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REVIEW ARTICLE

# Continuous subcutaneous insulin infusion vs modern multiple injection regimens in type 1 diabetes: an updated meta-analysis of randomized clinical trials

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## Abstract

Meta-analyses of clinical trials comparing CSII with traditional insulin injections usually show a small, but significant advantage of CSII with respect to HbA1c and risk of severe hypoglycemia. On the other hand, CSII is associated with a small, but relevant risk of ketoacidosis, mainly due to malfunction of insulin pump and/or catheter occlusion. During last time, the technology of insulin pumps and infusion sets has improved as the profound evolution in type and schemes with traditional insulin injections. Aim of the present study is to update previous meta-analyses comparing CSII with traditional insulin injections in subjects with type 1 diabetes. Specific subgroup analyses were designed for assessing the effects of CSII in comparison with basal-bolus MDI, with short-acting analogues as bolus and long-acting analogues as basal insulin. In addition, an exploratory analysis was performed to verify the effect of CSII in insulin-naïve patients with type 1 diabetes. The present analysis includes all randomized clinical trials comparing CSII with traditional injections in type 1 diabetes, with a duration of at least 12 weeks. Animal studies were excluded, whereas no language or date restriction was imposed. If duplicate publications of a single trial were present, the paper containing more adequate information was considered as principal publication. In trials comparing CSII with basal-bolus MDI, performed before the introduction of rapid-acting analogues, regular human insulin was used for CSII, and as prandial insulin in control groups. CSII was associated with a significant reduction of A1c, in comparison with MDI, irrespective of the use of either human insulin or rapid-acting analogues. However, in trials with rapid-acting analogue the advantage of CSII was significantly smaller than in trials with regular human insulin (HbA1c difference: −0.29[−0.46; −0.13] vs −1.93[−1.84; −0.42]%; $p=0.02$). Different rapid-acting analogues provided similar results (HbA1c reduction vs MDI: −0.25 [−0.48; −0.02]%, $p=0.03$, and −0.29 [−0.49; −0.09]%, $p=0.005$, for lispro and aspart, respectively). In addition, in trials comparing CSII with basal-bolus MDI, CSII reduced HbA1c to a similar extent irrespective of the use of either NPH or long-acting analogues as basal insulin in the control groups (HbA1c reduction vs MDI: −0.31 [−0.55; −0.06]%, $p=0.01$, and −0.20 [−0.38; −0.03]%, $p=0.02$, for NPH and long-acting analogues, respectively. With respect to severe hypoglycemia, CSII did not produce a significant reduction of risk in comparison with traditional insulin injections. Conversely, CSII was associated with a significant increase in the incidence of reported diabetic ketoacidosis (DKA). Notably, the increased risk of DKA was significant in trials comparing CSII with conventional insulin therapy, whereas only a nonsignificant trend toward an increased risk was observed in comparisons with basal-bolus MDI. Only two trials comparing CSII with basal-bolus MDI, both using rapid-acting analogues, were performed on insulin-naïve type 1 diabetic patients. When those two trials were analyzed separately, CSII did not produce any relevant effect on HbA1c (difference from control: −0.10[−0.38; +0.17]%; $p=0.46$). No meta-analysis could be performed on either severe hypoglycemia or DKA, which were not reported by one of the two trials. CSII seems to produce a small improvement in HbA1c in patients with type 1 diabetes inadequately controlled with MDI. This apparent effect, which could be partly due to

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publication bias, is smaller when MDI is properly performed using basal-bolus schemes with short-acting insulin analogues. Other outcomes different from HbA1c (such as quality of life) could be relevant for the choice of CSII instead of MDI. In addition, further studies are needed to better define the profile of patients who could benefit most from CSII.

**Keywords** Continuous subcutaneous insulin infusion (CSII) · Continuous glucose monitoring (CGM) · Flash glucose monitoring (FGM) · Sensor-augmented pump (SAP)

## Introduction

Continuous subcutaneous insulin infusion (CSII) has been used as an alternative to multiple daily injections (MDI) in type 1 diabetes for several decades (1).CSII, compared with multiple injections, has the advantage of a more accurate regulation of basal insulin supply, including the possibility of a temporary reduction or suspension of basal infusion in case of hypoglycemia or exercise; in addition, CSII allows the administration of additional boluses, if needed, with minimal patient's discomfort [1, 2].

Meta-analyses of clinical trials comparing CSII with traditional insulin injections usually show a small but significant advantage of CSII with respect to HbA1c [3–6] and risk of severe hypoglycemia [4–9]. On the other hand, CSII is associated with a small but relevant risk of ketoacidosis, mainly due to malfunction of insulin pump and/or catheter occlusion [10].

Randomized trials on CSII have been performed on a range of over 4 decades. During this time, the technology of insulin pumps and infusion sets has improved dramatically; at the same time, there has been a profound evolution in therapeutic schemes with traditional injections. As a consequence, both the active intervention (with CSII) and the control treatment (with injections) have different characteristics in studies designed at different times. First of all, in older studies CSII is compared with conventional insulin therapy (with 1–2 daily injections), which is not capable of providing a glycemic control comparable to that of modern basal-bolus therapy [11]. Another potentially relevant evolution is that of preparations used for rapid-acting insulin administration: presently available short-acting analogues provide a better glycemic control when used either for CSII or as bolus insulin in MDI [12, 13]. As a consequence, the results of older trials of CSII vs basal-bolus MDI, both with regular insulin, cannot be automatically applied to modern therapies with short-acting analogues. A further problem is represented by long-acting analogues used as basal insulin in MDI. Many trials were performed with NPH; however, long-acting insulin analogues with lower hypoglycemic risk may [7] allow for a more aggressive management of fasting glucose in MDI. As a consequence, trials using NPH as basal insulin in comparator groups may overestimate the advantage of CSII. Finally, it should be considered that in most instances patients enrolled in trials with CSII were inadequately controlled with MDI; this means that comparisons were performed in subjects defined for failure to the control treatment. For this reason, the actual advantages of CSII could have been overestimated.

Aim of the present study is to update previous meta-analyses comparing CSII with traditional insulin injections in subjects with type 1 diabetes. Specific subgroup analyses were designed for assessing the effects of CSII in comparison with basal-bolus MDI, with short-acting analogues as bolus and long-acting analogues as basal insulin. In addition, an exploratory analysis was performed to verify the effect of CSII in insulin-naïve patients with type 1 diabetes.

## Materials and methods

### Search strategy and selection criteria

This meta-analysis is a part of a wider meta-analysis of randomized clinical trials on CSII, glucose sensors, and sensor-augmented therapy in either type 1 or type 2 diabetes (registered on PROSPERO, http://www.crd.york.ac.uk/PROSPERO, at CRD42016042323). The present analysis includes all randomized clinical trials comparing CSII with traditional injections in type 1 diabetes, with a duration of at least 12 weeks. Animal studies were excluded, whereas no language or date restriction was imposed. If duplicate publications of a single trial were present, the paper containing more adequate information was considered as principal publication.

A Medline search (limits: Human studies; any date up to September 1st, 2018) was performed, using the following search string: CSII or "continuous subcutaneous insulin infusion" or CGM or "continuous glucose monitoring" or FGM or "flash glucose monitoring" or "sensor-augmented pump"; trials on glucose sensors or sensor-augmented pumps, as well as those with CSII in type 2 diabetes, were then excluded. Moreover, an additional manual search of the references of included trials and former meta-analyses was carried out to identify other newly published and unpublished studies. Completed but yet unpublished studies with the drugs specified above were searched in the http://www.clinicaltrials.gov register. Authors of included studies were not contacted for additional information.

This meta-analysis is reported following the criteria of preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [14].

### Data extraction

Summary estimates of the variables of interest were extracted from the principal publication, when available; whenever needed, secondary publications and cllinicaltrials.gov registry were used for retrieval of missing information, in the hierarchical order reported above. Data extraction was performed independently by two of the authors (L.P and I.D.), and conflicts resolved by a third investigator (E.M.).

The following information for each trial was collected: first author, publication year, NationalClinical Trial (NCT) number, insulin used in treatment arms, insulin regimen in control arms (conventional or basal-bolus), sample size, mean age, diabetes duration, baseline HbA1c, body mass index (BMI). Whenever available, data on endpoint incident severe hypoglycemia, diabetic ketoacidosis (DKA) and all-cause mortality were extracted. Severe hypoglycemia was defined as that requiring hospitalization and/or help from third parties; DKA was considered as an adverse event classified by the investigator ad "serious", and defined as "ketoacidosis".

The risk of bias was described and assessed in seven specific domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. The results of these domains were graded as 'low' risk of bias, 'high' risk of bias, or 'unclear' risk of bias.

### Data analysis

The principal endpoints were HbA1c and severe hypoglycemia, whereas secondary endpoints were DKA and all-cause mortality. Mean and 95% Confidence Intervals for continuous variables, and Mantel-Haenszel Odds Ratio [MH-OR] for categorial variables were calculated, using random effect models. A sensitivity analysis was performed using fixed effect models and, for categorial variables, calculating Peto's odds ratio. Separate analyses were performed for trials using either short-acting insulin analogues or regular insulin in both arms, and either long-acting insulin analogues or NPH in the control arm. Among trials comparing CSII with basal-bolus MDI, a separate analysis was performed for trials enrolling insulin-naïve subjects or patients already on MDI. Statistical heterogeneity was assessed by $I^2$ test, where as Funnel plots were used to detect publication bias.

The following post hoc analyses were performed on trials comparing CSII with basal-bolus MDI:

1. Subgroup analysis of HbA1c outcomes in trials enrolling only children and adolescents (maximun age: 18 years or less) and those enrolling only adult patients (minimun age: 18 years or more);
2. A metaregression of between-group differences in HbA1c vs mean baseline HbA1c, weighed for trial size;
3. A metaregression of between-group differences in HbA1c vs mean age at enrolment, weighed for trial size.

All analyses were performed using Review Manager (RevMan), Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and SPSS 24 (IBM Corporation).

### Role of the funding source

This research was performed independently of any funding, as part of the institutional activity of the investigators. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

The trial flow summary is reported in Fig. 1 of Supplementary Materials. Out of 40 trials fulfilling the inclusion criteria, 40, 24, and 20 reported information on endpoint HbA1c, severe hypoglycemia, diabetic ketoacidosis, respectively. Only few trials reported information on and all-cause mortality. Table 1 of Supplementary Materials summarizes the principal characteristics of the 40 included trials, which enrolled 1110 and 1142 patients in CSII and control comparator groups, respectively, with mean trial duration of 53 weeks. Comparators included conventional insulin therapy ($N=150$ trials), basal-bolus MDI ($N=40$ trials), or both ($N=1$ trial).

The quality of studies was variable. All trials were open-label, and in some instances blinding of assessors was inadequate. In addition, in several trials randomization and allocation procedures were not properly described, and attrition bias was possible. Older studies often showed greater methodological problems than newer ones (Fig. 2 of Supplementary Materials).

Publication bias was performed by means of funnel plot on HbA1c (Fig. 3 of Supplementary Materials), showing the possibility of selective disclosure of favourable results, particularly for studies comparing CSII with basal-bolus MDI.

Overall, CSII was associated with a significantly greater reduction of HbA1c when compared to traditional injections(Fig. 1).The $I^2$ analysis suggested a relevant heterogeneity across trials. The effect of CSII was apparently greater when it was compared to conventional insulin

