CONTINUOUS SUBCUTANEOUS INSULIN INFUSION (CSII) VERSUS MULTIPLE INSULIN INJECTIONS FOR TYPE 1 DIABETES MELLITUS

Misso Marie L, Egberts Kristine J, Page Matthew, O'Connor Denise, Shaw Jonathan

Cochrane Database of Systematic Reviews, Issue 12, 2010 (Status in this issue: NEW)

Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

DOI: 10.1002/14651858.CD005103.pub1

A B S T R A C T

Background
Type 1 diabetes is a metabolic disorder resulting from a defect in insulin secretion. Onset of type 1 diabetes mellitus may occur at any age and it is one of the most common chronic diseases of childhood and adolescence. Since there are no interventions known to prevent onset, it is vital that effective treatment regimes are available. Glycaemic control is maintained by replacement of insulin and may be in the form of 'conventional' insulin therapy (multiple injections per day) or continuous subcutaneous insulin infusion (CSII).

Objective
To assess the effects of CSII compared to multiple insulin injections (MI) in people with type 1 diabetes mellitus.

Criteria for considering studies for this review
Studies were obtained from electronic searches of The Cochrane Library, MEDLINE, EMBASE and CINAHL.

Selection criteria
Studies were included if they were randomised controlled trials comparing CSII with three or more insulin injections per day (MI) in people with type 1 diabetes mellitus.

Data collection and analysis
Two authors independently assessed risk of bias and extracted characteristics of included studies. Authors contacted study investigators to obtain missing information. Generic inverse variance meta-analyses using a random-effects model were performed.

Main results
Twenty three studies randomised 976 participants with type 1 diabetes to either intervention. There was a statistically significant difference in glycosylated haemoglobin A1c (HbA1c) favouring CSII (weighted mean difference -0.3% (95% confidence interval -0.1 to -0.4). There were no obvious differences between the interventions for non-severe hypoglycaemia, but severe hypoglycaemia appeared to be reduced in those using CSII. Quality of life measures suggest that CSII is preferred over MI. No significant difference was found for weight. Adverse events were not well reported, no information is available on mortality, morbidity and costs.

Authors' conclusions
There is some evidence to suggest that CSII may be better than MI for glycaemic control in people with type 1 diabetes mellitus. Non-severe hypoglycaemic events do not appear to be reduced with CSII. There is insufficient evidence regarding adverse events, mortality, morbidity and costs.

PLAIN LANGUAGE SUMMARY

Type 1 diabetes results from a defect in insulin secretion, leading to elevated levels of plasma sugar or glucose and disturbances in carbohydrate, fat and protein metabolism. Complications may effect the eyes, kidneys, nerves and the cardiovascular system. Type 1 diabetes may occur at any age and it is one of the most common chronic diseases of childhood and adolescence. Type 1 diabetes impacts heavily on the lifestyle of the individual as well as their families. Since there is no
cure or prevention for type 1 diabetes, life-long insulin replacement and monitoring of blood glucose levels are required. It is vital that effective insulin therapy regimes are available for optimal management and to minimise blood glucose fluctuation (known as too low or too high blood sugar levels - hypoglycaemia or hyperglycaemia).

Insulin therapy may be in the form of 'conventional' therapy of multiple (typically four) injections per day or continuous subcutaneous insulin infusion. Continuous subcutaneous insulin infusion involves attachment (via catheter on the outside of the body) to an insulin pump that is programmed to deliver insulin to match the individual's needs, and doses are activated by the individual to cover meals and correct blood glucose fluctuation. Here we explore whether continuous subcutaneous insulin infusion is better than three or more insulin injections per day for good management of type 1 diabetes.

Twenty three studies randomised 976 participants with type 1 diabetes to either continuous subcutaneous insulin infusion or multiple injections. Seven of the 23 studies were performed in participants under 18 years of age and the remainder were performed in adults. Study duration ranged from six days to four years. The body of evidence suggests that continuous subcutaneous insulin infusion may be better than multiple injections for glycaemic control in people with type 1 diabetes; continuous subcutaneous insulin infusion appears to provide no benefit for reducing non-severe hypoglycaemic events. Future studies need to consider the short and long term adverse effects, mortality, morbidity and costs of these interventions.

BACKGROUND

OBJECTIVES

To assess the effects of continuous subcutaneous insulin infusion (CSII) compared to multiple insulin injection for type 1 diabetes mellitus.

METHODS OF THE REVIEW

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All published and unpublished randomised and quasi-randomised controlled trials (blind and open, parallel and cross-over) designed to compare people with type 1 diabetes taking insulin in the form of either continuous subcutaneous insulin infusion (CSII) or multiple insulin injections (MI) (three or more insulin injections per day). There were no time or language restrictions.

Types of participants

Males and females with type 1 diabetes of any age taking insulin treatment were considered in this review. The diagnostic criteria for type 1 diabetes mellitus should have been described in the study. To remain consistent with changes in classification and diagnostic criteria through the years, diagnosis of type 1 diabetes status was based upon the diagnostic criteria valid at the time of beginning the study. Acceptable diagnostic criteria included those described by the National Diabetes Data Group standards (NDDG 1979), the World Health Organisation (WHO 1980), the American Diabetes Association (ADA 1997) or by the author of the study (in these cases, attempts were made to contact study investigators to determine specific criteria used to diagnose type 1 diabetes).

Types of intervention

Insulin preparation and dose of insulin varied depending on the study, therefore all insulin preparations and doses were accepted.

Types of outcome measures

Primary outcomes

glycaemic control (glycosylated haemoglobin A1c (HbA1c), daily mean blood glucose, fasting blood glucose or postprandial blood glucose);

number of overall, severe and non-severe hypoglycaemic episodes;

quality of life (ideally measured using a validated instrument).

Secondary outcomes

weight;

insulin requirement to maintain glycaemic control;

number and severity of adverse events (e.g. ketoacidosis, local infections);

diabetes late complications;

mortality;

costs.
Timing of outcome assessment

Short (less than or equal to one month), medium (more than one month and less than six months) and longer term (equal to or more than six months) outcome data were included in the review.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

Search methods for identification of studies

Electronic searches
We searched the following sources for the identification of studies up to 20 July 2009:
The Cochrane Library;
MEDLINE;
EMBASE;
CINAHL.
For detailed search strategies please see under Appendix 1.
We also planned to search databases of ongoing studies: Current Controlled Trials (www.controlled-trials.com - with links to other databases of ongoing trials) and the National Research Register (www.update-software.com/National/nrr-frame.html). This will be performed in future updates of this review.

Searching other resources
We handsearched abstracts from international diabetes meetings from 2002, 2003 and 2004 (including IDF, EASD, ADA).

DATA COLLECTION AND ANALYSIS

Data collection and analysis

Selection of studies
To determine the studies to be assessed further, two independent authors (MM, KE) scanned the titles, abstract sections and keywords of every record retrieved, where available. Full articles were retrieved for further assessment if the information provided was insufficient to decide eligibility or if information provided suggested that the study: 1. included people with type 1 diabetes mellitus; 2. compared CSII and MI (three or more insulin injections per day); 3. assessed one or more relevant clinical outcome measure(s); 4. was randomised. There were no disagreements about selection of studies between authors.

Dealing with duplicate publications
In the case of duplicate publications and companion papers of primary studies, we tried to maximise yield of information by simultaneous evaluation of all available data. In cases of doubt, the original publication (usually but not always the oldest version) obtained priority.

Data extraction and management
For studies that met the selection criteria, two out of three possible authors (MM, KE and MP) independently extracted relevant population and intervention characteristics using a standard data extraction template (for details see Characteristics of included studies and, Appendix 2, Appendix 8). The authors reached agreement about the data extracted through discussion.

Assessment of risk of bias in included studies
Two authors assessed risk of bias of each study independently (for details see Characteristics of included studies). The authors explored the influence of individual risk of bias criteria in a sensitivity analysis (see 'Sensitivity analysis'). The authors reached agreement about risk of bias assessments through discussion. Potential for bias was considered using the risk of bias table which addresses the following domains:

- sequence generation;
- allocation concealment;
- blinding of participants, personnel and outcome assessors;
- incomplete outcome data;
- selective outcome reporting;
- other sources of bias.

Each question was answered 'Yes', 'No' or 'Unclear', where 'Yes' suggests a low risk of bias, 'No' suggests a high risk of bias and 'Unclear' suggests doubt about the level of bias in that domain.

Summary assessments for risk of bias were made for each outcome across studies (see 'Effects of interventions') using the

**Measures of treatment effect**

Review Manager 5.0 software was used for data analysis. Results are expressed as mean differences, calculated from end of treatment values, with 95% confidence intervals (CI) for continuous outcomes. There are no dichotomous outcomes in this review. Pooled results were meta-analysed using the generic inverse variance method with a random-effects model. Statistical significance was set at a P value less than 0.05 for primary and secondary outcome measures.

**Dealing with missing data**

Relevant missing information about study design or results were sought from the study investigators, where feasible. Evaluation of important numerical data such as screened, eligible and randomised participants as well as intention-to-treat and per-protocol population is presented. Attrition rates like drop-outs, losses to follow-up and withdrawn study participants were investigated. Issues of last-observation-carried-forward were critically appraised and compared to specification of primary outcome parameters and power calculation.

