



Glycemic Control During Continuous Subcutaneous Insulin Infusion Versus Multiple Daily Insulin Injections in Type 2 Diabetes: Individual Patient Data Meta-analysis and Meta-regression of Randomized Controlled Trials

John C. Pickup,¹ Yves Reznik,²
and Alex J. Sutton³

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OBJECTIVE

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

RESEARCH DESIGN AND METHODS

Randomized controlled trials were selected comparing HbA_{1c} during CSII versus MDI in people with type 2 diabetes. Data sources included Cochrane database and Ovid Medline. We explored patient-level determinants of final HbA_{1c} level and insulin dose using Bayesian meta-regression models of individual patient data and summary effects using two-step meta-analysis. Hypoglycemia data were unavailable.

RESULTS

Five trials were identified, with 287 patients randomized to receive MDI and 303 to receive CSII. Baseline HbA_{1c} was the best determinant of final HbA_{1c}: HbA_{1c} difference (%) = 1.575 – (0.216 [95% credible interval 0.371–0.043] × baseline HbA_{1c}) for all trials, but with largest effect in the trial with prerandomization optimization of control. Baseline insulin dose was best predictor of final insulin dose: insulin dose difference (units/kg) = 0.1245 – (0.382 [0.510–0.254] × baseline insulin dose). Overall HbA_{1c} difference was –0.40% (–0.86 to 0.05 [–4.4 mmol/mol (–9.4 to 0.6)]). Overall insulin dose was reduced by –0.25 units/kg (–0.31 to –0.19) (26% reduction on CSII), and by –24.0 units/day (–30.6 to –17.5). Mean weight did not differ between treatments (0.08 kg [–0.33 to 0.48]).

CONCLUSIONS

CSII achieves better glycemic control than MDI in people with poorly controlled type 2 diabetes, with ~26% reduction in insulin requirements and no weight change. The best effect is in those worst controlled and with the highest insulin dose at baseline.

¹Division of Diabetes & Nutritional Sciences, King's College London, and Guy's Hospital, London, U.K.

²Department of Endocrinology, University of Caen Côte de Nacre Regional Hospital Center, Caen, France

³Department of Health Sciences, College of Medicine, Biological Sciences and Psychology, University of Leicester, Leicester, U.K.

Corresponding author: John C. Pickup, john.pickup@kcl.ac.uk.

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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 the best insulin injection regimens (multiple daily insulin injections [MDI]) and structured diabetes education (1,2). In many such patients, there can be a clinically valuable, sometimes substantial, reduction in HbA_{1c} level and all grades of hypoglycemia on switching to CSII.

The value of insulin pump therapy in people type 2 diabetes is less certain. Some national guidelines for insulin pump therapy (e.g., the U.K. National Institute for Health and Care Excellence Technology Appraisal of CSII) (2) do not recommend this treatment for type 2 diabetes. This is despite the fact that at least one-quarter of people with type 2 diabetes receiving insulin injections have very poor glycemic control, say an HbA_{1c} level $\geq 9\%$ (75 mmol/mol) (3), and new options for improving control are urgently needed. Present guidance on not using CSII in people with type 2 diabetes is largely based on the limited and variable evidence of the efficacy of insulin pump therapy in this type of diabetes in the relatively small-scale randomized controlled trials (RCTs) published over the last several years (4–7), where there is support both for and against the superiority of CSII versus MDI in reducing HbA_{1c}. A meta-analysis (8) of aggregate data from four trials of CSII versus MDI in type 2 diabetes (including one in newly diagnosed type 2 diabetes) reported no difference in HbA_{1c} levels between treatments.

A recent large-scale, multicenter RCT (9) reported that people with type 2 diabetes with poor glycemic control that persisted after a period of optimized MDI achieved a substantially better HbA_{1c} level while receiving treatment with CSII than while receiving 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 gain. 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 individuals with 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 the overall pooled effect size (reduction in HbA_{1c}), 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-making (10). The analysis approach that enables this most reliably and with most power is the use of individual patient data (11).