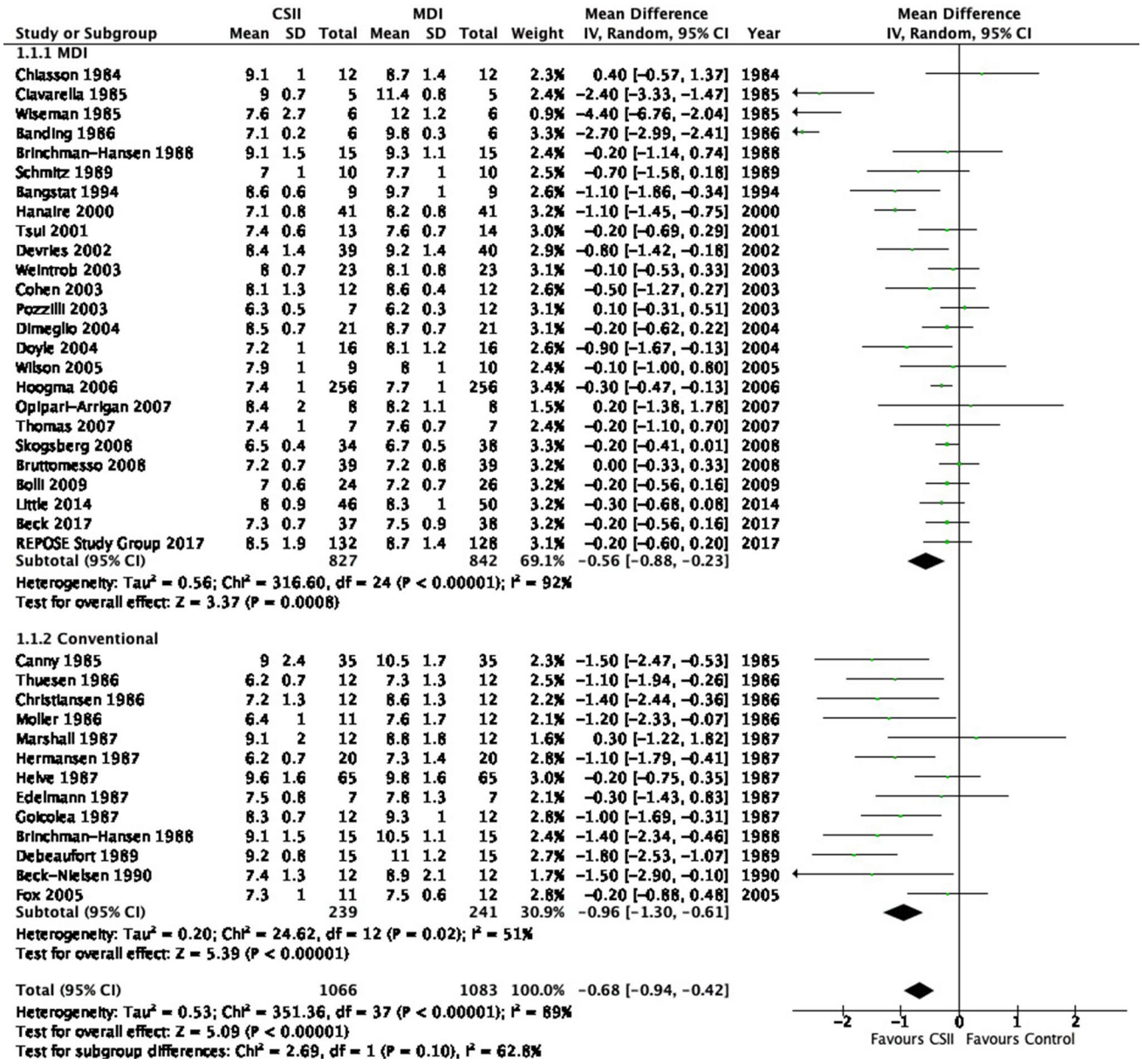



**Fig. 1** HbA1c with CSII and MDI

therapy than in comparisons with basal-bolus MDI (HbA1c difference: −0.96 [−1.30; −0.61] vs −0.26 [−0.88; −0.23]%), but the difference between the two subgroup of trials did not reach statistical significance ($p=0.10$).

In trials comparing CSII with basal-bolus MDI, performed before the introduction of rapid-acting analogues, regular human insulin was used for CSII, and as prandial insulin in control groups. CSII was associated with a significant reduction of A1c, in comparison with MDI, irrespective of the use of either human insulin or rapid-acting analogues (Fig. 4 of Supplementary Materials). However, in trials with rapid-acting analogue the advantage of CSII was significantly smaller than in trials with regular human insulin (HbA1c difference: −0.29 [−0.46; −0.13] vs −1.93[−1.84; −0.42]%; $p=0.02$). Different rapid-acting analogues provided similar results (HbA1c reduction vs MDI: −0.25 [−0.48; −0.02]%, $p=0.03$, and −0.29 [−0.49; −0.09]%, $p=0.005$, for lispro and aspart, respectively). In addition, in trials comparing CSII with basal-bolus MDI, CSII reduced HbA1c to a similar extent irrespective of the use of either NPH or long-acting analogues as basal insulin in the control groups (HbA1c reduction vs MDI: −0.31 [−0.55; −0.06]%, $p=0.01$, and −0.20 [−0.38; −0.03]%, $p=0.02$, for NPH and long-acting analogues, respectively). The effect of CSII (vs MDI) on HbA1c was −0.23 [−0.56; −0.11]% in trials enrolling only children and/or adolescents, and −0.42

[−0.66; −0.18]% in those enrolling only adult patients. At metaregression analysis, in trials comparing CSII with basal-bolus MDI, no significant correlation of between-group difference in HbA1c was observed with either mean age at enrolment ($r^2 = 0.031$, $p = 0.0197$) or mean baseline HbA1c ($r^2 = 0.036$, $p = 0.0633$; Fig. 5 of Supplementary Materials).