Six cross-over studies were not adequately analysed, and did not report correlations between baseline and end of study data, thereby ignoring within-person variation. We reanalysed the data from these studies assuming different correlation coefficients (0.3, 0.5, 0.7, 0.9) and have discussed the results based on the most conservative approach, assuming a correlation coefficient of 0.3. The data from these studies were also reanalysed assuming the largest standard deviation of the differences, derived from the cross-over studies that were adequately analysed. The results from these analyses can be found in Appendix 3.

**Assessment of heterogeneity**

Results of clinically and statistically homogenous studies were pooled to provide estimates of the efficacy of the interventions. Clinical homogeneity was satisfied when participants, interventions, outcome measures and timing of outcome measurement were considered to be similar. For studies that were clinically heterogeneous or presented insufficient information for pooling, a descriptive analysis was performed. Statistical homogeneity was assessed using the I² statistic where I² values under 50% indicated acceptable homogeneity (low heterogeneity) (Higgins 2003).

**Assessment of reporting biases**

Funnel plots were planned to be used in exploratory data analyses to assess for the potential existence of small study bias. There are a number of explanations for the asymmetry of a funnel plot, including true heterogeneity of effect with respect to study size, poor methodological design of small studies and publication bias (Sterne 2001). Thus, the findings using this exploratory data tool were interpreted with caution.

**Data synthesis**

Data were summarised statistically where available, sufficiently similar, and of sufficient quality. Generic inverse variance meta-analyses were performed using a random-effects model for the included continuous outcomes. Effect estimates are expressed as mean difference and 95% confidence interval (CI). Where data could not be combined, narrative tables of results are presented.

**Subgroup analysis and investigation of heterogeneity**

Subgroup analyses were conducted according to age of study participants and study duration, since these factors may cause variations in outcomes.

We also conducted post-hoc analyses where we explored studies that included less than 20 participants in subgroup analyses for each outcome (Appendix 4).

**Sensitivity analysis**

Sensitivity analyses were performed for every element on the risk of bias table by excluding studies that had a high risk of bias. Other elements that were employed in sensitivity analyses included:

- excluding very long or large studies to establish how much they dominate the results;
- excluding studies using the following filters: diagnostic criteria, date of publication, language of publication, source of funding (industry versus other), country.

**METHODOLOGICAL QUALITY**

**RESULTS**

**Results**

**Description of studies**

See: Characteristics of included studies; Characteristics of excluded studies.

**Results of the search**
The search conducted up until 20 July 2009 for all databases, identified 4343 records, from these, 201 full text papers were retrieved for further examination. After screening the full text of the selected papers, 23 studies finally met the inclusion criteria. An adapted PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow-chart of study selection is attached (Liberati 2009), see .

Assessment of inter-rater agreement

Two authors reviewed the studies, and were in agreement on those to be fully assessed. From these, studies eligible for inclusion in the review were identified. Both authors agreed on the final papers chosen for assessment and on the risk of bias assessment of the studies. There was complete agreement (100%) on the final papers chosen for further assessment.

Included studies

Designs of included studies

Twenty-three randomised controlled trials (RCTs) meeting the inclusion criteria of this review were identified. Details of these studies are shown in the 'Characteristics of included studies' table. Eleven of the 23 included studies were of parallel design, the other 12 had a cross-over design (Bak 1987 and Husted 1989; Bruttomesso 2008; Chiasson 1984 and 1985; Cohen 2003; Hanaire-Broutin 2000; Hirsch 2005; Home 1982; Hoogma 2005; Nathan 1982; Saurebey 1988; Schmitz 1989; Weintrob 2004). Six of the cross-over studies were analysed using adequate statistical methodology to account for within-person variation. Six cross-over studies were not adequately analysed, and ignored within-person variation, so we reanalysed the data from these studies as described above in 'Dealing with missing data'. The results from these analyses can be found in Appendix 3.

Seventy-eight percent (18) of the studies had an initial run-in phase lasting from two days to six months in order to achieve stable metabolic conditions. Of the 12 studies with a cross-over design, six reported a wash-out period before switching to the other treatment.

The single centre design was the dominating setting (70%) but multiple centre studies were also common (30%). Studies were published from 1982 to 2008. Sixty-one per cent (14 studies) could be clearly identified as partly or entirely industry sponsored and in two studies, funding was not specified. Diagnostic criteria for entry into the study was specified in eight of the studies.

Participants of included studies

In total, 976 people with type 1 diabetes took part in the 23 randomised controlled studies.

Seven of the 23 studies were performed in participants under 18 years of age (Cohen 2003; Doyle 2004; Meschi 1982; Nuboer 2008; Pozzilli 2003; Skogsberg 2008; Weintrob 2004).

All but one study investigated the effects in both genders. Botta 1986 only included pregnant females (n=10). It is important to note that other studies included in this review have excluded pregnant females, suggesting clinical heterogeneity among the studies in this review.

Interventions of included studies

All included studies compared continuous subcutaneous insulin infusion (CSII) and multiple insulin injections (MI) (three or more insulin injections per day). The duration of the intervention ranged from six days to four years. It is important to note that the study with an intervention period of six days (Meschi 1982) should not be considered a real life setting and so was explored in sensitivity analysis but the effect estimate was largely unaltered. Most studies tried to achieve a comparable insulin dose regimen throughout the investigation period, and treating physicians, together with the participants, tried to achieve optimisation of therapy, usually by means of flexible insulin dosage in order to achieve metabolic targets of heterogeneously defined adequate blood glucose control.

Excluded studies

In total, 178 studies were excluded after careful evaluation of the full publication. Reasons for exclusion of studies are given in the 'Characteristics of excluded studies' table. The main reasons for exclusion were inappropriate interventions, less than three injections per day in the MI group and non-randomised study design.

Risk of bias in included studies

For details of risk of bias in the included studies, see the 'Characteristics of included studies' tables, and . For each outcome in 'Effects of interventions', a summary assessment for the risk of bias is provided.

Allocation

All studies were described as randomised, however only eight studies (Bruttomesso 2008; DeVries 2002; Doyle 2004; Hoogma 2005; Lepore 2003; Oslo Study 1985 to 1992; Pozzilli 2003; Tsui 2001) adequately described the method of randomisation and only seven studies (Bruttomesso 2008; DeVries 2002; Hanaire-Broutin 2000; Hoogma 2005; Nosadini 1988; Nuboer 2008; Tsui 2001) adequately described allocation concealment.

Blinding

Given the nature of the interventions, participant blinding was not appropriate. Investigator blinding and outcome assessor blinding was not described in any of the studies, however it is not expected that this would introduce major bias since the majority of outcomes are not subjective.
Incomplete outcome data

Three studies (Doyle 2004; Hoogma 2005; Tsui 2001) reported the use of intention-to-treat analysis. Most studies described losses to follow-up or drop-outs, if any occurred in the study.

For details about the number of screened and randomised participants see .

Selective reporting

Selective reporting was unclear in all except one study, where this was apparent (Hirsch 2005). For the remaining studies it was not possible to track if all pre-specified outcomes were reported and if they were reported in the pre-specified way.

Other potential sources of bias

The risk for other bias is unclear in all of the included studies.

Effects of interventions

Baseline characteristics

For details of baseline characteristics see Appendix 2.

Primary outcomes

Glycosylated haemoglobin A1c (HbA1c) (%)

Of the 23 studies included, 20 studies were included in this analysis. Fifteen of these (Bruttomesso 2008; Chiasson 1984 & 1985; DeVries 2002; Doyle 2004; Home 1982; Lepore 2003; Meschi 1982; Nathan 1982; Nosadini 1988; Nuboer 2008; Oslo Study 1985 to 1992; Pozzilli 2003; Schmitz 1989; Skogsberg 2008; Tsui 2001) were parallel or cross-over studies using appropriate statistical methodology; and five (Cohen 2003; Hanaire-Broutin 2000; Hoogma 2005; Saurbrey 1988; Weintrob 2004) were cross-over studies with inadequate statistical methodology (i.e. ignoring within-person variation). Therefore, we reanalysed the data from these studies assuming different correlation coefficients (0.3, 0.5, 0.7, 0.9). The data from these studies were also reanalysed assuming the largest standard deviation of the differences derived from the cross-over studies with adequate statistical methodology. Three studies were excluded because they did not report HbA1c.

Assuming a conservative correlation of 0.3, and using generic inverse variance with a random-effects model, the mean difference of HbA1c was estimated to be -0.3% (95% CI -0.4 to -0.1) in favour of CSII compared with MI. The test of heterogeneity gave an I² statistic of 50% and the test for overall effect gave a P value of 0.001 (Analysis 1.2). The effect estimates, overall treatment effects and heterogeneity assuming other correlations and the largest standard deviation of the differences are presented in Appendix 3.

Risk of bias summary assessment

Most information is from studies at low or unclear risk of bias. Detailed risk of bias assessments can be found in 'Characteristics of included studies' tables and and .

Subgroup analyses

Subgroup analyses for all outcomes were performed assuming a conservative correlation of 0.3, using generic inverse variance with a random-effects model. The effect estimates, overall treatment effects and heterogeneity assuming other correlations and the largest standard deviation of the differences are presented in Appendix 3.

HbA1c - age of study participants

In studies that included participants less than 18 years of age (Cohen 2003; Doyle 2004; Meschi 1982; Nuboer 2008; Pozzilli 2003; Skogsberg 2008; Weintrob 2004) the mean difference of HbA1c was estimated to be -0.2% (95% CI -0.4 to -0.03) in favour of CSII compared with MI. The test of heterogeneity gave an I² statistic of 20%. The test for overall effect gave a P value of 0.02 (Analysis 1.2). In studies that included participants more than 18 years of age (Bruttomesso 2008; DeVries 2002; Hanaire-Broutin 2000; Home 1982; Hoogma 2005; Lepore 2003; Nathan 1982; Nosadini 1988; Oslo Study 1985 to 1992; Saurbrey 1988; Schmitz 1989; Tsui 2001) the mean difference of HbA1c was estimated to be -0.3% (95% CI -0.5 to -0.1) in favour of CSII compared with MI. The test of heterogeneity gave an I² statistic of 57%. The test for overall effect gave a P value of 0.21 (Analysis 1.3).

HbA1c subgroup analysis - study duration

There was only one short term study (up to one month), which is insufficient for subgroup analysis (Meschi 1982).

In medium term studies (from one to six months) (Bruttomesso 2008; Chiasson 1984 & 1985; Cohen 2003; DeVries 2002; Doyle 2004; Hanaire-Broutin 2000; Home 1982; Hoogma 2005; Nathan 1982; Saurbrey 1988; Schmitz 1989; Weintrob 2004), the mean difference of HbA1c was estimated to be -0.3% (95% CI -0.5 to -0.1) in favour of CSII compared with MI. The test of heterogeneity gave an I² statistic of 57%. The test for overall effect gave a P value of 0.002 (Analysis 1.2).

In long term studies (more than six months) (Lepore 2003; Nosadini 1988; Nuboer 2008; Oslo Study 1985 to 1992; Pozzilli 2003; Skogsberg 2008; Tsui 2001), the mean difference of HbA1c was estimated to be -0.2% (95% CI -0.4 to 0.1) in favour of CSII compared with MI. The test of heterogeneity gave an I² statistic of 57%. The test for overall effect gave a P value of 0.21 (Analysis 1.3).
Small study bias

Assuming a conservative correlation of 0.3, using generic inverse variance with a random-effects model for studies that included less than 20 participants (Chiasm 1984 and 1985; Cohen 2003; Home 1982; Meschi 1982; Nathan 1982; Schmitz 1989) the mean difference of HbA1c was estimated to be -0.7% (95% CI -1.6 to 0.1) in favour of CSII compared with MI. The test of heterogeneity gave an I2 statistic of 63%. The test for overall effect gave a P value of 0.09 (Analysis 1.4). The effect estimates, overall treatment effects and heterogeneity are presented in Appendix 3.

Daily mean blood glucose (mg/dl)

Of 23 studies included, 13 were included in this analysis. Nine of these (Bak 1987 and Husted 1989; Bruttomesso 2008; DeVries 2002; Home 1982; Meschi 1982; Nathan 1982; Nosadini 1988; Oslo Study 1985 to 1992; Schmitz 1989) were parallel or cross-over studies using appropriate statistical methodology; and four (Hanaire-Broutin 2000; Hoogma 2005; Saurbrey 1988; Weintrob 2004) were cross-over studies where appropriate statistical methodology was not used (i.e. ignoring within-person variation). Therefore, we reanalysed the data as described in the results section for HbA1c. Ten studies were excluded because they did not report daily mean blood glucose.

Assuming a conservative correlation of 0.3, and using generic inverse variance with a random-effects model, a pooled mean difference of daily mean blood glucose could not be reliably estimated due to substantial heterogeneity with an I2 statistic of 94%. The effect estimates, overall treatment effects and heterogeneity assuming other correlations and the largest standard deviation of the differences are presented in Appendix 3.

Risk of bias summary assessment

Most information is from studies at low or unclear risk of bias. Detailed risk of bias assessments can be found in "Characteristics of included studies" tables and and.

Subgroup analyses

Subgroup analyses were performed and presented as described in the HbA1c subgroup analysis section.

Daily mean blood glucose - age of study participants

In studies that included participants less than 18 years of age (Bak 1987 and Husted 1989; Meschi 1982; Weintrob 2004) the mean difference of daily mean blood glucose was estimated to be -4 mg/dl (95% CI -14 to 7) in favour of CSII compared with MI. The test of heterogeneity gave an I2 statistic of 0%. The test for overall effect gave a P value of 0.5 (Analysis 1.6). In studies that included participants more than 18 years of age (Bruttomesso 2008; DeVries 2002; Hanaire-Broutin 2000; Home 1982; Hoogma 2005; Nathan 1982; Nosadini 1988; Oslo Study 1985 to 1992; Schmitz 1989) the mean difference of daily mean blood glucose was estimated to be -14 mg/dl (95% CI -28 to -9) in favour of CSII compared with MI. The test of heterogeneity gave an I2 statistic of 98%. Therefore, the pooled effect estimate is not reliable (Analysis 1.8).

Daily mean blood glucose - study duration

There was only one short term study (up to one month), which is insufficient for subgroup analysis (Meschi 1982). In medium term studies (from one to six months) (Bak 1987 and Husted 1989; Bruttomesso 2008; DeVries 2002; Hanaire-Broutin 2000; Home 1982; Hoogma 2005; Nathan 1982; Saurbrey 1988; Schmitz 1989; Weintrob 2004) the mean difference of daily mean blood glucose was estimated to be -14 mg/dl (95% CI -23 to -5) in favour of CSII compared with MI. The test of heterogeneity gave an I2 statistic of 95%. Therefore, the pooled effect estimate is not reliable (Analysis 1.7).

In long term studies (more than six months) (Nosadini 1988; Oslo Study 1985 to 1992), the mean difference of daily mean blood glucose was estimated to be -21 mg/dl (95% CI -29 to -13) in favour of CSII compared with MI. The test of heterogeneity gave an I2 statistic of 0%. The test for overall effect gave a P value less than 0.00001 (Analysis 1.7).

Small study bias

Assuming a conservative correlation of 0.3, using generic inverse variance with a random effects model for studies that included less than 20 participants (Home 1982; Meschi 1982; Nathan 1982; Schmitz 1989) the mean difference of daily mean blood glucose was estimated to be -29 mg/dl (95% CI -51 to -7) in favour of CSII compared with MI. The test of heterogeneity gave an I2 statistic of 58%. The test for overall effect gave a P value of 0.009 (Analysis 1.8). The effect estimates, overall treatment effects and heterogeneity are presented in Appendix 3.

Fasting blood glucose (mg/dl)

Of 23 studies included, 11 were included in this analysis. Eight of these (Botta 1986; Bruttomesso 2008; Chiasson 1984 and 1985; DeVries 2002; Doyle 2004; Home 1982; Lepore 2003; Oslo Study 1985 to 1992) were parallel or cross-over studies using appropriate statistical methodology; and three (Hirsch 2005; Hoogma 2005; Weintrob 2004) were cross-over studies where appropriate statistical methodology was not used (i.e. ignoring within-person variation). Therefore, we reanalysed the data as described in the results section for HbA1c. Twelve studies were excluded because they did not report fasting blood glucose.

Assuming a conservative correlation of 0.3, and using generic inverse variance with a random-effects model, the mean difference of fasting blood glucose was estimated to be -14 mg/dl (95% CI -24 to -4) in favour of CSII compared with MI. The test of heterogeneity gave an I2 statistic of 71%. Therefore, the pooled effect estimate is not reliable (Figure 6). The effect estimates, overall treatment effects and heterogeneity assuming other correlations and the largest standard deviation of the differences are presented in Appendix 3.
Risk of bias summary assessment

The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results. Detailed risk of bias assessments can be found in 'Characteristics of included studies.' tables and.

Subgroup analyses

Subgroup analyses were performed and presented as described in the HbA1c subgroup analysis section.

Fasting blood glucose - age of study participants

In studies that included participants less than 18 years of age (Chiasson 1984 and 1985; Doyle 2004; Weintrob 2004) the mean difference of fasting blood glucose was estimated to be -8 mg/dl (95% CI -24 to 9) in favour of CSII compared with MI. The test of heterogeneity gave an I² statistic of 0%. The test for overall effect gave a P value of 0.35 (Analysis 1.10). In studies that included participants more than 18 years of age (Botta 1986; Bruttomesso 2008; DeVries 2002; Hirsch 2005; Home 1982; Hoogma 2005; Lepore 2003; Oslo Study 1985 to 1992) the mean difference of fasting blood glucose was estimated to be -16 mg/dl (95% CI -29 to -3) in favour of CSII compared with MI. The test of heterogeneity gave an I² statistic of 79%. Therefore, the pooled effect estimate is not reliable (Analysis 1.10).

Fasting blood glucose - study duration

There was only one short term study (up to one month), which is insufficient for subgroup analysis (Hirsch 2005).

In medium term studies (from one to six months) (Botta 1986; Bruttomesso 2008; Chiasson 1984 and 1985; DeVries 2002; Doyle 2004; Home 1982; Hoogma 2005; Weintrob 2004), the mean difference of fasting blood glucose was estimated to be -8 mg/dl (95% CI -19 to 2) in favour of CSII compared with MI. The test of heterogeneity gave an I² statistic of 63%. Therefore, the pooled effect estimate is not reliable (Analysis 1.11).

In long term studies (more than six months) (Lepore 2003; Oslo Study 1985 to 1992), the mean difference of fasting blood glucose was estimated to be -37 mg/dl (95% CI -73 to -1) in favour of CSII compared with MI. The test of heterogeneity gave an I² statistic of 61%. Therefore, the pooled effect estimate is not reliable (Analysis 1.11).

Small study bias

Assuming a conservative correlation of 0.3, using generic inverse variance with a random-effects model for studies that included less than 20 participants (Botta 1986; Chiasson 1984 & 1985; Home 1982) the mean difference of fasting blood glucose was estimated to be -8 mg/dl (95% CI -19 to 2) in favour of CSII compared with MI. The test of heterogeneity gave an I² statistic of 63%. Therefore, the pooled effect estimate is not reliable (Analysis 1.11). The effect estimates, overall treatment effects and heterogeneity are presented in Appendix 3.

Post prandial blood glucose (mg/dl)

Of 23 studies included, five were included in this analysis. Three of these (Botta 1986; Chiasson 1984 & 1985; DeVries 2002) were parallel or cross-over studies using appropriate statistical methodology; and two (Hirsch 2005; Weintrob 2004) were cross-over studies where appropriate statistical methodology was not used (ie. ignoring within-person variation). Therefore, we reanalysed the data as described in the results section for HbA1c. Eighteen studies were excluded because they did not report post prandial blood glucose.

Assuming a conservative correlation of 0.3, and using generic inverse variance with a random-effects model, the mean difference of post prandial blood glucose was estimated to be -4 mg/dl (95% CI -11 to 2) in favour of CSII compared with MI. The test of heterogeneity gave an I² statistic of 37%. The test for overall effect gave a P value of 0.18 (.). The effect estimates, overall treatment effects and heterogeneity assuming other correlations and the largest standard deviation of the differences are presented in Appendix 3.

Risk of bias summary assessment

The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results. Detailed risk of bias assessments can be found in 'Characteristics of included studies.' tables and.

Subgroup analyses

Subgroup analyses were performed and presented as described in the HbA1c subgroup analysis section.

Post prandial blood glucose - age of study participants

In studies that included participants less than 18 years of age (Chiasson 1984 and 1985; Weintrob 2004) the mean difference of post prandial blood glucose was estimated to be -3 mg/dl (95% CI -12 to 6) in favour of CSII compared with MI. The test of heterogeneity gave an I² statistic of 0%. The test for overall effect gave a P value of 0.49 (Analysis 1.14). In studies that included participants more than 18 years of age (Botta 1986, DeVries 2002, Hirsch 2005) the mean difference of post prandial blood glucose was estimated to be -8 mg/dl (95% CI -23 to 8) in favour of CSII compared with MI. The test of heterogeneity gave an I² statistic of 68%. Therefore, the pooled effect estimate is not reliable (Analysis 1.14).

Post prandial blood glucose - study duration

There was only one short term study (up to one month), which is insufficient for subgroup analysis (Hirsch 2005).
In medium term studies (from one to six months) (Botta 1986; Chiasson 1984 and 1985; DeVries 2002; Weintrob 2004), the mean difference of post prandial blood glucose was estimated to be -2 mg/dl (95% CI -4 to 0.3) in favour of CSII compared with MI. The test of heterogeneity gave an I2 statistic of 0%. The test for overall effect gave a P value of 0.08 (Analysis 1.15). There were no long term studies (more than six months) for subgroup analysis (Analysis 1.15).

Small study bias
Assuming a conservative correlation of 0.3, using generic inverse variance with a random-effects model for studies that included less than 20 participants (Botta 1986; Chiasson 1984 & 1985) the mean difference of post prandial blood glucose was estimated to be 1 mg/dl (95% CI -15 to 16) in favour of CSII compared with MI. The test of heterogeneity gave an I2 statistic of 0%. The test for overall effect gave a P value of 0.93 (Analysis 1.16). The effect estimates, overall treatment effects and heterogeneity are presented in Appendix 3.

Hypoglycaemic events

Non-severe hypoglycaemic events
Non-severe hypoglycaemia was often defined as a blood glucose level lower than 70 mg/dl. Some studies did not provide a definition. The 17 studies (Bak 1987 and Husted 1989; Bruttomesso 2008; Chiasson 1984 and 1985; Cohen 2003; DeVries 2002; Hanaire-Brouitin 2000; Hirsch 2005; Home 1982; Hoogma 2005; Meschi 1982; Nathan 1982; Nosadini 1988; Oslo Study 1985 to 1992; Pozzilli 2003; Schmitz 1989; Saurbrey 1988; Tsui 2001; Weintrob 2004) that reported non-severe hypoglycaemia used different scales and it was not appropriate to conduct a meta-analysis, however the data indicate that there is no relevant benefit of one intervention over the other for reducing non-severe hypoglycaemic events. A descriptive table of results can be found in Appendix 5.

Risk of bias summary assessment
Most information is from studies at low or unclear risk of bias. Detailed risk of bias assessments can be found in 'Characteristics of included studies' tables and and .

Severe hypoglycaemic events
Severe hypoglycaemia was often defined as requiring assistance from another person for recovery or resulting in coma or seizure. Some studies did not provide a definition. The 15 studies (Bruttomesso 2008; Cohen 2003; DeVries 2002; Doyle 2004; Hanaire-Brouitin 2000; Hirsch 2005; Hoogma 2005; Lepore 2003; Nosadini 1988; Nuboer 2008; Oslo Study 1985 to 1992; Schmitz 1989; Skogsgberg 2008; Tsui 2001; Weintrob 2004) that reported severe hypoglycaemia used different scales and it was not appropriate to conduct a meta-analysis, however the data indicate that there is no relevant benefit of one intervention over the other for reducing the incidence of severe hypoglycaemic events. A descriptive table of results can be found in Appendix 6.

Risk of bias summary assessment
Most information is from studies at low or unclear risk of bias. Detailed risk of bias assessments can be found in 'Characteristics of included studies' tables and and .

Quality of life
Quality of life was measured using different instruments by 15 studies (Bak 1987 and Husted 1989; Bruttomesso 2008; Chiasson 1984 and 1985; Cohen 2003; DeVries 2002; Doyle 2004; Hanaire-Brouitin 2000; Home 1982; Hoogma 2005; Nathan 1982; Nuboer 2008; Saurbrey 1988; Schmitz 1989; Skogsgberg 2008; Tsui 2001), none of which have reported minimal clinically important differences. Four studies (Bruttomesso 2008; Cohen 2003; DeVries 2002; Skogsgberg 2008) used the validated diabetes treatment satisfaction questionnaire (DTSQ) of which two of these included participants less than 18 years of age. In all four studies the CSII groups had higher scores, representing better treatment satisfaction, than the MI group. Of the two studies (Cohen 2003; Doyle 2004) that used the validated diabetes quality of life for youth scale (DQOLY), one study in adults (Cohen 2003) reported a higher score, representing better quality of life, in the CSII group than the MI group. The other study (Doyle 2004), including participants less than 18 years of age, did not report scores but noted that a difference between the groups was not found. Two studies (Hoogma 2005; Tsui 2001) used the validated diabetes quality of life scale (DQoL) and found that the MI group scored lower, representing better quality of life, than the CSII group. Use of the SF-12 questionnaire (Hoogma 2005), SF36 general health perceptions scale (DeVries 2002) and the paediatric quality of life inventory (PedsQL) (Nuboer 2008) (all validated) revealed that CSII was favoured over MI for perception of better mental health, perception of better general health and better quality of life, respectively. It is difficult to determine which treatment is better when independent questionnaires (Bak 1987 and Husted 1989; Chiasson 1984 and 1985; Hanaire-Brouitin 2000; Home 1982; Hoogma 2005; Nathan 1982; Saurbrey 1988; Schmitz 1989) were used to measure satisfaction, acceptability, preferred treatment and reaction to treatment. It was not appropriate to conduct a meta-analysis, however the data suggest that the majority of participants were more satisfied with CSII than MI. A descriptive table of results can be found in Appendix 7.

Risk of bias summary assessment
Most information is from studies at low or unclear risk of bias. Detailed risk of bias assessments can be found in 'Characteristics of included studies' tables and and .

Secondary outcomes

Weight (kg)
Of 23 studies included, eight were included in this analysis. Six of these (Bak 1987 and Husted 1989; DeVries 2002; Home 1982; Lepore 2003; Oslo Study 1985 to 1992; Schmitz 1989) were parallel or cross-over studies using appropriate statistical methodology; and two (Hanaire-Broutin 2000; Hoogma 2005) were cross-over studies where appropriate statistical methodology was not used (i.e. ignoring within-person variation). Therefore, we reanalysed the data as described in the results section for HbA1c. Fifteen studies were excluded because they did not report weight.

Assuming a conservative correlation of 0.3, and using generic inverse variance with a random-effects model, the mean difference of weight was estimated to be -0.4 kg (95% CI -2 to 1.3). The test of heterogeneity gave an I² statistic of 0%. The test for overall effect gave a P value of 0.65. The effect estimates, overall treatment effects and heterogeneity assuming other correlations and the largest standard deviation of the differences are presented in Appendix 3.

Risk of bias summary assessment

Most information is from studies at low or unclear risk of bias. Detailed risk of bias assessments can be found in 'Characteristics of included studies' tables and and .

Subgroup analyses

Subgroup analyses were performed and presented as described in the HbA1c subgroup analysis section.

Weight - age of study participants

There were no studies that included participants less than 18 years of age, therefore it was not possible to conduct subgroup analyses.

Weight - study duration

There were no short term studies (up to one month) for subgroup analysis (Analysis 1.21).

In medium term studies (from one to six months) (Bak 1987 and Husted 1989; DeVries 2002; Hanaire-Broutin 2000; Home 1982; Hoogma 2005; Schmitz 1989), the mean difference of weight was estimated to be -0.2 kg (95% CI -1.2 to 1.5) in favour of CSII compared with MI. The test of heterogeneity gave an I² statistic of 0%. The test for overall effect gave a P value of 0.78 (Analysis 1.21).

