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ORIGINAL ARTICLE

Continuous subcutaneous insulin infusion versus multiple daily insulin injections in type 1 diabetes: a meta-analysis

Matteo Monami · Caterina Lamanna · Niccolò Marchionni · Edoardo Mannucci

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Abstract Continuous subcutaneous insulin infusion (CSII) is considered an option for type 1 diabetic patients unsatisfactorily controlled with multiple daily injections (MDI). Short-acting analogs are superior to regular human insulin in CSII. This meta-analysis is aimed at assessing the advantages of short-acting analog-based CSII over MDI in type 1 diabetes. Randomized clinical trials (RCTs) comparing CSII (with analogs) and MDI for at least 12 weeks in type 1 diabetic patients were retrieved, assessing between-group differences in HbA1c and incidence of hypoglycemia. A total of 11 RCTs was included in the analysis. CSII was associated with a significant improvement of HbA1c in comparison with MDI (standardized difference in mean: −0.3 [−0.4;−0.1]%; $P < 0.001$). No significant difference was observed in the rate of severe hypoglycemic episodes. The reduction of HbA1c with CSII was evident in trials enrolling patients with mean age greater than 10 years, but not in younger children. Available data justify the use of CSII for basal-bolus insulin therapy in type 1 diabetic patients unsatisfactorily controlled with MDI.

Keywords Insulin therapy · Clinical science · Humans

M. Monami · C. Lamanna · N. Marchionni · E. Mannucci (✉)
Section of Geriatric Cardiology,
Department of Cardiovascular Medicine,
Azienda Ospedaliero-Universitaria Careggi,
Via delle Oblate 4, 50141 Florence, Italy
e-mail: edoardo.mannucci@unifi.it

M. Monami
e-mail: mmonami@libero.it

Introduction

Intensive (basal-bolus) insulin regimens with multiple daily injections allow a satisfactory control of blood glucose, with a limited risk of major hypoglycemia, in many persons with type 1 diabetes. However, glycemic targets are not reached with this approach in all patients. Continuous subcutaneous insulin infusion (CSII) with external pumps is a treatment option for patients with type 1 diabetes unsatisfactorily controlled with multiple daily injection regimens [1, 2].

Available evidence suggests that short-acting insulin analogs are superior to regular human insulin (RHI) for CSII [3, 4] as well as for traditional multiple injection therapy in type 1 diabetes [5]. Several randomized clinical trials, usually on small samples of patients, comparing CSII using short-acting analogs and multiple daily injections (MDI) have been performed, reporting either a similar efficacy of the two approaches [6–16] or a superiority of CSII [17, 18]. A meta-analysis on patient-level data from three clinical trials suggests an improvement of HbA1c with CSII (with lispro) as compared with MDI [19].

The aim of the present meta-analysis is the assessment of differences in efficacy and hypoglycemic risk between CSII, using short-acting analogs, and MDI, in patients with type 1 diabetes.

Research design and methods

A meta-analysis was performed including all published randomized clinical trials, either with a cross-over or a parallel series design, enrolling patients with type 1 diabetes, with a duration of at least 12 weeks, comparing continuous subcutaneous insulin injection (CSII) and

multiple daily insulin injections (MDI) using short-acting insulin analogs. Trials with a shorter duration were excluded because they could not yield relevant information on glycated hemoglobin, which had been chosen as the principal outcome variable.

An extensive Medline search for "continuous subcutaneous insulin injection", "insulin pump", or "CSII" was performed, collecting all randomized clinical trials on humans up to July 10, 2008. The identification of relevant abstracts, the selection of studies based on the criteria described above, and the subsequent data extraction were performed independently by two of the authors (Edoardo Mannucci and Matteo Monami), and conflicts were resolved by the third investigator (Niccolò Marchionni). The quality of trials was assessed using the following parameters: adequate description of randomization, allocation, blinding, and dropout procedures.

The principal outcome was the effect of CSII, as compared with MDI, on HbA1c at the end of trial. Furthermore, data on the incidence of nocturnal, severe, or any hypoglycemia (number of patients with at least one event) were extracted whenever possible.

