	0.03

Figures

Figure 1: Flow chart showing number of people assessed and analyzed for CSII and MDI groups and exclusions

Figure 2: Retinopathy progression in comparator treatment groups (a) and HbA1c subgroups (b-e)

Kaplan-Meier survival plot comparing event-free survival in CSII/MDI treatment groups (a) and HbA1c subgroups (b-e). An event corresponds to DR progression and was defined as a minimum one grade worsening in either eye from the baseline grading. Vertical dashes indicate participants who were censored due to incomplete three year follow up. (a) Comparison of CSII (blue) and MDI (red) participants for entire cohort. CSII was associated with significantly reduced retinopathy progression over three years compared to MDI (p=0.0097) (b+c). Comparison of participants with baseline HbA1c <7.5% (Low: lilac), 7.5-9% (Middle: blue), >9% (High: red) in CSII group (b) and MDI group (c). High baseline HbA1c (>9%) was associated with increased DR progression in MDI group (p=0.0049) but was not a determinant of DR progression in CSII group (p=0.93) (d+e). Comparison of unmatched participants with change in HbA1c at one year of less than -0.5% (Decrease: lilac), -0.5 to 0.5% (Stable: blue), more than 0.5% (Increase: red) in CSII group (d) and MDI group (e). Change in HbA1c at follow up did not significantly impact DR progression in either cohort.


Enrolment
Patients eligible during specified dates identified from SCI Diabetes (n=570)
Treatment Group Determined
CSII Group
Assessed n= 293
MDI Group
Assessed n= 277
Exclusions (n= 89)
Age <16 (n=23)
No graded baseline/follow up retinal images (n=23)
Under active ophthalmology management (n=31)
Maximum severity of retinopathy at baseline (n=9)
Unable to verify CSII dates (n=3)
Exclusions (n= 66)
No graded baseline/follow up retinal images (n=34)
Under active ophthalmology management (n=28)
Maximum severity of retinopathy at baseline (n=1)
Unable to verify education dates (n=1)
Analysis of Retinopathy Progression by Treatment Group
CSII Group
Analysed n= 204
MDI Group
Analysed n= 211
Analysis of HbA1c Subgroups
CSII Group
Baseline HbA1c
Analysed n= 193
Exclusions due to no baseline HbA1c
(n=11)
CSII Group
Change in HbA1c
Analysed n= 189
Exclusions due to no follow up HbA1c
(n=4)
MDI Group
Baseline HbA1c
Analysed n= 209
Exclusions due to no baseline HbA1c
(n=2)
MDI Group
Change in HbA1c
Analysed n= 188
Exclusions due to no follow up HbA1c
(n=21)

Electronic Supplementary Material

Supplementary Results

Results for secondary analyses, where study entry was calculated as 841 days from the date of completion of the diabetes education course, using the median lag time from education to CSII commencement, are shown below.

Three people who were excluded in the primary analysis due to lack of follow up retinal data were able to be included following the shift in study entry time, bringing the total number of people included in the MDI group to 214.

The number of events in MDI group was 55 versus 38 events in CSII group which were unchanged. This remained significant on univariate (p=0.03) and multivariate (p=0.045) analyses, with no evidence of early DR worsening in the CSII group. The updated survival curve is also shown below (Supplementary Figure 1).

Supplementary Figure 1: Survival curve using T0 for MDI group as 841 days from the structured education course, based on median lag time from the education to commencement of CSII therapy: