Glycemic control during continuous subcutaneous insulin infusion vs. multiple daily insulin injections in type 2 diabetes: individual patient data meta-analysis and meta-regression of randomised controlled trials

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Abstract

OBJECTIVE

To compare glycemic control during CSII and multiple daily insulin injections (MDI) in type 2 diabetes to identify patient characteristics that determine those best treated by CSII.

RESEARCH DESIGN AND METHODS

Randomised controlled trials were selected comparing HbA1c during CSII vs. MDI in people with type 2 diabetes. Data sources included Cochrane database and Ovid Medline. We explored patient-level determinants of final HbA1c and insulin dose using Bayesian metaregression models of individual patient data, and summary effects using two-step meta-analysis. Hypoglycemia data was unavailable.

RESULTS

Five trials were identified, with 287 patients randomised to MDI and 303 to CSII. Baseline HbA1c was the best determinant of final HbA1c: HbA1c difference (%) = 1.575 – (0.216 [95% credible interval 0.371 to 0.043] x baseline HbA1c) for all trials, but with largest effect in the trial with pre-randomisation optimisation of control.

Baseline insulin dose was best predictor of final insulin dose: insulin dose difference (units/kg) = 0.1245 – (0.382 [0.510 to 0.254] x baseline insulin dose). Overall HbA1c difference was -0.40 (-0.86 to 0.05)%, -4.4 (-9.4 to 0.6) mmol/mol. Overall insulin dose was reduced by -0.25 (-0.31 to -0.19) units/kg (26% reduction on CSII), and by -24.0 (-30.6 to -17.5) units/day. Mean weight did not differ between treatments (0.08 [-0.33 to 0.48] kg).

CONCLUSIONS
CSII achieves better glycemic control than MDI in poorly controlled type 2 diabetes, with approximately 26% reduction in insulin requirements and no weight change. The best effect is in those worst controlled and with highest insulin dose at baseline.
There is now a well-established evidence base for the routine clinical use of continuous subcutaneous insulin infusion (CSII, insulin pump therapy) in selected people with type 1 diabetes who have failed to achieve target levels of glycemic control with best insulin injection regimens (multiple daily insulin injections, MDI) and structured diabetes education\textsuperscript{1,2}. In many such patients, there can be a clinically valuable, sometimes substantial, reduction in HbA\textsubscript{1c} and all grades of hypoglycemia on switching to CSII.

The value of insulin pump therapy in type 2 diabetes is less certain. Some national guidelines for insulin pump therapy, e.g. the UK National Institute for Health and Care Excellence (NICE) Technology Appraisal of CSII\textsuperscript{2}, do not recommend this treatment for type 2 diabetes. This is in spite of the fact that at least one quarter of people with type 2 diabetes receiving insulin injections have very poor glycemic control, say an HbA\textsubscript{1c} level ≥9\% (75 mmol/mol)\textsuperscript{3}, and new options for improving control are urgently needed. Present guidance on not using CSII in type 2 diabetes is largely based on the limited and variable evidence of efficacy of insulin pump therapy in this type of diabetes in the relatively small-scale randomised controlled trials (RCTs) published over the last several years, where there is support both for and against the superiority of CSII vs. MDI in reducing HbA\textsubscript{1c}\textsuperscript{4-7}. A meta-analysis of aggregate data from four trials of CSII vs. MDI in type 2 diabetes (including one in newly diagnosed type 2 diabetes) reported no difference in HbA\textsubscript{1c} between treatments\textsuperscript{8}. 
A recent large-scale, multicenter RCT reported that people with type 2 diabetes with poor glycemic control that persisted after a period of optimised MDI achieved a substantially better HbA₁c on CSII than with MDI (mean difference between groups: 0.7% (8 mmol/mol), with 20% less total daily insulin dosage and without an increase in hypoglycemia or weight gain⁹. With data from this new trial, it is likely that a meta-analysis of all available RCTs may now provide a more robust view of the comparative effectiveness of CSII and MDI in type 2 diabetes. However, since the differing efficacy of CSII in trials may be due to the different characteristics of the participants at baseline, such as level of glycemic control, rather than estimating just overall pooled effect size (reduction in HbA₁c) it is more important to explore how the effectiveness of CSII depends on patient characteristics such as age, baseline quality of control and insulin requirements, a strategy that has the potential to inform patient-centered therapeutic decision-making¹⁰. The analysis approach which enables this most reliably and with most power is the use of individual patient data¹¹.

The purpose of this study, therefore, was to perform an individual patient data meta-analysis and meta-regression of RCTs that have compared glycaemic control on CSII vs. MDI in type 2 diabetes, in order to test the hypothesis that CSII achieves significantly lower HbA₁c levels than MDI in identifiable patient groups. We aimed to model the determinants of final HbA₁c and insulin requirements on these therapies, as this may identify the individuals with type 2 diabetes most likely to benefit from CSII and, in due course, allow appropriate cost-effectiveness analyses to be performed, if insulin pump therapy is found to be clinically valuable.
RESEARCH DESIGN AND METHODS

We followed recent guidance on the conduct and reporting of individual patient data meta-analyses\textsuperscript{12,13}. The protocol was predefined, and the meta-analysis registered with ClinicalTrials.com, identifier NCT02910141. All original trials selected for analysis operated under supervision of an appropriate human ethics committee. The current analysis involved anonymised data only.

Data sources and searches

Trials were identified without language restriction as those published up to January 2016 that met the inclusion criteria. We searched the Cochrane database for RCTs, Ovid Medline, Embase and Google Scholar (search terms 'diabetes mellitus, diabetes mellitus type 2, continuous subcutaneous insulin infusion, CSII, multiple daily insulin injections, MDI, insulin pump therapy and randomised controlled trial). We also searched literature cited in retrieved articles, previous meta-analyses and lists of papers supplied by manufacturers of insulin pumps.

Study selection and eligibility criteria

Two independent reviewers (JCP, YR) decided trial eligibility. We selected for inclusion RCTs comparing glycemic control during CSII and MDI in participants with type 2 diabetes, studied for at least 2 months. We excluded observational studies; reviews, surveys and meta-analyses; cost-effectiveness analyses; trials of CSII in type 1 diabetes, pregnant women and newly diagnosed diabetes; studies that were
short-term (<2 months) or where MDI was not the comparator; studies where participants had not previously been treated by insulin; duplicate reports; and extensions of previous trials. Differences concerning trial eligibility or data interpretation were resolved by consensus after discussion.

Data extraction and quality assessment

Trial quality was assessed by the components of a six-point scale, according to the method of Jadad et al.14, based on the study being randomised, the randomisation scheme being described and being appropriate, whether the study was double blind, a description of the method and appropriateness of blinding, and a description of withdrawals and drop-outs) but with an additional item for reporting allocation concealment (the person randomising is blinded to next treatment allocation). A score of 3 or above was considered appropriate quality for inclusion in the meta-analysis.

Data on individual participants in the trials that met the criteria for meta-analysis were obtained from the original research team or the funding sponsors who held the trial data. We asked the sources to provide information on individual trial participants, including age, sex, duration of diabetes, treatment group (CSII or MDI), and baseline and final HbA1c, insulin dose, weight and body mass index (BMI). We re-contacted authors for further clarification when there were issues over interpretation of data or when additional data were required. For aggregate-data meta-analysis, summary information was extracted from text, tables and graphs in published papers.
The primary outcome was glycemic control at study completion, as measured by HbA$_{1c}$. The secondary outcomes were insulin dose (total units/day and units/kg) and weight at study completion. We did not analyse data on hypoglycemia because we could not obtain complete information on this for all trials; BMI at study completion was also analysed but was recorded in only four studies. Center information was not available for multicenter trials.

We included data from the participants who had completed each trial. In the two crossover trials, we analysed data from the first period only in the primary analysis because of evidence of a carry-over effect and absence of a washout period in one study.

We checked consistency of data by comparing major participant characteristics and results in published reports of the trials with analyses of files from individual patient data. Clarifications were sought and discrepancies were resolved when possible by contacting investigators. Assessment of potential study bias included baseline imbalances, design of crossover studies (presence of wash-out period, evidence of carry-over) and inclusion of patients of one type in studies (e.g. only elderly or obese participants).

Data synthesis and analysis

Patients with missing data were excluded from analysis. To explore the effect of patient-level covariates on outcome, we carried out a one-step meta-regression analysis (modelling the impact of potential effect size modifiers on the effect size) by creating a single, large dataset from the individual patient data. In this way, we
explored determinants of final HbA1c and insulin dosage using a hierarchical random effects regression model considering the covariates sex, age, study duration, diabetes duration, baseline HbA1c, insulin dose and weight. Initially, we fitted all covariates separately, and then we created best-fit models considering all covariates of interest for each outcome. The deviance information criterion (a Bayesian method for model comparison that balances 'goodness-of-fit' with model complexity, calculated by WinBUGS) was used for choosing between models, with differences in the criterion of three or more considered to be important.

We assessed the potential impact of ecological/aggregation biases by decomposing the variability accounted for by covariates into between- and within-study variability to check covariate effects were not being influenced by between-study information. Deviance residuals were examined for extreme points and models recalculated to ensure robustness to exclusion of the most influential points.

To explore overall mean effect sizes, we carried out a meta-analysis of individual patient data for HbA1c, insulin dose, weight and BMI using a two-step approach. Initially, we modelled individual patient data for each trial using a linear regression model including terms that distinguished between CSII and MDI treatment groups and baseline measurements to produce a treatment effect estimate and associated standard error for each trial. Using a random effects meta-analysis, we then combined these to calculate an overall effect size for difference in means between treatments. In sensitivity analyses, we explored robustness by also carrying out meta-analysis with a fixed-effect model.
We did not explore potential publication bias using a funnel plot because the number of trials analysed were less than ten\(^{17}\); but we quantified heterogeneity between trials by the I-squared statistic (the percentage of variability in effect due to heterogeneity rather than sample error), with greater than 50% representing substantial heterogeneity and greater than 75% considerable heterogeneity.

Stata version 11 was used for the meta-analysis of aggregate data and the two-stage individual patient data meta-analysis. We used the Bayesian Markov Chain Monte Carlo software in WinBUGS version 1.4.3 to carry out the one-stage regression analyses on all the individual patient data. Prior distributions for all model parameters were specified as vague. For all models we used a minimum burn-in of 10,000 and sample size of 30,000. All models were checked for the convergence of all variables using the history and density plots available in WinBUGS version 1.4.3. To confirm convergence of the best-fitting regression models, we fitted these with two different sets of initial values and produced a Gelman-Rubin plot to check convergence. Further details of statistical procedures are available from the authors on request.
RESULTS

The initial literature search identified 90 publications, of which 70 concerned insulin pump therapy in type 2 diabetes (Fig. 1). We then excluded 22 reviews, surveys, cost-effectiveness analyses or methods papers; 10 short-term studies; 3 trials of CSII in pregnancy; 5 trials in newly diagnosed diabetes; 6 where the comparator was not MDI; 13 trials which were not RCTs; and 6 duplicate papers. Five RCTs\textsuperscript{4-7,9} that compared glycemic control during CSII or MDI were selected as being eligible for meta-analysis. Individual patient data were obtained from all five eligible trials, consisting of 590 participants with type 2 diabetes who were randomly allocated to MDI (n = 287) or CSII (n = 303).