With respect to severe hypoglycemia, CSII did not produce a significant reduction of risk in comparison with traditional insulin injections. Conversely, CSII was associated with a significant increase in the incidence of reported diabetic ketoacidosis (DKA). Notably, the increased risk of DKA was significant in trials comparing CSII with conventional insulin therapy, whereas only a nonsignificant trend toward an increased risk was observed in comparisons with basal-bolus MDI (Fig. 2).

Only two trials comparing CSII with basal-bolus MDI, both using rapid-acting analogues, were performed on insulin-naïve type 1 diabetic patients [15, 16]. When those two trials were analyzed separately, CSII did not produce any relevant effect on HbA1c (difference from control: −0.10 [−0.38; +0.17]%; $p = 0.46$). No meta-analysis could be performed on either severe hypoglycemia or DKA, which were not reported by one of the two trials [15].

## Discussion

Most practitioners conceive CSII as a means of improving glucose control when multiple injections are insufficient to reach and maintain desired therapeutic targets. In fact, some guidelines, such as those issued by the National Institute of Clinical Excellence (NICE) in the UK [17] and those published by Diabetes Canada [18], recommend the switch to CSII when basal-bolus MDI does not provide satisfactory results, either for persistently elevated HbA1c or recurrent hypoglycemia. Conversely, current Standards of Care of the American Diabetes Association state that CSII can be used in "selected" patients, provided that active patient/family participation is available, without clearly specifying the criteria which should be used for such a patient selection [19].

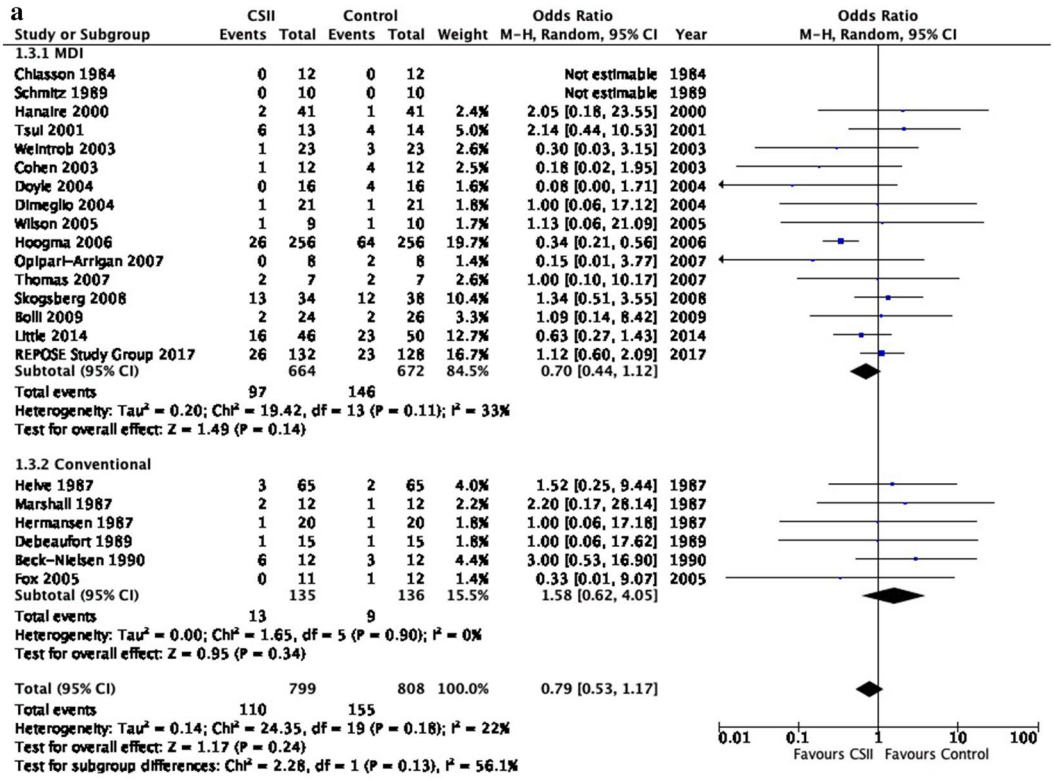
The prescription of CSII in patients with type 1 diabetes who do not reach desired HbA1c targets, or who experience hypoglycemia, is based on the belief that CSII could be more effective and safer than MDI. Several trials reported small, but significant reductions of HbA1c with CSII, in comparisons with traditional injections [4]. This result is confirmed by the present meta-analysis. However, the effect size appears to be dependent upon the structure of insulin therapy in the control group. First of all, the advantage of CSII in terms of HbA1c appear to wider when it is compared to conventional (i.e., non-intensive) insulin therapy. This is not surprising, considering that basal-bolus therapy is capable of providing a greater glycemic control than traditional schemes of conventional insulin therapy [11]. In addition, the use as bolus insulin of rapid-acting analogues, rather than regular human insulin, substantially improves glycemic control in patients with type 1 diabetes on basal-bolus MDI [20]. Although rapid-acting analogues provide an advantage over regular human insulin also in CSII [20], the difference between CSII and MDI seems to be substantially smaller with the use of analogues. Since treatment with rapid-acting analogues in basal-bolus schemes has become a recognized standard for the treatment of type 1 diabetes [17–19], it is reasonable to compare CSII only with this updated treatment approach, rather than with obsolete insulin schemes.