In long term studies (more than six months) (Lepore 2003; Oslo Study 1985 to 1992), the mean difference of weight was estimated to be -1.6 kg (95% CI -7.7 to 4.5) in favour of CSII compared with MI. The test of heterogeneity gave an I² statistic of 27%. The test for overall effect gave a P value of 0.61 (Analysis 1.22). The effect estimates, overall treatment effects and heterogeneity are presented in Appendix 3.

Small study bias

Assuming a conservative correlation of 0.3, using generic inverse variance with a random-effects model in studies that included less than 20 participants (Botta 1986; Chiasson 1984 and 1985; Home 1982), the mean difference of weight was estimated to be -13.7 kg (95% CI -50.4 to 23) in favour of CSII compared with MI. The test of heterogeneity gave an I² value of 79%. Therefore, the pooled effect estimate is not reliable (Analysis 1.22). The effect estimates, overall treatment effects and heterogeneity are presented in Appendix 3.

Daily insulin requirement

Studies presented daily insulin requirement as either U or as U/kg, therefore data were analysed separately according to the unit used by the study investigators.

Daily insulin requirement (units - U)

Of 23 studies included, nine were included in this analysis. Seven of these (Bak 1987 and Husted 1989; Botta 1986; Chiasson 1984 and 1985; DeVries 2002; Home 1982; Lepore 2003; Nathan 1982) were parallel or cross-over studies using appropriate statistical methodology; and two (Hanaire-Broutin 2000; Hirsch 2005) were cross-over studies where appropriate statistical methodology was not used (i.e. ignoring within-person variation). Therefore, we reanalysed the data as described in the results section for HbA1c. Fourteen studies were excluded because they did not report daily insulin requirement (U).

Assuming a conservative correlation of 0.3, and using generic inverse variance with a random-effects model, the mean difference of daily insulin requirement (U) was estimated to be -7 U (95% CI -11 to -3) in favour of CSII compared with MI. The test of heterogeneity gave an I² statistic of 32%. The test for overall effect gave a P value of 0.0003. The effect estimates, overall treatment effects and heterogeneity assuming other correlations and the largest standard deviation of the differences are presented in Appendix 3.

Risk of bias summary assessment

The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results. Detailed risk of bias assessments can be found in 'Characteristics of included studies' tables and and .

Subgroup analyses

Subgroup analyses were performed and presented as described in the HbA1c subgroup analysis section.

Daily insulin requirement (U) - age of study participants
There was only one study that included participants less than 18 years of age, which is insufficient for subgroup analysis (Chiasson 1984 and 1985). In studies that included participants more than 18 years of age (Bak 1987 and Husted 1989; Botta 1986; DeVries 2002; Hanaire-Broutin 2000; Hirsch 2005; Home 1982; Lepore 2003; Nathan 1982) the mean difference of daily insulin requirement (U) was estimated to be -7 U (95% CI -11 to -3) in favour of CSII compared with MI. The test of heterogeneity gave an I2 statistic of 31%. The test for overall effect gave a P value of 0.14 (Analysis 1.29).

**Daily insulin requirement (U) - study duration**

There was only one short term study (up to one month), which is insufficient for subgroup analysis (Hirsch 2005).

In medium term studies (from one to six months) (Bak 1987 and Husted 1989; Botta 1986; Chiasson 1984 and 1985; DeVries 2002; Hanaire-Broutin 2000; Home 1982; Nathan 1982), the mean difference of daily insulin requirement (U) was estimated to be -9 U (95% CI -14 to -3) in favour of CSII compared with MI. The test of heterogeneity gave an I2 statistic of 37%. The test for overall effect gave a P value of 0.001 (Analysis 1.24).

There was only one long term study (more than six months), which is insufficient for subgroup analysis (Lepore 2003).

**Small study bias**

Assuming a conservative correlation of 0.3, using generic inverse variance with a random-effects model in studies that included participants less than 18 years of age (Chasson 1984 and 1985; Cohen 2003; Doyle 2004; Meschi 1982; Naboer 2008; Pozzilli 2003; Schutz 1989; Skogberg 2008; Tsui 2001) were parallel or cross-over studies using appropriate statistical methodology; and two (Hoogma 2005; Saurbrey 1988) were cross-over studies where appropriate statistical methodology was not used (i.e. ignoring within-person variation). Therefore, we reanalysed the data as described in the results section for HbA1c. Ten studies were excluded because they did not report daily insulin requirement (U/kg).

Assuming a conservative correlation of 0.3, and using generic inverse variance with a random-effects model, a pooled mean difference of daily mean blood glucose could not be reliably estimated due to substantial heterogeneity with an I2 statistic of 94%. The effect estimates, overall treatment effects and heterogeneity assuming other correlations and the largest standard deviation of the differences are presented in Appendix 3.

**Risk of bias summary assessment**

Most information is from studies at low or unclear risk of bias. Detailed risk of bias assessments can be found in 'Characteristics of included studies.' tables and and.

**Subgroup analyses**

Subgroup analyses were performed and presented as described in the HbA1c subgroup analysis section.

**Daily insulin requirement (U/kg) - age of study participants**

In studies that included participants less than 18 years of age (Cohen 2003; Doyle 2004; Meschi 1982; Naboer 2008; Pozzilli 2003; Schutz 1989; Skogberg 2008) the mean difference of daily insulin requirement (U/kg) was estimated to be -0.16 U/kg (95% CI -0.31 to -0.01) in favour of CSII compared with MI. The test of heterogeneity gave an I2 statistic of 84%. Therefore, the pooled effect estimate is not reliable (Analysis 1.28). In studies that included participants more than 18 years of age (Bruttomesso 2008; Hoogma 2005; Oslo Study 1985 to 1992; Saurbrey 1988; Schmitz 1989; Tsui 2001) the mean difference of daily insulin requirement (U/kg) was estimated to be -0.08 U/kg (95% CI -0.15 to -0.01) in favour of CSII compared with MI. The test of heterogeneity gave an I2 value of 94%. Therefore, the pooled effect estimate is not reliable (Analysis 1.28).

**Daily insulin requirement (U/kg) - study duration**

There was only one short term study (up to one month), which is insufficient for subgroup analysis (Meschi 1982).

In medium term studies (from one to six months) (Bruttomesso 2008; Cohen 2003; Doyle 2004; Hoogma 2005; Saurbrey 1988; Schmitz 1989), the mean difference of daily insulin requirement (U/kg) was estimated to be -0.12 U/kg (95% CI -0.21 to -0.03) in favour of CSII compared with MI. The test of heterogeneity gave an I2 statistic of 94%. Therefore, the pooled effect estimate is not reliable (Analysis 1.29).

In long term studies (more than six months) (Naboer 2008; Oslo Study 1985 to 1992; Pozzilli 2003; Skogberg 2008; Tsui 2001), the mean difference of daily insulin requirement (U/kg) was estimated to be -0.14 U/kg (95% CI -0.32 to 0.04) in favour of CSII compared with MI. The test of heterogeneity gave an I2 statistic of 95%. Therefore, the pooled effect estimate is not reliable (Analysis 1.29).

**Small study bias**

Assuming a conservative correlation of 0.3, using generic inverse variance with a random-effects model in studies that included less than 20 participants (Cohen 2003; Meschi 1982; Schmitz 1989) the mean difference of daily insulin requirement (U/kg) was estimated to be -0.04 U/kg (95% CI -0.13 to 0.05) in favour of CSII compared with MI. The test of heterogeneity gave an I2 statistic of 37%. The test for overall effect gave a P value of 0.001 (Analysis 1.24).
I2 statistic of 0%. The test for overall effect gave a P value of 0.41 (Analysis 1.30). The effect estimates, overall treatment effects and heterogeneity are presented in Appendix 3.

Adverse events

Information about adverse events was not well reported. Twenty-one studies reported that there were no deaths, one study did not address this outcome and one study (Nosadini 1988) reported a death in the CSII group, further details were not provided. Among eight studies that did not describe the nature of adverse events, there were more than 19 events in the CSII group and more than 10 in the MI group. Ketoacidosis was reported in two studies (Cohen 2003; DeVries 2002), where there was one event of ketoacidosis in the CSII group of each study and one event of ketoacidosis in the MI group of DeVries et al. Hoogma et al (Hoogma 2005) reported 21 injection and infusion site injuries reactions in the CSII group and Weintrob et al (Weintrob 2004) reported 12 minor infusion site infections, 16 blockages and 42 dislodgments. All but one of the studies (Hoogma 2005) either did not report serious adverse events or reported that there were no serious adverse events. Hoogma et al reported 33 serious adverse events in the CSII group and 58 in the MI group. Three studies reported drop-outs as a result of adverse events. One of these (DeVries 2002) reported one femur fracture but did not report which group the participant was in. A second study (Doyle 2004) reported one case of dehydration and ketosis in the MI group and the third study (Home 1982) reported one undescribed event. In total, five CSII participants and six MI participants were hospitalised (Bak 1987 and Husted 1989; Doyle 2004; Nuboer 2008; Saurbrey 1988) and one CSII participant received out-patient treatment (Home 1982). For details of adverse events see Appendix 8.

Diabetes late complications

None of the studies reported on morbidity.

Mortality

None of the studies reported on mortality.

Costs

Costs were not addressed in any of the included studies.

Heterogeneity

In the HbA1c analysis comparing CSII and MI, heterogeneity was reflected by an I2 statistic of 50%. After elimination of Nathan 1982, the study with high risk of bias, heterogeneity was significantly reduced to 34% without altering the direction of effect.