Standardized mean differences were calculated for HbA1c and a random effect model was used for the meta-analysis. Mantel-Haenszel odds ratio for 95% confidence interval (MH-OR) was calculated for hypoglycemia, using a random effect model. All analyses were performed using Comprehensive Meta-analysis Version 2, Biostat, (Englewood, NJ, USA).

Results

The trial flow is summarized in Fig. 1. The principal characteristics of the 11 trials included in the meta-analysis, which were all open-label, were reported in Tables 1 and 2. When combining results of trials, HbA1c was significantly lower with CSII than with conventional insulin treatment (Fig. 2). A significant reduction of HbA1c with CSII was observed either with lispro [−0.2 (−0.4; −0.1)%, $P = 0.001$] or aspart [−0.6 (−1.0; −0.2)%; $P = 0.002$]. Furthermore, a significant improvement of HbA1c with CSII was detected in trials using different prandial (lispro or aspart) and basal (glargine or NPH) insulins in MDI (data not shown). CSII produced a significant advantage over MDI in trials enrolling patients with a mean age >10 years (−0.3 [−0.4; −0.2]%; $P < 0.001$), but not in studies performed on younger subjects (−0.1 [−0.5; 0.3]%; $P = 0.48$).

Sixteen and 21 patients in CSII and comparator groups, respectively, experienced at least one episode of severe hypoglycemia; the difference between treatment arms was not significant (MH-OR 0.80[0.39;1.63]; $P = 0.53$).

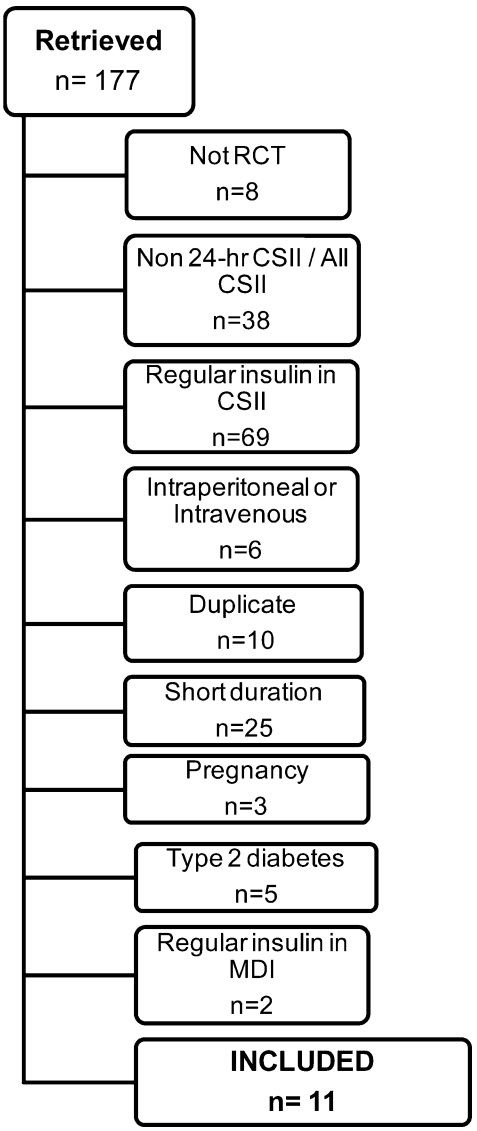

Fig. 1 Trial flow diagram. *RCT* Randomized clinical trial, *CSII* Continuous subcutaneous insulin infusion

A formal meta-analysis on the overall incidence of hypoglycemia could not be performed, because this information was not consistently reported across trials (i.e., some studies reported number of events or incidence rates, but not the number of patients with at least one event).

Discussion

CSII is usually proposed as a treatment option in type 1 diabetic patients who are unable to maintain a satisfactory glycemic control with MDI. The present meta-analysis confirms that CSII is associated with a lower HbA1c at endpoint in comparison with MDI, supporting the utility of this therapeutic approach. Notably, the reduction of HbA1c