*Study characteristics*

Table 1 shows the characteristics of the trials included in the meta-analysis. Three studies were parallel RCTs (one multicentre)\textsuperscript{4,5,9} and two were crossover RCTs\textsuperscript{6,7}. The study duration ranged from 3 to 24 mo and the drop-out rate ranged from zero to 27.5%. The baseline HbA\textsubscript{1c} varied between trials from 8.1\% (65 mmol/mol) to 9.6\% (81 mmol/mol) and the baseline insulin dose from 0.72 to 1.16 units/kg. Oral antihyperglycemic agents were either not used or discontinued in three trials\textsuperscript{4,5,7} or prior use of metformin was continued\textsuperscript{6,9} in the others. All five trials scored 3 out of 6 on the study quality scale because of the absence of double blinding (not possible with trials of insulin pump therapy) and because of lack of allocation concealment or information on this.
Notable features in the design, the risk of bias and the interpretation of trials are also shown in Table 1. These include an absence of a washout period in one crossover trial\textsuperscript{7}; evidence of carry-over effect in a crossover trial\textsuperscript{7}; baseline imbalances in age\textsuperscript{7}, sex\textsuperscript{5}, insulin dosages\textsuperscript{5} and weight\textsuperscript{6}; missing BMI data in one trial\textsuperscript{6}; inclusion of only older participants in one study\textsuperscript{5} or obese participants in another\textsuperscript{6}; and some discrepancies between the individual patient data and the published information\textsuperscript{6}. Most agreement between IPD and reported data was found for the OpT2mise trial.\textsuperscript{9} Two studies employed long-acting insulin analogues as the basal insulin with short-acting insulin analogues before meals, two studies used types of isophane insulin as the basal insulin and one study used three daily injections of premixed isophane/short-acting insulin. In one study\textsuperscript{9}, participants underwent a pre-randomisation run-in period designed to optimise glycemic control on MDI, and only those who still had poor control (HbA\textsubscript{1c} 8-12\%, 64-108 mmol/mol) and were insulin resistant (0.7-1.8 U/kg) were then randomised to CSII or continued MDI.

**Independent determinants of HbA\textsubscript{1c} treatment difference**

Using the entire data set of 590 patients in the five trials, we explored the independent determinants of the HbA\textsubscript{1c} difference between MDI and CSII at study completion by including a range of covariates in regression models. The best-fit model included only baseline HbA\textsubscript{1c} as a predictor of final HbA\textsubscript{1c}; age, sex, baseline weight and baseline insulin requirements did not affect outcome. For all trials combined, HbA\textsubscript{1c} difference was best described by the equation:
HbA\textsubscript{1c} difference, CSII vs. MDI (%\textsuperscript{1}) = 1.575 – (0.216 [95% credible interval 0.371 to 0.043] \times \text{baseline HbA} \textsubscript{1c}).

The effect of baseline HbA\textsubscript{1c} on HbA\textsubscript{1c} treatment difference varied between trials. Fig. 2 illustrates the increase in treatment difference as baseline HbA\textsubscript{1c} levels increase, for all trials and for the OpT2mise trial, calculated from the best-fit models. The largest effect was in the OpT2mise trial\textsuperscript{9}, where there was pre-randomisation optimisation of glycemic control on MDI; here, the regression equation for HbA\textsubscript{1c} difference = 5.39 – (0.669 [0.326 to 1.011] \times \text{baseline HbA} \textsubscript{1c}). With an example baseline HbA\textsubscript{1c} of 10% (86 mmol/mol), the effect size in this study is expected to be -1.3% (14 mmol/mol), compared to -0.59% (7 mmol/mol) for all participants combined. The effect size was minimal below a baseline HbA\textsubscript{1c} of about 8.0% (64 mmol/mol) (Fig. 2).

\textit{Independent determinants of final insulin dosage}

Best-fit models showed that baseline insulin dose was the best predictor of the final insulin dose and the difference in dose between treatments. The best-fit model for difference in insulin dose (units/kg), CSII vs. MDI was:

\begin{align*}
\text{Insulin dose difference (units/day)} &= 0.148 – (0.238 [0.364 to 0.111] \times \text{baseline insulin dose}) \\
\text{And insulin dose difference (units/kg)} &= 0.125 – (0.382 [0.510 to 0.254] \times \text{baseline insulin dose}).
\end{align*}
With an example baseline dose of 100 units/day, the effect size is predicted to be a difference of -23.6 units/day insulin dose; with a baseline of 150 units/day the effect size would be 35.5 units/day.