The purpose of this study, therefore, was to perform an individual patient data meta-analysis and meta-regression of RCTs that have compared glycemic control with CSII with MDI in patients with type 2 diabetes in order to test the hypothesis that CSII achieves significantly lower HbA_{1c} levels than MDI in identifiable patient groups. We aimed to model the determinants of final HbA_{1c} level and insulin requirements on these therapies, as this may identify the individuals with type 2 diabetes who are 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 (12,13). The protocol was predefined, and the meta-analysis registered with ClinicalTrials.gov (clinical trial reg. no. NCT02910141). All original trials selected for analysis operated under the supervision of an appropriate human ethics committee. The current analysis involved anonymized 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,” “CSII,” “MDI,” “insulin pump therapy,” and “randomized controlled trial”). We also searched literature cited in retrieved articles, previous meta-analyses, and lists of articles supplied by the manufacturers of insulin pumps.

Study Selection and Eligibility Criteria

Two independent reviewers (J.C.P. and Y.R.) decided on trial eligibility. We selected for inclusion RCTs comparing glycemic control during CSII and MDI in participants with type 2 diabetes who had been 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 6-point scale, according to the method of Jadad et al. (14) (based on the study being randomized, the randomization 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 dropouts) but with an additional item for reporting allocation concealment (the person randomizing is blinded to next treatment allocation). A score of ≥ 3 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 HbA_{1c} levels, insulin dose, weight, and BMI. We recontacted authors for further clarification when there were issues over the 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 articles.

The primary outcome was glycemic control at study completion, as measured by HbA_{1c} level. The secondary outcomes were insulin dose (total units per day and units per kilogram) and weight at study

completion. We did not analyze data on hypoglycemia because we could not obtain complete information on this for all trials; BMI at study completion was also analyzed 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 analyzed data from the first period only in the primary analysis because of evidence of a carryover effect and the absence of a washout period in one study.

We checked the 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 washout period, evidence of carryover), 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 (modeling the impact of potential effect size modifiers on the effect size) by creating a single, large data set from the individual patient data. In this way, we explored the determinants of final HbA_{1c} level and insulin dosage using a hierarchical random-effects regression model considering the covariates sex, age, study duration, diabetes duration, baseline HbA_{1c} level, 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 (15).

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 (16).

Deviance residuals were examined for extreme points and models recalculated to ensure robustness to the exclusion of the most influential points.

To explore overall mean effect sizes, we carried out a meta-analysis of individual patient data for HbA_{1c}, insulin dose, weight, and BMI using a two-step approach. Initially, we modeled 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 SE for each trial. Using a random-effects meta-analysis, we then combined these to calculate an overall effect size for the 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 analyzed was <10 (17); however, we quantified heterogeneity between trials by the *I*² statistic (the percentage of variability in effect due to heterogeneity rather than sample error), with >50% representing substantial heterogeneity and >75% representing 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 the 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 persons with type 2 diabetes (Fig. 1). We then excluded 22 reviews, surveys, cost-effectiveness analyses, or methods articles; 10 short-term studies; 3 trials of CSII in pregnancy; 5 trials in newly diagnosed diabetes; 6 trials where the comparator was not MDI; 13 trials that were not RCTs; and

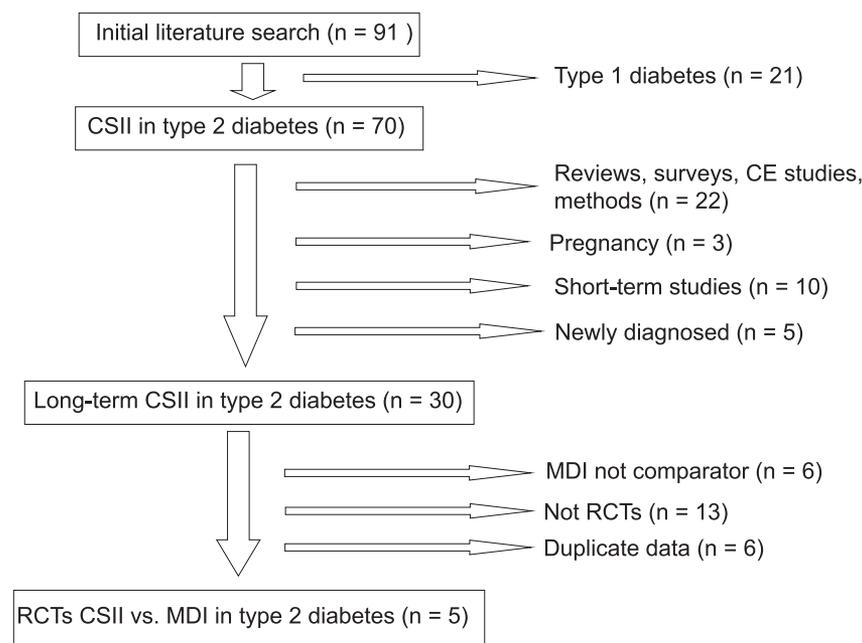


Figure 1—Flow diagram showing selection of studies for individual patient data meta-analysis of glycemic control during CSII and MDI in type 2 diabetes. CE, cost-effectiveness.

6 duplicate articles. Five RCTs (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 receive 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 multicenter) (4,5,9), and two studies were crossover RCTs (6,7). The study duration ranged from 3 to 24 months, and the dropout rate ranged from zero to 27.5%. The baseline HbA_{1c} level varied between trials from 8.1% (65 mmol/mol) to 9.6% (81 mmol/mol), and the baseline insulin dose ranged from 0.72 to 1.16 units/kg. Oral antihyperglycemic agents were either not used or discontinued in three trials (4,5,7) or prior use of metformin was continued (6,9) in the others. All five trials scored 3 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 the lack of allocation concealment or information on this.

Notable features of 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 (7); evidence of carryover effect in a crossover trial (7); baseline imbalances in age (7), sex (5), insulin dosages (5), and weight (5); missing BMI data in one trial (6); inclusion of only older participants in one study (5) or obese participants in another (6); and some discrepancies between the individual patient data and the published information (6). Most agreement between individual participant data (IPD) and reported data were found for the OpT2mise trial (9). Two studies used long-acting insulin analogs as the basal insulin with short-acting insulin analogs 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 (9), participants underwent a prerandomization run-in period designed to optimize glycemic control with MDI, and only those who still had poor control (HbA_{1c} 8–12% [64–108 mmol/mol]) and were

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

| | Raskin et al. (2003) (4) | Herman et al. (2005) (5) | Wainstein et al. (2005) (6) | Berthe et al. (2007) (7) | Reznik et al. (2014) (9) |
|---|--|---|---|--|---|
| No. randomized | 132 | 107 | 40 | 17 | 331 |
| No. analyzed | 115 | 98 | 29 | 17 | 331 |
| Study design | RCT, parallel | RCT, parallel | RCT, crossover | RCT, crossover | RCT, parallel |
| Dropout rate (%) | 12.9 | 8.4 | 27.3 | 0 | 13.8 |
| Age (years) | 55.6 | 66.4 | 56.8 | 55.2 | 56.0 |
| Diabetes duration (years) | 15.4 | 16.2 | * | 16.8 | 15.1 |
| Study duration (months) | 24 | 12 | 4.5 | 3 | 6 |
| Baseline HbA _{1c} (%) (mmol/mol) | 8.1 (65) | 8.3 (67) | 9.6 (81) | 9.0 (75) | 9.0 (75) |
| Baseline insulin (units/kg) | 0.72 | 0.77 | 1.16 | 1.04 | 1.10 |
| MDI regimen | Aspart before meals, isophane (Novolin N) once or twice daily as basal | Lispro before meals, glargine once daily as basal | Actrapid or Humulin R before meals, isophane (insulatard/Humulin N) as basal | Humalog Mix 50 (lispro/isophane) three times daily | Aspart, lispro, or glulisine before meals, glargine or detemir as basal |
| Trial features | No run-in period | Older adults with type 2 diabetes | Original data files lost, IPD analysis performed on original statistics files | No missing data | Patients had 2 month run-in optimization of control on MDI; only those with HbA _{1c} >8% and insulin 0.7–1.8 units/kg after run-in were randomized |
| | | Trial stopped early** | Did not record BMI | No washout period between periods 1 and 2 | Good agreement between article and IPD results |
| | | Baseline imbalances (sex, insulin dose, weight) | All participants obese | Baseline group imbalance for age | |
| | | | Several discrepancies between results in article and IPD | Baseline HbA _{1c} for period 2 not used in published analysis | |
| | | | Discrepancies of labeling and citing of tables and figures in article | Some evidence of carryover | |