Table 1 Characteristics of the studies included in the meta-analysis

Study (Ref.)	Insulin (type)	Comparator	# Adminis. (basal insulin)	Failure to	Trial duration (weeks)	Design	# patients (CSII/C)	Random	Allocation	Drop-out
Fox [6]	ANAL	ANAL/NPH	2 or 3	Insulin	26	PS	11/12	NA	NA	A
DiMeglio [7]	LIS	LIS/NPH or GL	NR	Insulin	26	PS	21/21	A	A	A
Hanaire-Broutin [8]	LIS	LIS/NPH	2	Insulin	16	CO	41/41	NA	NA	A
Hoogma [9]	LIS	LIS/NPH	1 or more	Insulin	26	CO	256/256	NA	NA	A
Opipari-Arrigan [10]	LIS	LIS/NPH or GL	NR	Insulin	26	PS	6/8	NA	NA	A
Thomas [11]	LIS	LIS/GL	1	Insulin	24	PS	7/7	NA	NA	A
Tsui [12]	LIS	LIS/NPH	1 or 2	Insulin	36	PS	13/14	A	A	A
Wilson [13]	LIS	ANAL/NPH/GL	NR	Insulin	52	PS	9/10	A	A	A
DeVries [17]	ASP	ASP/NPH	1 or 2	Insulin	16	PS	40/39	A	A	A
Doyle [18]	ASP	ASP/GL	1	Insulin	16	PS	16/16	A	A	A
Bruttomesso [16]	LIS	LIS/GL	1 or 2	CSII	16	CO	24/15	A	A	A

Admin Administrations, *CSII* Continuous subcutaneous insulin injection, *C* Comparator, *Random* Randomization, *NR* Not reported, *ANAL* Unspecified short-acting analogue, *LIS* Lispro, *ASP Aspart*, *GL* Glargine, *HRI* Human regular Insulin, *PS* Parallel series, *CO* Cross-over, *NA* Not Adequate, *A Adequate*, *NR* Not reported

Table 2 Moderators and outcome variables in individual studies included in the meta-analysis

Study (Ref.)	Age (years)	Duration of DM (years)	BMI baseline (kg/m^2)	HbA1c baseline (%)	HbA1c endpoint[a] (%, CSII/C)	Insulin doses endpoint[a] (*n*, CSII/C)	Severe hypoglycemia (*n*, A/R)
Fox [6]	4	1.0	NR	7.5	7.2 ± 1.0/7.5 ± 0.7	NR	0/1
DiMeglio [7]	4	2.0	NR	9.0	8.5 ± 0.6/8.7 ± 0.7	NR	1/1
Hanaire-Broutin [8]	43	20.0	24.0	8.4	7.9 ± 0.8/8.2 ± 0.8	39 ± 10/47 ± 15	2/1
Hoogma [9]	36	15.0	24.8	8.2	7.4 ± 1.1/7.7 ± 1.4	NR	NR
Opipari-Arrigan [10]	4	NR	16.5	8.1	8.4 ± 0.8/8.2 ± 0.4	NR	0/2
Thomas [11]	43	25.0	NR	8.5	7.4 ± 1.1/7.6 ± 0.7	29 ± 7/62 ± 23	2/2
Tsui [12]	36	16.0	27.0	7.9	7.4 ± 0.6/7.6 ± 0.7	NR	6/4
Wilson [13]	4	1.0	NR	8.0	8.0 ± 0.8/7.9 ± 0.8	NR	1/1
DeVries [17]	37	18.0	NR	9.3	8.4 ± 1.4/9.1 ± 1.4	54 ± 22/73 ± 31	3/6
Doyle [18]	13	6.0	NR	8.1	7.2 ± 1.0/8.1 ± 1.2	NR	2/4
Bruttomesso [16]	37	16.0	23.0	7.4	7.1 ± 0.7/7.2 ± 0.8	36 ± 8/45 ± 11	NR
Total	21.2	10.0	22.5	8.5	7.6 ± 0.9/7.9 ± 0.8	39.4 ± 13.0/56.9 ± 23.1	18/25

[a] Mean value between the two treatment groups. *CSII* Continuous subcutaneous insulin injection, *C* Comparator, *DM* Diabetes mellitus, *BMI* Body mass index, *NR* Not reported

with CSII was not associated with an increased risk of severe hypoglycemia. This result is consistent with those of a previous meta-analysis on a patient-level data from three small trials [19], and of two larger meta-analyses which included trials applying CSII with RHI [1, 2].