Considerable heterogeneity was found and investigated for daily mean blood glucose, fasting blood glucose and daily insulin required (measured in U/kg), but could not be explained by subgroup analyses.

Statistical heterogeneity was either not present or low in the meta-analyses of the outcomes post-prandial blood glucose, daily insulin requirement (measured in units) and weight.

Subgroup analyses

Subgroup analyses are described in detail for each outcome in 'Effects of interventions'.

Sensitivity analyses

Sensitivity analyses were performed for every element on the risk of bias table by excluding studies that had a high risk of bias. Other sensitivity analyses included:

excluding very long or large studies to establish how much they dominate the results;

excluding studies using the following filters: diagnostic criteria, date of publication, language of publication, source of funding (industry versus other), country.

Values were noted (data not shown) and found to be similar to overall effect estimates.

Assessment of reporting biases

Funnel plot symmetry was not found in any of the meta-analysis.

DISCUSSION

Discussion

Summary of main results

Twenty-three studies randomised 976 participants with type 1 diabetes to either continuous subcutaneous insulin infusion (CSII) or multiple insulin injections (MI) (three or more insulin injections per day). Study duration ranged from six days to four years. Upon meta-analysis of 20 studies that reported glycosylated haemoglobin A1c (HbA1c) (overall unclear risk of bias), there was a statistically significant difference in favour of CSII, the mean difference was -0.3% (95% confidence interval (CI) -0.4 to -0.1, P = 0.001). Without altering the direction of effect, heterogeneity was reduced from an I2 statistic of 50% to 34%
upon removal of Nathan 1982, a study with high risk of bias. Subgroup analyses for age did not significantly alter the effect estimate, however subgroup analyses for study duration showed that medium term studies (12 studies, one to six months) had a higher effect estimate (-0.3% (95% CI -0.5 to -0.1)) and long term studies (seven studies, more than six months) had a lower non-significant effect estimate (-0.2% (95% CI -0.4 to 0.1)).

Thirteen studies were meta-analysed for daily blood glucose (overall unclear risk of bias). Due to considerable heterogeneity (I2 statistic of 94%) a reliable pooled effect estimate could not be established. Subgroup analysis for age demonstrated that the effect estimate and heterogeneity were lower and non-significant among the two studies with participants under 18 years of age (-4 mg/dl (95% CI -14 to 7), I2 statistic of 0%). Subgroup analysis for study duration showed that combination of the two long term studies resulted in a higher effect estimate (-21 mg/dl (95% CI -29 to -13), I2 statistic of 0%).

Eleven studies reported fasting blood glucose (overall high risk of bias). Due to considerable heterogeneity (I2 statistic of 71%) a reliable pooled effect estimate could not be established. Subgroup analysis for age demonstrated that the effect estimate and heterogeneity were lower among the three studies with participants under 18 years of age (-8 mg/dl (95% CI -24 to 9), I2 statistic of 0%).

Meta-analysis of the five studies that reported post-prandial blood glucose (overall high risk of bias) demonstrated a non-significant difference between the interventions with an effect estimate of -4 mg/dl (95% CI -11 to 2, I2 statistic of 37%) in favour of CSII compared with MI. Subgroup analyses for age and study duration did not substantially alter the effect estimates or heterogeneity.

Non-severe hypoglycaemia, often defined in the studies as a blood glucose level lower than 70 mg/dl, was reported in 17 studies (overall unclear risk of bias) using different scales. It was not appropriate to conduct a meta-analysis, however the data suggested that there is no relevant benefit of one intervention over the other for reducing non-severe hypoglycaemic events.

Severe hypoglycaemia, often defined in the studies as requiring assistance from another person for recovery or resulting in coma or seizure, was reported in 15 studies (overall unclear risk of bias) using different scales. Despite it not being appropriate to conduct a meta-analysis, the data suggest that CSII may be better than MI for reducing the incidence of severe hypoglycaemic events.

Quality of life was reported in 15 studies (overall unclear risk of bias) using different scales. It was not appropriate to conduct a meta-analysis, however many of the studies used validated questionnaires and found that CSII was preferred over MI for treatment satisfaction, quality of life and perception of better general and mental health. Often, participants randomised to CSII preferred to continue with CSII at study completion rather than return to MI.

There was a statistically significant decrease in daily insulin requirement measured in units (U) by nine studies (overall high risk of bias). The mean difference was -7 U (95% CI -11 to -3, P = 0.0003, I2 statistic of 32%). There was an insufficient number of studies for subgroup analyses for age and study duration. When measured in units per kilogram (U/kg), the daily insulin requirement mean difference found among 12 studies (overall unclear risk of bias) could not be reliably pooled due to considerable heterogeneity (I2 statistic of 94%).

No significant difference was found for weight (-0.4 kg (95% CI -2 to 1.3), I2 statistic of 0%) among eight studies (overall unclear risk of bias). Subgroup analysis for age did not significantly alter the effect estimate, however subgroup analysis for study duration showed that long term studies (seven studies) had a higher non-significant effect estimate -1.6 kg (95% CI -7.7 to 4.5, I2 statistic of 27%).

Information about adverse events other than non-severe and severe hypoglycaemic events was not well reported. Most common other adverse events included ketoacidosis, dehydration and injection or infusion site complications. There were high numbers of injection or infusion site complications, suggesting that training on the use and care of these interventions is vital.

None of the studies reported on mortality, morbidity or costs.

Exploration of small study bias revealed that the effect estimates for HbA1c, daily mean blood glucose, daily insulin requirement (U/kg) and weight were higher than the effect estimates for these outcomes when all studies were included, suggesting that small study bias may be present for these outcomes.

Funnel plot asymmetry was found in all meta-analyses. It should be noted that there are a number of explanations for the asymmetry of a funnel plot, including true heterogeneity of effect with respect to study size, poor methodological design of small studies and publication bias (Sterne 2001).
Using the approach described in 'Assessment of risk of bias in included studies', the body of evidence was classified as high, unclear or low risk of bias for each outcome. Risk of bias was unclear for most of the evidence, but for studies reporting the outcomes daily insulin requirement (U), fasting blood glucose and post-prandial blood glucose, the body of evidence was at high risk of bias.

**Potential biases in the review process**

This review consists of published data only. In future, updates will attempt to identify non-published studies.

The selection criteria specified that MI required three or more injections per day, therefore many studies were excluded because their definition of MI was two or more injections per day. We are uncertain whether these studies would have altered the effect estimates seen in this review.

Many different scales and units were used to report measures of non-severe and severe hypoglycaemia and quality of life. There were insufficient studies to conduct meta-analyses for each of the scales and units, and as a result, our interpretation of the overall effects of the interventions on these outcomes is subjective and open to bias.

**Agreements and disagreements with other studies or reviews**

A systematic review by Pickup et al. (Pickup 2002), a health-technology assessment (HTA) report (HTA 2004) and a NICE report (NICE 2008) were in agreement with the findings of this review.

The systematic review by Pickup et al. found that glycosylated haemoglobin A1c and mean blood glucose concentration were lower in people receiving CSII compared with those receiving MI. Blood glucose concentrations were less variable during CSII and the insulin dose required to maintain glycaemic control was reduced with CSII.

The HTA report found that the quality of included studies was generally poor. When compared with at least three injections per day (MI), CSII resulted in a modest but important improvement in glycosylated haemoglobin A1c and a short term reduction in insulin dose in adults with type 1 diabetes. Overall hypoglycaemic events did not differ between CSII and MI. The authors of the HTA review were unable to identify any economic evaluations comparing these two interventions, however it is estimated that the additional cost associated with using CSII over MI varies from £1091 (1208 EURO, 11/2009 exchange rate) to £1680 (1860 EURO, 11/2009 exchange rate), per annum (including the cost of the pump and consumables).

The NICE report focused on recommendations for when to use CSII. The report included non-randomised and randomised studies and found improvement in HbA1c and reduction in insulin dose. No difference was found for hypoglycaemic events and weight between the two interventions but patient preference slightly favoured CSII.

**Authors' Conclusions**

**Implications for practice**

Both continuous subcutaneous insulin infusion (CSII) and multiple insulin injections (MI) are currently used in practice. There may be benefit in using CSII over MI for improving glycaemic control and improving health-related quality of life in people with type 1 diabetes. Non-severe hypoglycaemic events do not appear to be influenced differently by either intervention.

It is important to note that there is insufficient evidence regarding adverse events, diabetes late complications, mortality and cost – all essential considerations in deciding which treatment to administer in practice. Until evidence is available for these outcomes we are unable to make a recommendation about whether either intervention is superior over the other in the management of glycaemic control in people with type 1 diabetes.

**Implications for research**

Long term, large scale and methodologically rigorous studies are required to determine the effect of CSII and MI on outcomes such as hypoglycaemia, mortality, diabetes late complications and other adverse effects, using validated scales. Cost effectiveness data are also required to determine superiority between the two interventions.

**Acknowledgements**

The authors would like to acknowledge several colleagues for their assistance in preparation of this review: Steve McDonald from the Australasian Cochrane Centre and Karla Bergerhoff, the Trials Search Coordinator of the Cochrane Metabolic and Endocrine Disorders Group for their assistance in developing the search strategy. Joanne McKenzie from the Australasian Cochrane Centre and Damien Jolley from Monash Institute of Health Services Research for biostatistical advice. Miranda Cumpston and Veronica Pitt from the Australasian Cochrane Centre for methodological advice.