Data are that reported in the published articles. *Not given. **Interim safety analysis by data safety monitoring board recommended recruitment halt because HbA_{1c} difference between treatment groups considered unlikely to become significant if trial continued to planned duration; age, diabetes duration, HbA_{1c}, and insulin dosages are means.

insulin resistant (0.7–1.8 units/kg) were then randomized to receive CSII or continue treatment with MDI.

Independent Determinants of HbA_{1c} Treatment Difference

Using the entire data set of 590 patients in the five trials, we explored the independent determinants of the HbA_{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_{1c} as a predictor of final HbA_{1c}; age, sex, baseline weight, and baseline insulin requirements did not affect outcome. For all trials combined, HbA_{1c} difference was best described by the equation:

$$\begin{aligned} \text{HbA}_{1c} \text{ difference, CSII vs. MDI (\%)} &= 1.575 \\ &- (0.216 [95\% \text{ credible interval } 0.371 \text{ to } 0.043] \\ &\times \text{baseline HbA}_{1c}) \end{aligned}$$

The effect of baseline HbA_{1c} on HbA_{1c} treatment difference varied between trials. Figure 2 illustrates the increase in treatment difference as baseline HbA_{1c} levels increase for all trials and for the Opt2mise trial, which were calculated from the best-fit models. The largest effect was in the Opt2mise trial (9), where there was prerandomization optimization of glycemic control on MDI; here, the regression equation for HbA_{1c} difference = 5.39 – (0.669 [0.326–1.011] × baseline HbA_{1c}). With an example baseline HbA_{1c} of 10% (86 mmol/mol), the effect size in this study is expected to be –1.3% (14 mmol/mol) compared with –0.59% (7 mmol/mol) for all participants combined. The effect size was minimal below a baseline HbA_{1c} of ~8.0% (64 mmol/mol) (Fig. 2).

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 versus MDI was:

$$\begin{aligned} \text{Insulin dose difference (units/day)} &= 0.148 - (0.238 [0.364 \text{ to } 0.111] \\ &\times \text{baseline insulin dose}) \end{aligned}$$

$$\begin{aligned} \text{And insulin dose difference (units/kg)} &= (0.382 [0.510 \text{ to } 0.254] \\ &\times \text{baseline insulin dose}) \end{aligned}$$

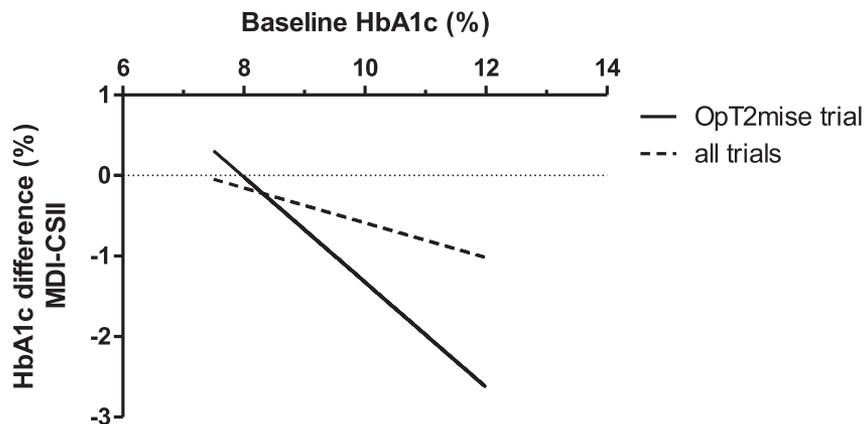


Figure 2—The effect of baseline HbA_{1c} (%) on HbA_{1c} treatment difference (MDI vs. CSII) for all trials combined and for the Opt2mise trial, calculated from the best-fit models.