In all the trials included in the meta-analysis, MDI was administered with a basal-bolus scheme, namely, with short-acting insulin analogs or RHI before meals and one or two injections of long-acting analogs or NPH insulin for basal requirements. However, the type of prandial and basal insulin in MDI was not consistent across trials. Short-acting insulin analogs produce a significant reduction of HbA1c in type 1 diabetic patients in comparison with RHI [5]; therefore, the comparison of short-analogs as CSII with RHI as MDI could produce a bias in favor of CSII. This could account for the greater reduction of HbA1c reported in a recent meta-analysis of CSII versus MDI, which included also a large number of trials with RHI [20]. Most available studies used NPH as basal insulin in MDI; it is possible that long-acting analogs would have produced better results, although the advantage of these preparations in type 1 diabetes is controversial [5, 21]. In fact, long-acting analogs are associated with a lower hypoglycemic risk; however, they do not seem to produce a further reduction of HbA1c in comparison with NPH [21]. Unfortunately, the number of trials comparing CSII with

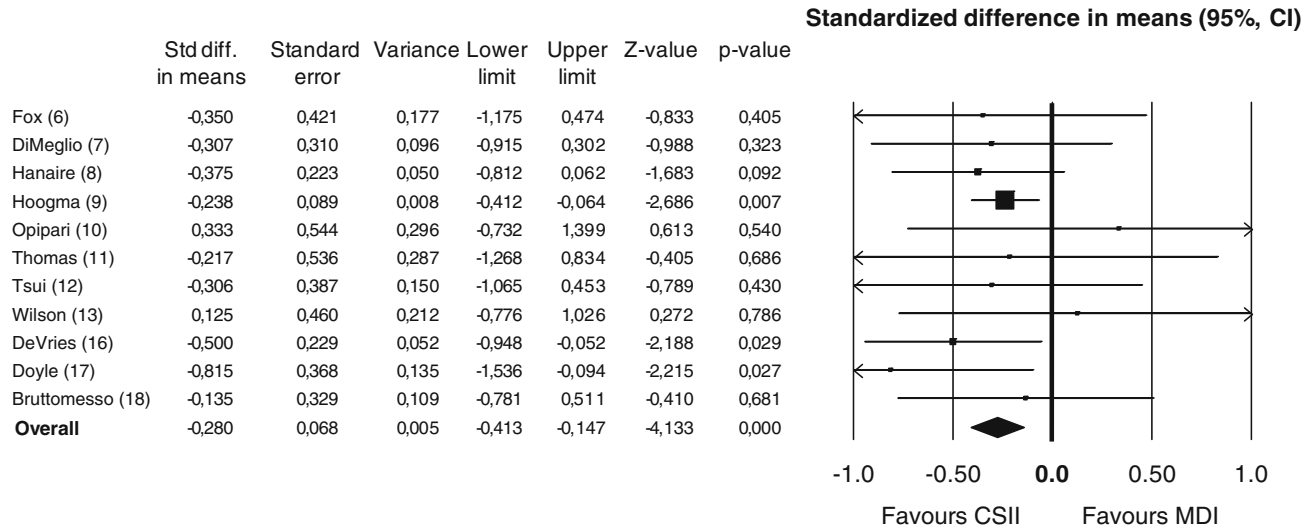

Fig. 2 Differences (with 95%CI) between CSII and conventional treatment in the effects on HbA1c at endpoint. The size of the data markers represents the relative weight of the trial according to patient-years

MDI using analogs (glargine) as basal insulin is still too small to produce reliable meta-analytical results. Further research is needed to clarify this point.

It should be considered that available trials except one [15] enrolled patients failing to MDI, who were randomized to continue the same unsatisfactory treatment or to switch to CSII. Therefore, CSII, which is more expensive than traditional injections, should be considered as a more effective alternative only in patients who are unable to maintain a good control with MDI, while there is no evidence of an overall superiority of CSII over MDI in type 1 diabetes [22–25].

The possible mechanisms for the improvement of metabolic control with CSII include a more appropriate supply of basal insulin and a easier adjustment of boluses in the case of suboptimal blood glucose [26]. It should be considered that subgroup analysis failed to detect any relevant improvement of metabolic control with CSII in younger children, even if this result is controversial [27]. The reasons for the apparent lack of superiority in children are speculative; it can be hypothesized that young children are unable to perform accurate adjustments of prandial insulin doses, or that they are less likely to administer additional boluses in case of moderate hyperglycemia. Notably, in this sub-population of patients, CSII failed to produce further benefits on metabolic control, despite its potential for optimizing basal insulin supply.