**Summary meta-analysis of difference in HbA1c, insulin dose, weight and BMI on MDI vs. CSII**

Fig. 3A shows a forest plot (a graphical representation of the results of aggregate meta-analysis, with the effect size of all studies, associated confidence intervals and the summary/overall effect measure) for the mean HbA1c difference between MDI and CSII using a random effects model and with covariate adjustment for potential baseline imbalance between treatment groups in each study. The overall mean HbA1c difference for the five trials combined was -0.40 (95% confidence interval -0.86 to 0.05)%,- 4.4 (-9.4 to 0.6) mmol/mol, favoring CSII. The I-squared statistic was 81%, indicating considerable heterogeneity between trials. Using a fixed effect model, the overall HbA1c difference was lower at -0.30% but with a narrower CI (-0.47 to -0.13)%,-3.3 (-5.2 to -1.5) mmol/mol, favoring CSII. Similar results for HbA1c difference, favouring CSII, were obtained with an aggregate-data meta-analysis of summary effect sizes extracted from the published papers, rather than individual patient data: random effects model, -0.45 (-0.81 to -0.09)% [-5.0 (-8.9 to -1.0) mmol/mol] and fixed effect model, -0.47 (-0.65 to -0.29)% [-5.2 (-7.1 to -3.2) mmol/mol].

Fig 3B shows a forest plot of the difference in insulin requirements on MDI and CSII using individual patient data meta-analysis (random effects model). The overall insulin dose was reduced by -0.25 (-0.31 to -0.19) units/kg on CSII vs. MDI (26%
reduction of the baseline insulin requirements), with an I-squared statistic of 4.7%, indicating little heterogeneity between trials. The fixed effect model gave an almost identical effect size (-0.26 [-0.31 to -0.20] units/kg). Meta-analysis (random effects and fixed effect models) showed that the total daily insulin dose was reduced by -24.0 (-30.6 to -17.5) units/day on CSII vs. MDI (27% of baseline daily insulin), with an I-squared of 0%, indicating little heterogeneity (forest plot not shown).

Two-stage individual patient data meta-analysis with baseline adjustment indicated that the mean weight at study completion did not differ between treatments (0.08 [-0.33 to 0.48]) kg, I-squared 0%, random and fixed effect models (Fig. 3C). BMI data was available for four trials, and two-stage individual patient data meta-analysis with baseline adjustment also indicated no difference in final mean BMI between treatment groups (0.00 [-0.23 to 0.24] kg/m²), random and fixed effect models (forest plot not shown).
Discussion

We show in this individual patient data meta-analysis and meta-regression of five RCTs involving 590 participants with type 2 diabetes that insulin pump therapy achieves better glycemic control than MDI in participants with poor diabetes control at baseline. Using Bayesian statistical best-fit models where we explored a wide range of potential effect modulators, we found that the HbA1c treatment difference was dependent on pre-randomisation HbA1c on MDI, increasing as baseline HbA1c increases. For example, the expected all-study difference increases from -0.15% (2 mmol/mol) with a baseline of 8.0% (64 mmol/mol) to -0.59% (6 mmol/mol) with a baseline HbA1c of 10% (86 mmol/mol). We also found that the reduction in insulin requirements on switching to CSII was dependent on baseline insulin dose: the treatment difference would increase to -35.5 units/day, for example, when the baseline insulin dose is 150 units/day, compared to a treatment difference of -23.6 units/day for a baseline insulin dose of 100 units/day. The percentage insulin dose reduction with CSII at the end of the study period was about -25%, irrespective of baseline insulin dose.

The overall mean difference in HbA1c for meta-analysis of all trials was -0.40% (4 mmol/mol), for a mean HbA1c baseline of 8.8% (73 mmol/mol), with the mean difference varying between -0.3% (3 mmol/mol) and -0.47% (5 mmol/mol), depending on meta-analysis model and individual patient data vs. aggregate data meta-analysis. This improvement was accompanied by a reduction in insulin requirements (mean 24 units/day), but no weight change. The large degree of heterogeneity in HbA1c effect size between trials (I-squared 81%) was likely due to
the wide variation in baseline HbA1c, from 8.1% (65 mmol/mol) to 9.6% (81 mmol/mol), which we show is a major determinant of CSII efficacy.