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 HbA_{1c}, Insulin Dose, Weight, and BMI on MDI Versus CSII

Figure 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 HbA_{1c} 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 HbA_{1c} difference for the five trials combined was –0.40% (95% CI –0.86 to 0.05 [–4.4 mmol/mol (–9.4 to 0.6)]), favoring CSII. The *I*² statistic was 81%, indicating considerable heterogeneity between trials. Using a fixed-effect model, the overall HbA_{1c} difference was lower at –0.30% but with a narrower CI (–0.47 to –0.13 [–3.3 mmol/mol (–5.2 to –1.5)]), favoring CSII. Similar results for HbA_{1c} difference, favoring CSII, were obtained with an aggregate data meta-analysis of summary effect sizes extracted from the published articles rather than individual patient data: random-effects model, –0.45% (–0.81 to –0.09 [–5.0 mmol/mol (–8.9 to –1.0)]); and fixed-effect model, –0.47% (–0.65 to –0.29 [–5.2 mmol/mol (–7.1 to –3.2)]).

Figure 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 units/kg (–0.31 to –0.19) on CSII versus MDI (26% reduction of the baseline insulin requirements), with an *I*² statistic of 4.7%, indicating little heterogeneity between trials. The fixed-effect model gave an almost identical effect size (–0.26 units/kg [–0.31 to –0.20]). Meta-analysis (random-effects and fixed-effect models) showed that the total daily insulin dose was reduced by –24.0 units/day (–30.6 to –17.5) on CSII versus MDI (27% of baseline daily insulin) with an *I*² of 0%, indicating little heterogeneity (forest plot not shown).

A 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 kg [95% CI –0.33 to 0.48], *I*² 0%, random-effects and fixed-effect models) (Fig. 3C). BMI data were available for four trials, and a two-stage individual patient data meta-analysis with baseline adjustment also indicated no difference in the final mean BMI between treatment groups (0.00 kg/m² [–0.23 to 0.24]), random-effects and fixed-effect models (forest plot not shown).