Some of the available trials found an improvement of health-related quality of life associated with CSII [9, 10, 17], but this result was not confirmed by other studies [11, 12, 18]. No trial reported a better quality of life with MDI in comparison with CSII. Unfortunately, a formal meta-analysis on the effects of CSII on quality of life is prevented by the heterogeneity of methods used across trials for the assessment of this parameter.

In conclusion, continuous subcutaneous infusion of short-acting insulin analogs can improve metabolic control in patients with type 1 diabetes who are unable to reach glycemic targets with conventional basal-bolus regimens with multiple daily injections.

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References

1. Pickup JC, Renard E (2008) Long-acting insulin analogs versus insulin pump therapy for the treatment of type 1 and type 2 diabetes. Diabetes Care 31(Suppl 2):S140–S145
2. Weissberg-Benchell J, Ntisdel-Lomaglio J, Seshadri R (2003) Insulin pump therapy: a meta-analysis. Diabet Care 26:1079–1087
3. Siebenhofer A, Plank J, Berghold A, Jeitler K, Horvath K, Narath M, Gfrerer R, Pieber TR (2006) Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. Cochrane Database Syst Rev CD003287
4. Colquitt J, Royle P, Waugh N (2003) Are analogue insulins better than soluble in continuous subcutaneous insulin infusion? Results of a meta-analysis. Diabet Med 20:863–866
5. Siebenhofer A, Plank J, Berghold A, Jeitler K, Horvath K, Narath M, Gfrerer R, Pieber TR (2006) Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. Cochrane Database Syst Rev CD003287
6. Fox LA, Buckloh LM, Smith SD, Wysocki T, Mauras N (2005) A randomized controlled trial of insulin pump therapy in young children with type 1 diabetes. Diabet Care 28:1277–1281