We found that the HbA1c difference varied markedly between trials and was greatest for the study in which patients underwent pre-randomisation optimisation of control and only those who continued to have poor control were entered into the trial\textsuperscript{9}. For this study, the mean HbA1c difference from individual patient data analysis was 0.63% (6 mmol/mol) and the expected effect at 10% (86 mmol/mol) baseline HbA1c was 1.3% (14 mmol/mol). One may speculate that the greater treatment difference for this trial was because, in the non-optimised trials, glycemic control on MDI continued to improve after randomisation, thus minimising the difference between CSII and MDI. This highlights the notion that CSII in type 2 diabetes may be best targeted at those who have failed to achieve target HbA1c levels after best attempts with MDI, including dose titration, optimization of dietary counselling and physical activity\textsuperscript{18}. A likely mechanism for improved control on CSII is that the traditional large bolus injections of insulin required during MDI in type 2 diabetes are absorbed less well than the slow basal insulin infusion of CSII. In this respect, Parkner et al.\textsuperscript{19} found that the same dose of insulin given via the basal rate of CSII achieved better glycemic control and higher circulating insulin concentrations than when given as an injection of long-acting (glargine) insulin. Another reason for improved control on CSII may be the increased treatment satisfaction of insulin pump therapy in type 2 diabetes\textsuperscript{4} which may improve adherence to treatment compared to MDI. A lack of treatment adherence may also be more easily detected with CSII than MDI because of the computer download function of modern insulin pumps that allows survey of
events such as number of meal boluses given per day, and detection of basal-rate
suspends.

In our analysis, the improved glycemic control associated with CSII was not
associated with a greater weight gain in this group, and one may speculate that any
decrease in glycosuria and retained calories with better control (favoring weight gain)
was balanced by lower insulin dosages and therefore less anabolic insulin effect in
the insulin pump-treated participants.

Strengths and limitations of the study

The strengths of our study include the fact that we were able to obtain individual data
from investigators on all patients in all eligible RCTs and were thus able to explore
patient-level covariates as effect size modulators in a way that is not possible with
conventional summary meta-analysis. A further strength is that we used Bayesian
statistical methods including Markov chain Monte Carlo simulation that enables
highly complex, multi-parameter probability models to be analysed. Advantages and
further details and discussion of Bayesian methods in meta-analysis and evidence
synthesis are reviewed elsewhere.21,22

Our study also has some considerations in its interpretation. Firstly, the best MDI
regimen for type 2 diabetes is debateable (for example, the choice of long-acting
insulin that will offer the best glycemic control) and participants in the trials studied
used a variety of regimens. The extent to which participants underwent a structured
diabetes education programme varied between trials. A range of adjunctive agents
are currently being investigated for improving control in insulin-treated type 2
diabetes, including glucagon-like peptide (GLP)-1 agonists\textsuperscript{23,24}, dipeptidyl peptidase (DPP)-4 inhibitors and sodium-glucose cotransporter (SGLT)-2 inhibitors\textsuperscript{25}, though none are widely established in clinical practice. Possibly then, further improvement in glycemic control on MDI might be achieved in some patients by additional therapeutic approaches before switching to CSII, and this needs further study.

It is a limitation that we were unable to analyse data on hypoglycemia frequency in this meta-analysis because there was incomplete information on this for all trials but, in the largest RCT, the lower mean HbA\textsubscript{1c} in the CSII vs. MDI group was obtained without an increase in hypoglycemia\textsuperscript{9}. It should also be noted that there was a relatively small number of studies in the meta-analysis and two of the trials\textsuperscript{6,7} had small numbers of participants (40 and 17), whilst there was a large number of participants in one trial\textsuperscript{9}.

In the individual patient data meta-analysis, and as recommended by the Cochrane Collaboration\textsuperscript{17}, we analysed the first period only from crossover trials because we detected evidence of carry-over and because one trial had no washout period between periods\textsuperscript{7}, and because the lower baseline HbA\textsubscript{1c} for both treatments at the start of the second period might result in a lower effect size if baseline HbA\textsubscript{1c} was found to be a determinant of glycemic outcome.

\textit{Implications for clinical practice and further study}

The implication of our meta-analysis for clinical practice is that insulin pump therapy in type 2 diabetes is effective at lowering HbA\textsubscript{1c} but, as with type 1 diabetes, it should be targeted at those with worst glycemic control and highest insulin dose after best
attempts with MDI. In a previous meta-analysis of CSII vs. MDI in type 1 diabetes we also found that mean HbA1c is reduced with insulin pump therapy and that the greatest effect was in those with highest baseline HbA1c on MDI. In the present study, the effect size for HbA1c and insulin dose reduction was greatest in poorly controlled insulin resistant participants and therefore the cost-effectiveness will likely be best in these patients. We found that the difference in glycemic control is small below a baseline HbA1c of about 8% (64 mmol/mol), though treatment satisfaction may still be superior for CSII vs. MDI at this level of control and this topic needs investigation.