CONCLUSIONS

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,

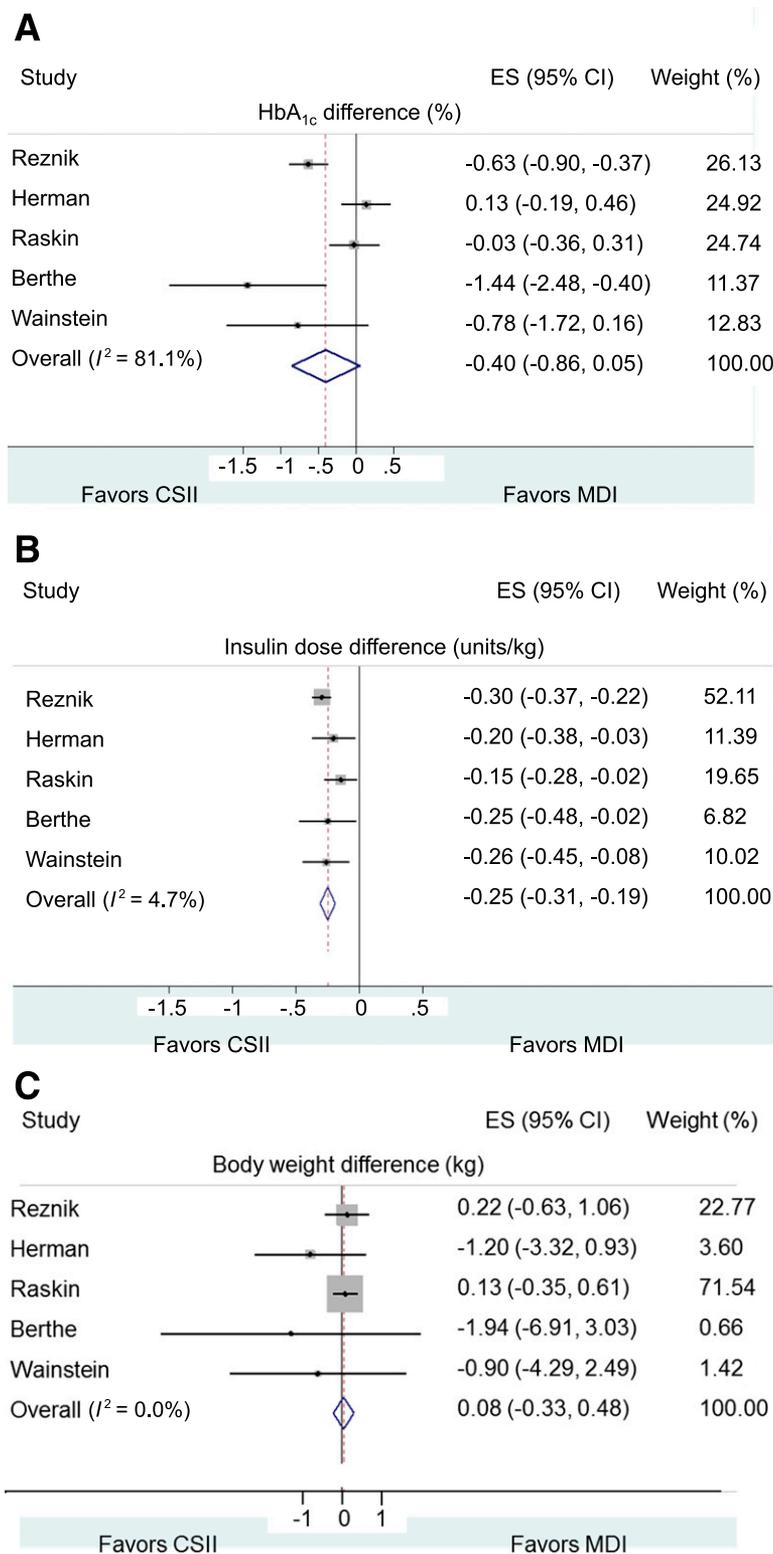


Figure 3—Forest plots showing the results of a two-step approach individual patient data meta-analysis in trials comparing glycemic control, insulin requirements, and body weight in people with type 2 diabetes treated by MDI or CSII. A: Mean HbA_{1c} (%) difference. B: Mean difference in insulin dose (units/kg). C: Mean difference in body weight (kg). ES, effect size.

where we explored a wide range of potential effect modulators, we found that the HbA_{1c} treatment difference was

dependent on prerandomization HbA_{1c} level with MDI, increasing as baseline HbA_{1c} level 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 HbA_{1c} level of 10% (86 mmol/mol). We also found that the reduction in insulin requirements on switching to CSII was dependent on the 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 with 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 HbA_{1c} level for the meta-analysis of all trials was -0.40% (4 mmol/mol), for a mean HbA_{1c} baseline level 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 the meta-analysis model and individual patient data versus 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 HbA_{1c} effect size between trials ($I^2 = 81\%$) was likely due to the wide variation in baseline HbA_{1c}, 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 HbA_{1c} difference varied markedly between trials and was greatest for the study (9) in which patients underwent prerandomization optimization of control and only those who continued to have poor control were entered into the trial. For this study, the mean HbA_{1c} difference from individual patient data analysis was 0.63% (6 mmol/mol) and the expected effect at 10% (86 mmol/mol) baseline HbA_{1c} was 1.3% (14 mmol/mol). One may speculate that the greater treatment difference for this trial was due to the fact that, in the nonoptimized trials, glycemic control with MDI continued to improve after randomization, thus minimizing 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 HbA_{1c} levels after best attempts with MDI, including dose titration,

optimization of dietary counseling, and physical activity (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. (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 with CSII may be the increased treatment satisfaction of insulin pump therapy in persons with type 2 diabetes (4), which may improve adherence to treatment compared with 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 the survey of events such as the number of meal boluses given per day and the 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 a conventional summary meta-analysis. A further strength is that we used Bayesian statistical methods including Markov chain Monte Carlo simulation that enables highly complex, multiparameter probability models to be analyzed. Advantages and further details and discussion of Bayesian methods in meta-analysis and evidence synthesis are reviewed elsewhere (20,21).