In the present analysis, the advantage of CSII in comparison with basal-bolus MDI is similar, irrespective of the use of either NPH or long-acting analogues as basal insulin in the control group. This result could appear to be surprising, considering that long-acting analogues, which are associated with a lower risk of nocturnal hypoglycemia [21] could facilitate a more aggressive approach to the management of fasting glucose. However, the number of available trials is quite small, and the characteristics of the trials are heterogeneous; for these reasons, the present results are inconclusive on this point.

Interestingly, CSII does not seem to produce any improvement of glycemic control in comparison with MDI when it is used as first-line therapy in insulin-naïve patients. This suggests that the superiority of CSII over basal-bolus MDI, observed in a majority of available studies, could be partly due to the selection of patients: in fact, most trials enroll subjects who are not adequately controlled with MDI, using failure to control therapy as a inclusion criterion. This approach could lead to an overestimation of the efficacy of the experimental treatment, i.e., CSII. On the other hand, we should recognize that there only two trials were performed on insulin-naïve patients, and that available evidence on this point cannot be considered conclusive. Most current guidelines, prudently, suggest to use CSII in patients failing to MDI [18, 19].

Several trials reported a reduction of the incidence of hypoglycemia with CSII in comparison with MDI. Unfortunately, the definition of hypoglycemia varies broadly across studies, not allowing a reliable synthesis of results. The only unequivocal category of hypoglycemia, i.e., severe hypoglycemia (defined as that requiring third-party assistance or hospital admission) is a relatively rare event. The present metanalysis failed to detect any significant difference in the incidence of severe hypoglycemia between CSII and MDI, but the number of events recorded was too low to allow a reliable analysis.

Overall, CSII is associated with an increased risk of ketoacidosis in comparison with MDI. This phenomenon is more evident in trials comparing CSII with conventional insulin therapy, and it is blunted in trials with basal-bolus