In spite of treatment targeting, there are likely to be many people with type 2 diabetes with continued poor control after best attempts with MDI who are thus candidates for a trial of CSII, and that will present notable logistic and economic issues. The technologically sophisticated and relatively costly infusion pumps traditionally used for type 1 diabetes, with flexible rate adjustments and meal-bolus calculators, which were used in the trials of type 2 diabetes analysed here, are probably not required for type 2 diabetes. There is emerging evidence that pumps with a limited number of fixed basal rate options and with simple meal bolusing will be adequate for most people with type 2 diabetes, indicating that smaller, cheaper and more cost-effective devices might eventually be used for this type of diabetes.

In conclusion, we have found that insulin pump therapy achieves better glycemic control than MDI in poorly controlled type 2 diabetes, with a substantial reduction in
insulin requirements and no change in weight. The best effect of CSII in type 2 diabetes is in those worst controlled and with highest insulin dose at baseline.

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**Duality of interests**

JCP has received speaker and/or consultancy fees from Medtronic, Roche, Insulet, Eli Lilly, Novo Nordisk and CeQur, not connected with the present work. YR has received research funds from Medtronic, Eli Lilly and Novo Nordisk, and consultancy and/or speaker fees from Medtronic, Abbott and Eli Lilly, not connected with the present work. AJS has nothing to declare.

**Author contributions**

JCP initiated and designed the study, collected individual patient data from trialists and other sources and wrote the first draft of the manuscript. JCP and YR performed the literature search, review and data extraction from published articles. AJS designed the statistical plan, performed the statistical analyses and contributed to the study design; all authors read, revised and approved the final version of the manuscript. JCP is the guarantor.

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References


**Table 1. Study characteristics of the five trials selected for meta-analysis.**

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<td>Lispro before meals, glargine once daily as basal</td>
<td>Actrapid or Humulin R before meals, isophane (Insulatard/Humulin N) as basal</td>
<td>Humalog Mix 50 (lispro/isophane) three times daily</td>
<td>Aspart, lispro or glulisine before meals, glargine or detemir as basal</td>
</tr>
<tr>
<td>Trial features</td>
<td>No run-in period</td>
<td>Older adults with type 2 diabetes Trial stopped early** Baseline imbalances (sex, insulin dose, weight)</td>
<td>Original data files lost, IPD analysis performed on original statistics files Did not record BMI All participants obese Several discrepancies between results in paper and IPD Discrepancies of labelling, and citing of tables and figures in paper</td>
<td>No missing data No wash-out period between periods 1 and 2 Baseline group imbalance for age Baseline HbA₁c for period 2 not used in published analysis Some evidence of carry-over</td>
<td>Patients had 2 mo run-in optimisation of control on MDI; only those with HbA₁c &gt;8% and insulin 0.7-1.8 U/kg after run-in were randomised Good agreement between paper and IPD results</td>
</tr>
</tbody>
</table>

*Not given; **interim safety analysis by data safety monitoring board recommended recruitment halt because HbA₁c difference between treatment groups considered unlikely to become significant if trial continued to planned duration; age, diabetes duration, HbA₁c and insulin dosages are means; BMI = body mass index; IPD = individual patient data meta-analysis; MDI = multiple daily insulin injections; RCT = randomised controlled trial. Data is that reported in the published papers.
Figure legends

Fig. 1. Flow diagram showing selection of studies for individual patient data meta-analysis of glycemic control during CSII and MDI in type 2 diabetes.

Fig. 2. The effect of baseline HbA1c (%) on HbA1c treatment difference (MDI vs. CSII) for all trials combined and for the OpT2mise trial, calculated from the best-fit models.

Fig. 3. Forest plots showing the results of a two-step approach individual patient data meta-analysis in trials comparing glycemic control, insulin requirements and body weight in people with type 2 diabetes treated by MDI or CSII. A: mean HbA1c (%) difference; B: mean difference in insulin dose (units/kg); and C: mean difference in body weight (kg). ES, effect size.