Our study also has some considerations in its interpretation. First, the best MDI regimen for type 2 diabetes is debatable (22) (e.g., 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 program 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 1 agonists (23,24), dipeptidyl peptidase 4 inhibitors and sodium-glucose cotransporter 2 inhibitors (25), although none are widely established in clinical practice. Possibly then, further improvement in glycemic control with 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 analyze 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_{1c} level in the CSII versus MDI group was obtained without an increase in hypoglycemia (9). It should also be noted that there was a relatively small number of studies in the meta-analysis and two of the trials (6,7) had small numbers of participants ($n = 17$ and 40), while there was a large number of participants in one trial ($n = 331$) (9).

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

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_{1c} levels, but, as with type 1 diabetes, it should be targeted at those persons with worst glycemic control and highest insulin dose after best attempts with MDI (26). In a previous meta-analysis of treatment with CSII versus MDI in persons with type 1 diabetes (27), we also found that the

mean HbA_{1c} level is reduced with insulin pump therapy and that the greatest effect was in those with the highest baseline HbA_{1c} level with MDI. In the current study, the effect size for HbA_{1c} and insulin dose reduction was greatest in poorly controlled insulin-resistant participants, and therefore the cost-effectiveness will likely be best in these patients (28). We found that the difference in glycemic control is small below a baseline HbA_{1c} level of $\sim 8\%$ (64 mmol/mol), although treatment satisfaction may still be superior for CSII versus MDI at this level of control (4,9); this topic needs investigation.

Despite 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 analyzed 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 (18,29,30), 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 patients with the worst control and with the highest insulin dose at baseline.