7. DiMeglio LA, Pottorff TM, Boyd SR, France L, Fineberg N, Eugster EA (2004) A randomized, controlled study of insulin pump therapy in diabetic preschoolers. J Pediatr 145:380–384
8. Hanaire-Broutin H, Melki V, Bessieres-Lacombe S, Tauber JP (2000) Comparison of continuous subcutaneous insulin infusion and multiple daily injection regimens using insulin lispro in type 1 diabetic patients on intensified treatment: a randomized study. The Study Group for the Development of Pump Therapy in Diabetes. Diabet Care 23:1232–1235
9. Hoogma RP, Hammond PJ, Gomis R, Kerr D, Bruttomesso D, Bouter KP, Wiefels KJ, de la CH, Schweitzer DH, Pfohl M, Torlone E, Krinelke LG, Bolli GB (2006) Comparison of the effects of continuous subcutaneous insulin infusion (CSII) and NPH-based multiple daily insulin injections (MDI) on glycaemic control and quality of life: results of the 5-nations trial. Diabet Med 23:141–147
10. Opipari-Arrigan L, Fredericks EM, Burkhart N, Dale L, Hodge M, Foster C (2007) Continuous subcutaneous insulin infusion benefits quality of life in preschool-age children with type 1 diabetes mellitus. Pediatr Diabet 8:377–383
11. Thomas RM, Aldibbiat A, Griffin W, Cox MA, Leech NJ, Shaw JA (2007) A randomized pilot study in Type 1 diabetes complicated by severe hypoglycaemia, comparing rigorous hypoglycaemia avoidance with insulin analogue therapy, CSII or education alone. Diabet Med 24:778–783
12. Tsui E, Barnie A, Ross S, Parkes R, Zinman B (2001) Intensive insulin therapy with insulin lispro: a randomized trial of continuous subcutaneous insulin infusion versus multiple daily insulin injection. Diabet Care 24:1722–1727
13. Wilson DM, Buckingham BA, Kunselman EL, Sullivan MM, Paguntalan HU, Gitelman SE (2005) A two-center randomized controlled feasibility trial of insulin pump therapy in young children with diabetes. Diabet Care 28:15–19
14. Weintrob N, Benzaquen H, Galatzer A, Shalitin S, Lazar L, Fayman G, Lilos P, Dickerman Z, Phillip M (2003) Comparison of continuous subcutaneous insulin infusion and multiple daily injection regimens in children with type 1 diabetes: a randomized open crossover trial. Pediatrics 112:559–564
15. Pozzilli P, Crino A, Schiaffini R, Manfrini S, Fioriti E, Coppolino G, Pitocco D, Visalli N, Corbi S, Spera S, Suraci C, Cervoni M, Matteoli MC, Patera IP, Ghirlanda G (2003) A 2-year pilot trial of continuous subcutaneous insulin infusion versus intensive insulin therapy in patients with newly diagnosed type 1 diabetes (IMDIAB 8). Diabet Technol Ther 5:965–974
16. Bruttomesso D, Crazzolara D, Maran A, Costa S, Dal PM, Girelli A, Lepore G, Aragona M, Iori E, Valentini U, Del PS, Tiengo A, Buhr A, Trevisan R, Baritussio A (2008) In Type 1 diabetic patients with good glycaemic control, blood glucose variability is lower during continuous subcutaneous insulin infusion than during multiple daily injections with insulin glargine. Diabet Med 25:326–332
17. DeVries JH, Snoek FJ, Kostense PJ, Masurel N, Heine RJ (2002) A randomized trial of continuous subcutaneous insulin infusion and intensive injection therapy in type 1 diabetes for patients with long-standing poor glycemic control. Diabet Care 25:2074–2080
18. Doyle EA, Weinzimer SA, Steffen AT, Ahern JA, Vincent M, Tamborlane WV (2004) A randomized, prospective trial comparing the efficacy of continuous subcutaneous insulin infusion with multiple daily injections using insulin glargine. Diabet Care 27:1554–1558
19. Retnakaran R, Hochman J, DeVries JH, Hanaire-Broutin H, Heine RJ, Melki V, Zinman B (2004) Continuous subcutaneous insulin infusion versus multiple daily injections: the impact of baseline A1c. Diabet Care 27:2590–2596
20. Jeitler K, Horvath K, Berghold A, Gratzer TW, Neeser K, Pieber TR, Siebenhofer A (2008) Continuous subcutaneous insulin infusion versus multiple daily insulin injections in patients with diabetes mellitus: systematic review and meta-analysis. Diabetologia 51:941–951
21. Monami M, Marchionni N, Mannucci E (2009) Long-acting insulin analogues vs. NPH human insulin in type 1 diabetes. A meta-analysis. Diabetes Obes Metab [Epub ahead of print]
22. Lapolla A, Dalfrà MG, Masin M, Bruttomesso D, Piva I, Crepaldi C, Tortul C, Dalla Barba B, Fedele D (2003) Analysis of outcome of pregnancy in type 1 diabetics treated with insulin pump or conventional insulin therapy. Acta Diabetol 40:143–149
23. Cimino A, Valentini U, Rotondi A, Candrina R, Salvi A, Spandrio S, Radaeli E, Giustina G (1987) Continuous basal insulin infusion without premeal boluses in insulin-dependent diabetes mellitus therapy. Acta Diabetol Lat 24:193–198
24. Hofmann HM, Weiss PA, Haas JG (1986) Continuous insulin delivery systems for the pregnant diabetic patient. Acta Diabetol Lat 23:201–214
25. Gimenez M, Conget I, Nicolau J, Pericot A, Levy I (2007) Outcome of pregnancy in women with type 1 diabetes intensively treated with continuous subcutaneous insulin infusion or conventional therapy. A case-control study. Acta Diabetol 44:34–37
26. Colino E, Álvarez MA, Carcavilla A, Alonso M, Ros P, Barrio R (2009) Insulin dose adjustment when changing from multiple daily injections to continuous subcutaneous insulin infusion in the pediatric age group. Acta Diabetol. doi:10.1007/s00592-009-0103-x
27. Pankowska E, Blazik M, Dziechciarz P, Szypowska A, Szajewska H (2009) Continuous subcutaneous insulin infusion vs. multiple daily injections in children with type 1 diabetes: a systematic review and meta-analysis of randomized control trials. Pediatr Diabet 10(5):2–58