The authors would like to acknowledge the following study investigators for providing additional study information or data: JF Bak, H Hanaire Broutin, RPLM Hoogma, JH DeVries, G Lepore, N Weintrob and B Zinman (for Tsui 2001).

**Notes**

References to studies included in this review
Bak 1987 and Husted 1989 \{published and unpublished data\}


Botta 1986 \{published data only\}


Bruttomesso 2008 \{published data only\}


Chiasson 1984 and 1985 \{published data only\}


Cohen 2003 \{published data only\}


DeVries 2002 \{published and unpublished data\}


Doyle 2004 \{published data only\}


Hanaire-Broutin 2000 \{published and unpublished data\}


Hirsch 2005 \{published data only\}


Home 1982 \{published data only\}


Hoogma 2005 \{published and unpublished data\}


Lepore 2003 \{published and unpublished data\}

Lepore G, Dodesini AR, Nosari I, Trevisan R. Both continuous subcutaneous insulin infusion and a multiple daily insulin injection regimen with glargine as basal insulin are equally better than traditional multiple daily insulin injection treatment. Diabetes Care 2003;26:1321-2.

Meschi 1982 \{published data only\}


Nathan 1982 \{published data only\}

Nathan Dm LP AJ. Intensive conventional and insulin pump therapeutics in adult type I diabetes. A crossover study.
Nosadini 1988 (published data only)


Nuboer 2008 (published data only)


Oslo Study 1985 to 1992 (published data only)


Dahl Jorgensen K. Blood glucose control and progression of diabetic neuropathy: eight years results from the Oslo study. Diabetologia 1992;35:A15-.


Pozzilli 2003 (published data only)


Saurbrey 1988 (published data only)


Schmitz 1989 (published data only)


Skogsberg 2008 (published data only)


Tsui 2001 (published and unpublished data)

Tsui E, Barnie A, Ross S, Parkes R, Zinman B. Intensive insulin therapy with insulin lispro: a randomized trial of continuous subcutaneous insulin infusion versus multiple daily insulin injection. [see comment]. Diabetes Care...
Weintrob 2004 {published and unpublished data}

* indicates the major publication for the study

References to studies excluded from this review

Alemzadeh 2005 {published data only}

Amemiya 1983 {published data only}

Arias 1985 {published data only}

Bagdade 1991 {published data only}

Bangstad 1994 {published data only}

Barbosa 1981 {published data only}

Barrett 1995 {published data only}

Bech 1996 {published data only}

Beck-Nielsen 1984 {published data only}

Beck-Nielsen 1985 {published data only}

Beck-Nielsen 1985a {published data only}

Beck-Nielsen 1990 {published data only}

Behme 1984 {published data only}

Bell 1985 {published data only}

Bell 1985a (published data only)

Bending 1986 (published data only)

Berg 1998 (published data only)

Bergenstal 1985 (published data only)

Berger 1989 (published data only)

Bibergel 1987 (published data only)

Biesenbach 1988 (published data only)

Bode 1996 (published data only)

Bode 2004 (published data only)

Bombor 1984 (published data only)

Borisova 1989 (published data only)

Brunetti 1984 (published data only)

Buysschaert 1981 (published data only)

Buysschaert 1983 (published data only)

Calabrese 1982 (published data only)

**Canny 1985** *(published data only)*


**Carta 1986** *(published data only)*


**Cavallo-Perin 1983** *(published data only)*


**Chisholm 1984** *(published data only)*


**Christensen 1986** *(published data only)*


**Christensen 1987** *(published data only)*


**Christiansen 1987** *(published data only)*


**Ciavarella 1985** *(published data only)*


**Colette 1986** *(published data only)*


**Colette 1989** *(published data only)*


**Connis 1989** *(published data only)*


**Coustan 1986** *(published data only)*


**Davies 1984** *(published data only)*


**de Beaufort 1985** *(published data only)*

de Beaufort 1989 {published data only}


Dicker 1987 {published data only}


DiMeglio 2004 {published data only}


Edelmann 1987 {published data only}


Feldt-Rasmussen 1986 {published data only}


Feldt-Rasmussen 1986a {published data only}


Feldt-Rasmussen 1991 {published data only}


Flores 1984 {published data only}


Garg 2004 {published data only}


Garmo 2004 {published data only}


Giocolea 1988 {published data only}


Giocolea 1986 {published data only}


Giocolea 1987 {published data only}


Giocolea 1988 {published data only}


Giocolea 1989 {published data only}

Greene 1983 {published data only}

Grimm 1987 {published data only}

Guerci 1998 {published data only}

Gulan 1988 {published data only}

Haakens 1989 {published data only}

Haakens 1990 {published data only}

Hall 1989 {published data only}

Haug 1987 {published data only}

Heber 1977 {published data only}

Helve 1987 {published data only}

Helve 1987a {published data only}

Helve 1987b {published data only}

Hermansen 1987 {published data only}

Hermansen 1988 {published data only}
Hermansen K, Schmitz O, Boye N, Christensen CK, Christiansen JS, Alberti KG. Glucagon responses to intravenous arginine and oral glucose in insulin-dependent diabetic patients during six months conventional or

**Hoogma 2004 {published data only}**


**Hung 1984 {published data only}**


**Jakobsen 1988 {published data only}**


**Jensen 1986 {published data only}**


**Kamoi 2004 {published data only}**


**Kelly 1984 {published data only}**


**Knight 1986 {published data only}**


**Kobayashi 1987 {published data only}**


**Koivisto 1983 {published data only}**


**Kordonouri 2006 {published data only}**


**Kritz 1983 {published data only}**


**Kroc 1984 {published data only}**


**Kroc 1988 {published data only}**


**Kuno 1996 {published data only}**


**Lager 1983 (published data only)**


**Lager 1986 (published data only)**


**Lapolla 2003 (published data only)**


**Lauritzen 1985 (published data only)**


**Lawson 1984 (published data only)**


**Lawson 1985 (published data only)**


**Leblanc 1986 (published data only)**


**Lecavalier 1987 (published data only)**


**Lepore 2004 (published data only)**


**Levy 1984 (published data only)**


**Levy-Marchal 1983 (published data only)**


**Levy-Marchal 1988 (published data only)**


**Litton 2002 (published data only)**


**Ludvigsson 2003 (published data only)**


**Lunetta 1996 (published data only)**


**Mancuso 1986 (published data only)**

Marshall 1987 {published data only}


Marshall 1988 {published data only}


McDonald 1982 {published data only}


Mecklenburg 1982 {published data only}


Minkina-Pedras 2005 {published data only}


Moberg 1994 {published data only}


Moller 1986 {published data only}


Monnier 1987 {published data only}


Muller 1999 {published data only}


Nathan 1996 {published data only}


Ng 1986 {published data only}


Nijs 1991 {published data only}


Olsen 1985 {published data only}


Olsen 1987 {published data only}


Pickup 1979 {published data only}

http://cochrane.bvsalud.org/cochrane/show.php?db=reviews&mfn=3045...

Pickup 1979a {published data only}


Pickup 1984 {published data only}


Pickup 1985 {published data only}


Pickup 1989 {published data only}


Pietri 1980 {published data only}


Pietri 1983 {published data only}


Reeves 1982 {published data only}


Regal 1988 {published data only}


Rizza 1980 {published data only}


Rodger 1985 {published data only}

Rodger NW, Dupre J, Canny CLB. Continuous subcutaneous insulin infusion in adults: Glycemic advantage is predicted by venous plasma C-peptide concentrations. Diabetes Care 1985;8:447-55.

Rodger 1988 {published data only}


Saibene 1981 {published data only}


Schaepelynck-Belicar 2003 {published data only}


Schiffrin 1982 {published data only}


Schiffrin 1982a {published data only}

Schiffrin 1983 \{published data only\}


Schiffrin 1984 \{published data only\}


Schiffrin 1984a \{published data only\}


Schiffrin 1985 \{published data only\}


Schiffrin 1987 \{published data only\}


Schmitz 1987 \{published data only\}


Schottenfeld-Naor 1985 \{published data only\}


Scuffham 2003 \{published data only\}


Service 1985 \{published data only\}


Siebenhofer 2004 \{published data only\}


Simonson 1985 \{published data only\}


Skare 1986 \{published data only\}


Skyler 1982 \{published data only\}


Sleightholm 1986 \{published data only\}


Slijper 1990 \{published data only\}


Sulli 2003 {published data only}

Tamborlane 1979 {published data only}

Tamborlane 1979a {published data only}

Tamborlane 1981 {published data only}

Tamborlane 1982 {published data only}

Testa 1985 {published data only}

Thuesen 1986 {published data only}

Tilvis 1986 {published data only}

Toni 2004 {published data only}

Turk 1996 {published data only}

van Ballegooie 1985 {published data only}

Viberti 1981 {published data only}

Viberti 1984 {published data only}

Warmolts 1987 {published data only}

Weinzimer 2004 {published data only}

Willi 2003 {published data only}


Wilson 2005 {published data only}


Wredling 1997 {published data only}


Yki-Jarvinen 1984 {published data only}


Ziegler 1988 {published data only}


Additional references

ADA 1997


APEG 2004

Clinical Practise Guidelines: Type 1 Diabetes in Children and Adolescents. 2004:-.

Couper 2002


Dabelea 2009


DPT 2002


ENDIT 2003

Intervening before the onset of Type 1 diabetes: baseline data from the European Nicotinamide Diabetes Intervention Trial (ENDIT). Diabetologia 2003;46:339-46.