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References

- Pickup JC. Insulin-pump therapy for type 1 diabetes mellitus. *N Engl J Med* 2012;366:1616–1624
- National Institute for Health and Clinical Excellence. *Continuous Subcutaneous Insulin Infusion for the Treatment of Diabetes Mellitus. Technology Appraisal Guidance 151 (Review of Technology Appraisal Guidance 57)*. London, England, NICE, 2008
- Dodd AH, Colby MS, Boye KS, Fahlman C, Kim S, Briefel RR. Treatment approach and HbA1c control among US adults with type 2 diabetes: NHANES 1999–2004. *Curr Med Res Opin* 2009;25:1605–1613
- Raskin P, Bode BW, Marks JB, et al. Continuous subcutaneous insulin infusion and multiple daily injection therapy are equally effective in type 2 diabetes: a randomized, parallel-group, 24-week study. *Diabetes Care* 2003;26:2598–2603
- Herman WH, Ilag LL, Johnson SL, et al. A clinical trial of continuous subcutaneous insulin infusion versus multiple daily injections in older adults with type 2 diabetes. *Diabetes Care* 2005;28:1568–1573
- Wainstein J, Metzger M, Boaz M, et al. Insulin pump therapy vs. multiple daily injections in obese type 2 diabetic patients. *Diabet Med* 2005;22:1037–1046
- Berthe E, Lireux B, Coffin C, et al. Effectiveness of intensive insulin therapy by multiple daily injections and continuous subcutaneous infusion: a comparison study in type 2 diabetes with conventional insulin regimen failure. *Horm Metab Res* 2007;39:224–229
- Monami M, Lamanna C, Marchionni N, Mannucci E. Continuous subcutaneous insulin infusion versus multiple daily insulin injections in type 2 diabetes: a meta-analysis. *Exp Clin Endocrinol Diabetes* 2009;117:220–222
- Reznik Y, Cohen O, Aronson R, et al.; OpT2mise Study Group. Insulin pump treatment compared with multiple daily injections for treatment of type 2 diabetes (OpT2mise): a randomised open-label controlled trial. *Lancet* 2014;384:1265–1272
- Pickup JC. The evidence base for diabetes technology: appropriate and inappropriate meta-analysis. *J Diabetes Sci Technol* 2013;7:1567–1574
- Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *BMJ* 2010;340:c221
- Tierney JF, Vale C, Riley R, et al. Individual participant data (IPD) meta-analyses of randomised controlled trials: guidance on their use. *PLoS Med* 2015;12:e1001855
- Stewart LA, Clarke M, Rovers M, et al.; PRISMA-IPD Development Group. Preferred reporting items for a systematic review and meta-analysis of individual participant data. The PRISMA-IPD Statement. *JAMA* 2015;313:1657–1665
- Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1–12
- Spiegelhalter DJ, Best NG, Carline BP, et al. Bayesian measures of model complexity and fit. *J R Stat Soc Series B Stat Methodol* 2002;64:583–639
- Riley RD, Steyerberg EW. Meta-analysis of a binary outcome using individual participant data and aggregate data. *Res Synth Methods* 2010;1:2–19
- Higgins JPT, Green S (eds). *Cochrane Handbook for Systematic Reviews of Interventions*, version 5.1.0 [Internet], 2011. Available from <http://handbook.cochrane.org>. Accessed 11 July 2016
- Pickup JC. Diabetes: insulin pump therapy for type 2 diabetes mellitus. *Nat Rev Endocrinol* 2014;10:647–649
- Parkner T, Laursen T, Vestergaard ET, et al. Insulin and glucose profiles during continuous subcutaneous insulin infusion compared with injection of a long-acting insulin in type 2 diabetes. *Diabet Med* 2008;25:585–591
- Sutton AJ, Abrams KR. Bayesian methods in meta-analysis and evidence synthesis. *Stat Methods Med Res* 2001;10:277–303
- Welton NJ, Sutton AJ, Cooper NJ, Abrams KR, Ades AE. Meta-analysis using Bayesian methods. In *Evidence Synthesis for Decision Making in Healthcare*. Chichester, John Wiley & Sons Ltd, 2012, p. 76–93
- Mosenzon O, Raz I. Intensification of insulin therapy for type 2 diabetic patients in primary care: basal-bolus regimen versus premix insulin analogs: when and for whom? *Diabetes Care* 2013;36(Suppl. 2):S212–S218
- Vanderheiden A, Harrison L, Warshauer J, Li X, Adams-Huet B, Lingvay I. Effect of adding liraglutide vs placebo to a high-dose insulin regimen in patients with type 2 diabetes. A randomized clinical trial. *JAMA Intern Med* 2016;176:939–947
- Lind M, Hirsch IB, Tuomilehto J, et al. Liraglutide in people treated for type 2 diabetes with multiple daily insulin injections: randomised clinical trial (MDI Liraglutide trial). *BMJ* 2015;351:h5364
- Gururaj Setty S, Crasto W, Jarvis J, Khunti K, Davies MJ. New insulins and newer insulin regimens: a review of their role in improving glycaemic control in patients with diabetes. *Postgrad Med J* 2016;92:152–164
- Schütz-Fuhrmann I, Castañeda J, Reznik Y, et al. Factors affecting the benefit of insulin dose intensification in people with type 2 diabetes: an analysis from the OpT2mise randomized trial. *Diabet Med* 2017;34:291–292
- Pickup JC, Sutton AJ. Severe hypoglycaemia and glycaemic control in type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. *Diabet Med* 2008;25:765–774
- Roze S, Duteil E, Smith-Palmer J, et al. Cost-effectiveness of continuous subcutaneous insulin infusion in people with type 2 diabetes in the Netherlands. *J Med Econ* 2016;19:742–749
- Edelman SV, Bode BW, Bailey TS, et al. Insulin pump therapy in patients with type 2 diabetes safely improved glycemic control using a simple insulin dosing regimen. *Diabetes Technol Ther* 2010;12:627–633
- King AB, Clark D, Wolfe GS. The number of basal rates required to achieve near-normal basal glucose control in pump-treated type 2 diabetes. *Diabetes Technol Ther* 2012;14:900–903