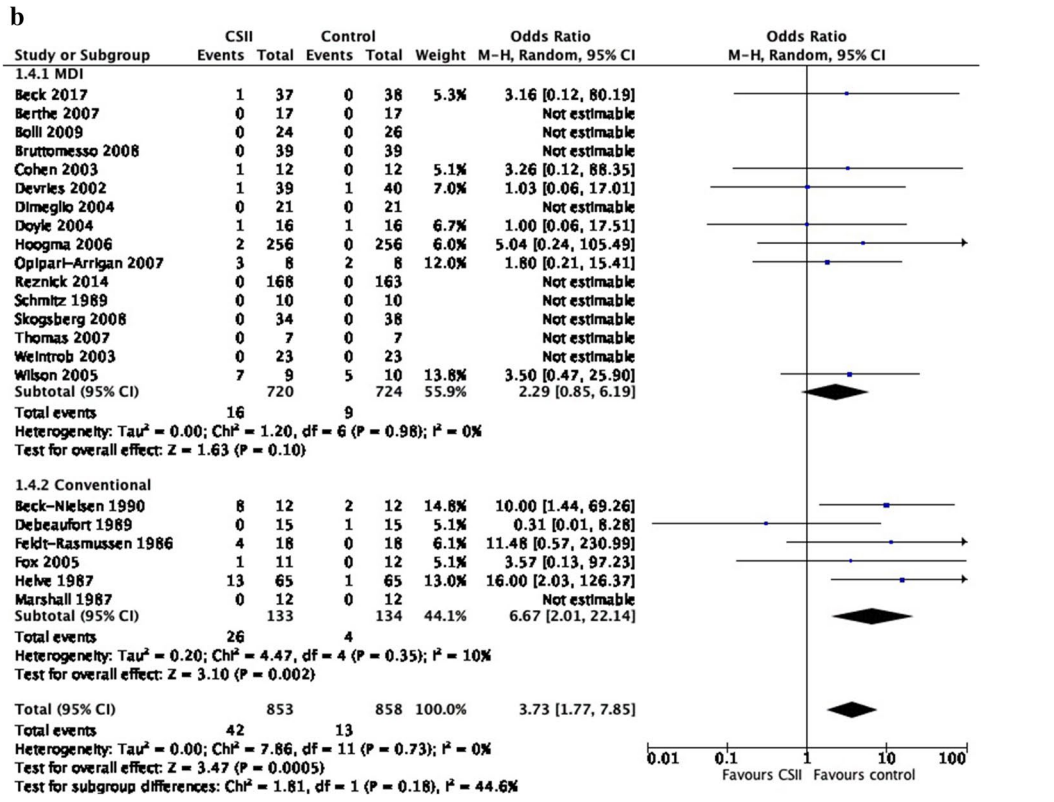




**Fig. 2** Adverse events with CSII and MDI. **a** Severe hypoglycemia, **b** DKA

MDI as comparator group. It is conceivable that the risk of CSII was higher in older studies, using less reliable models of insulin pumps and infusion sets. In more recent trials, the risk of ketoacidosis could be less relevant.

A metanalysis provides the opportunity of obtaining a simple synthesis of the results of many trials; however, the limitations of this approach should be clearly recognized, and carefully considered when interpreting results. Although the clinical use of CSII is widespread in several countries [22], the overall number of trials assessing its efficacy and safety is relatively small. In addition, available trials are often very small and with a short duration of follow-up. Further problems are generated by the heterogeneity of trials, which limits the reliability of metanalytical results. Last, but not the least, available results suggest a relevant risk of publication bias, which could have generated an overestimation of the advantages of CSII with respect to HbA1c.

Technology rapidly evolves over time. In the last decade, sufficiently accurate devices for the continuous measurement of interstitial glucose have become widely available, providing data on new glycemic outcomes, such as glucose variability, time in range, etc. In the large majority of trials with CSII, such devices (and the consequent outcomes) were unavailable, possibly preventing the observation of some clinically relevant advantages of CSII. Furthermore, it is possible that the use of CSII in combination with systems for continuous measurement of interstitial glucose provides different results from those observed with traditional self-monitoring of capillary blood glucose. Another limitation of this study is represented by fact that the impact of quality of life was not assessed. Although we are conscious of the paramount relevance of this outcome, many trials lack information on quality of life; the use of different instruments for its measurement in available trials prevents a reliable meta-analysis.

In conclusion, CSII seems to produce a small improvement in HbA1c in patients with type 1 diabetes inadequately controlled with MDI. This apparent effect, which could be partly due to publication bias, is smaller when MDI is properly performed using basal-bolus schemes with short-acting insulin analogues. Other outcomes different from HbA1c (such as quality of life) could be relevant for the choice of CSII instead of MDI. In addition, further studies are needed to better define the profile of patients who could benefit most from CSII.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** This article does not contain any studies with human participant or animals performed by any of the authors.

**Informed consent** For this type of study, formal consent is not required.

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