Guinn 1988


Higgins 2003


Higgins 2008


HTA 2004


Karvonen 2000

Liberati 2009

NDDG 1979

NICE 2008
Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus. ±·.

Pickup 1980a

Pickup 2002

Sterne 2001

Sutton 1990

WHO 1980

GRAPHS

Graphs and Tables
To view a graph or table, click on the outcome title of the summary table below.
## CSII versus MI

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>20</td>
<td></td>
<td>Mean Difference</td>
<td>-0.25 [-0.40, -0.10]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Random, 95% CI)</td>
<td></td>
</tr>
<tr>
<td>1.1 Cross-over trials</td>
<td>10</td>
<td></td>
<td>Mean Difference</td>
<td>-0.25 [-0.45, -0.05]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Random, 95% CI)</td>
<td></td>
</tr>
<tr>
<td>1.2 Parallel trials</td>
<td>10</td>
<td></td>
<td>Mean Difference</td>
<td>-0.26 [-0.52, -0.00]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Random, 95% CI)</td>
<td></td>
</tr>
<tr>
<td>HbA1c subgroup analysis - age</td>
<td>20</td>
<td></td>
<td>Mean Difference</td>
<td>-0.25 [-0.40, -0.10]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Random, 95% CI)</td>
<td></td>
</tr>
<tr>
<td>2.1 &lt; 18 years</td>
<td>8</td>
<td></td>
<td>Mean Difference</td>
<td>-0.22 [-0.41, -0.03]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Random, 95% CI)</td>
<td></td>
</tr>
<tr>
<td>2.2 &gt; 18 years</td>
<td>12</td>
<td></td>
<td>Mean Difference</td>
<td>-0.29 [-0.52, -0.06]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Random, 95% CI)</td>
<td></td>
</tr>
<tr>
<td>HbA1c subgroup analysis - study duration</td>
<td>20</td>
<td></td>
<td>Mean Difference</td>
<td>-0.25 [-0.40, -0.10]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Random, 95% CI)</td>
<td></td>
</tr>
<tr>
<td>3.1 Short term (&lt; 1 month)</td>
<td>1</td>
<td></td>
<td>Mean Difference</td>
<td>0.2 [-1.94, 2.34]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Random, 95% CI)</td>
<td></td>
</tr>
<tr>
<td>3.2 Medium term (&gt; 1 month ≤ 6 months)</td>
<td>12</td>
<td></td>
<td>Mean Difference</td>
<td>-0.32 [-0.52, -0.11]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Random, 95% CI)</td>
<td></td>
</tr>
<tr>
<td>3.3 Long term (&gt; 6 months)</td>
<td>7</td>
<td></td>
<td>Mean Difference</td>
<td>-0.17 [-0.44, 0.10]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Random, 95% CI)</td>
<td></td>
</tr>
<tr>
<td>HbA1c small study bias</td>
<td>6</td>
<td></td>
<td>Mean Difference</td>
<td>-0.72 [-1.55, 0.10]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Random, 95% CI)</td>
<td></td>
</tr>
<tr>
<td>Daily mean blood glucose</td>
<td>13</td>
<td></td>
<td>Mean Difference</td>
<td>Subtotals only</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Random, 95% CI)</td>
<td></td>
</tr>
<tr>
<td>Daily mean blood glucose subgroup analysis - age</td>
<td>13</td>
<td></td>
<td>Mean Difference</td>
<td>-15.26 [-23.37, -7.14]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Random, 95% CI)</td>
<td></td>
</tr>
<tr>
<td>6.1 &lt; 18 years</td>
<td>3</td>
<td></td>
<td>Mean Difference</td>
<td>-3.70 [-14.38, 6.98]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Random, 95% CI)</td>
<td></td>
</tr>
<tr>
<td>6.2 &gt; 18 years</td>
<td>10</td>
<td></td>
<td>Mean Difference</td>
<td>-17.60 [-26.71, -8.48]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Random, 95% CI)</td>
<td></td>
</tr>
<tr>
<td>Daily mean blood glucose subgroup analysis - study duration</td>
<td>13</td>
<td></td>
<td>Mean Difference</td>
<td>-15.26 [-23.37, -7.14]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Random, 95% CI)</td>
<td></td>
</tr>
<tr>
<td>7.1 Short term (&lt; 1 month)</td>
<td>1</td>
<td></td>
<td>Mean Difference</td>
<td>-3.0 [-80.47, 74.47]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Random, 95% CI)</td>
<td></td>
</tr>
<tr>
<td>7.2 Medium term (&gt; 1 month ≤ 6 months)</td>
<td>10</td>
<td></td>
<td>Mean Difference</td>
<td>-14.12 [-23.11, -5.13]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Random, 95% CI)</td>
<td></td>
</tr>
<tr>
<td>7.3 Long term (&gt; 6 months)</td>
<td>2</td>
<td></td>
<td>Mean Difference</td>
<td>-21.41 [-29.40, -13.43]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Random, 95% CI)</td>
<td></td>
</tr>
<tr>
<td>Daily mean blood glucose small study bias</td>
<td>4</td>
<td></td>
<td>Mean Difference</td>
<td>-29.33 [-51.36, -7.31]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Random, 95% CI)</td>
<td></td>
</tr>
<tr>
<td>Fasting blood glucose</td>
<td>11</td>
<td></td>
<td>Mean Difference</td>
<td>-14.02 [-24.42, -3.61]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Random, 95% CI)</td>
<td></td>
</tr>
<tr>
<td>Fasting blood glucose subgroup analysis - age</td>
<td>11</td>
<td></td>
<td>Mean Difference</td>
<td>-14.02 [-24.42, -3.61]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Random, 95% CI)</td>
<td></td>
</tr>
<tr>
<td>10.1 &lt; 18</td>
<td>3</td>
<td></td>
<td>Mean Difference</td>
<td>-7.67 [-23.88, 8.53]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Random, 95% CI)</td>
<td></td>
</tr>
<tr>
<td>10.2 &gt; 18</td>
<td>8</td>
<td></td>
<td>Mean Difference</td>
<td>-16.25 [-29.07, -3.42]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Random, 95% CI)</td>
<td></td>
</tr>
<tr>
<td>Fasting blood glucose subgroup analysis - study duration</td>
<td>11</td>
<td></td>
<td>Mean Difference</td>
<td>-14.02 [-24.42, -3.61]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Random, 95% CI)</td>
<td></td>
</tr>
<tr>
<td>11.1 Short term (&lt; 1 month)</td>
<td>1</td>
<td></td>
<td>Mean Difference</td>
<td>-20.0 [-35.48, -4.52]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Random, 95% CI)</td>
<td></td>
</tr>
<tr>
<td>11.2 Medium term (&gt; 1 month ≤ 6 months)</td>
<td>8</td>
<td></td>
<td>Mean Difference</td>
<td>-8.48 [-19.35, 2.39]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Random, 95% CI)</td>
<td></td>
</tr>
<tr>
<td>12 Fasting blood glucose small study bias</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 Post prandial blood glucose</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 Post prandial blood glucose subgroup analysis - age</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14.1 &lt; 18</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14.2 &gt; 18</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 Post prandial blood glucose subgroup analysis - study duration</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15.1 Short term (&lt; 1 month)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15.2 Medium term (&gt; 1 month ≤ 6 months)</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15.3 Long term (&gt; 6 months)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 Post prandial blood glucose small study bias</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17 Non-severe hypoglycaemic events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 Severe hypoglycaemic events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19 Quality of life</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 Weight</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21 Weight subgroup analysis - study duration</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21.1 Short term (&lt; 1 month)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21.2 Medium term (&gt; 1 month ≤ 6 months)</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21.3 Long term (&gt; 6 months)</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22 Weight small study bias</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23 Daily insulin requirement (U)</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 Daily insulin requirement (U) subgroup analysis - age</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24.1 &lt; 18</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24.2 &gt; 18</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 Daily insulin requirement (U) subgroup analysis - study duration</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25.1 Short term (&lt; 1 month)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25.2 Medium term (&gt; 1 month ≤ 6 months)</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25.3 Long term (&gt; 6 months)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26 Daily insulin requirement (U) small study bias</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27 Daily insulin requirement (U/kg)</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28 Daily insulin requirement (U/kg) subgroup analysis - age</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>N</td>
<td>Mean Difference (Random, 95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------</td>
<td>---</td>
<td>----------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28.1 &lt; 18</td>
<td>6</td>
<td>-0.16 [-0.31, -0.01]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28.2 &gt; 18</td>
<td>6</td>
<td>-0.08 [-0.15, -0.01]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29 Daily insulin requirement (U/kg) subgroup analysis - study duration</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29.1 Short term (&lt; 1 month)</td>
<td>1</td>
<td>-0.12 [-0.19, -0.05]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29.2 Medium term (&gt; 1 month ≤ 6 months)</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29.3 Long term (&gt; 6 months)</td>
<td>5</td>
<td>-0.14 [-0.32, 0.04]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 Daily insulin requirement (U/kg) small study bias</td>
<td>3</td>
<td>-0.04 [-0.13, 0.05]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
KEYWORDS

Adult; Child; Humans; Adolescent; Diabetes Mellitus, Type 1 [*drug therapy]; Hypoglycemic Agents [*administration & dosage]; Infusions, Subcutaneous; Insulin [*administration & dosage]; Randomized Controlled Trials as Topic

HISTORY

Protocol first published: Issue 1, 2005
Review first published: Issue 1, 2010

Copyright: The Cochrane Library