Meta-analysis of short-acting insulin analogues in adult patients with type 1 diabetes: continuous subcutaneous insulin infusion versus injection therapy

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Abstract

Aims/hypothesis. This study aimed to compare the effect of treatment with short-acting insulin (SAI) analogues versus structurally unchanged short-acting insulin (regular insulin) on glycaemic control and on the risk of hypoglycaemic episodes in type 1 diabetic patients using different insulin treatment strategies.

Methods. We performed a meta-analysis of 27 randomised controlled trials that compared the effect of SAI analogues with regular insulin in patients with type 1 diabetes mellitus. The treatments were administered either via continuous subcutaneous insulin infusion (CSII) or by conventional intensified insulin therapy (IIT) with short-acting insulin injections before meals and basal insulin administered once or twice daily in most cases.

Results. HbA_{1c} levels were reported for 20 studies. For studies using CSII, the weighted mean difference between values obtained using SAI analogues and regular insulin was -0.19% (95% CI: -0.27 to -0.12), whereas the corresponding value for injection

studies was -0.08% (95% CI: -0.15 to -0.02). For the analysis of overall hypoglycaemia, we used the results from nine studies that reported the mean frequency of hypoglycaemic episodes per patient per month. For studies using CSII, the standardised mean difference between SAI analogues and regular insulin was -0.07 (95% CI: -0.43 to 0.28), whereas for IIT studies the corresponding value was -0.04 (95% CI: -0.24 to 0.16).

Conclusions/interpretation. Taking into consideration the low quality of the trials included, we can conclude that use of a short-acting insulin analogue in CSII therapy provides a small, but statistically significant improvement in glycaemic control compared with regular insulin. An even smaller effect was obtained with the use of IIT. The rate of overall hypoglycaemic episodes was not significantly reduced with short-acting insulin analogues in either injection regimen.

Keywords Complications · Continuous subcutaneous insulin infusion · Diabetes mellitus · Hypoglycaemia · Intensified insulin therapy · Meta-analysis · Randomised controlled trial

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Abbreviations: CSII, continuous subcutaneous insulin infusion · IIT, conventional intensified insulin therapy · SAI, short-acting insulin

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Introduction

It is difficult to achieve day-long normoglycaemia using structurally unchanged short-acting insulin (regular insulin) preparations [1] because regular insulin tends to associate in 'clusters' of six molecules (hexamers), and these clusters take time after injection to dissociate into single molecules that can be used by the body [2]. The dissociation of hexamers is facilitated in short-acting insulin analogues (SAI analogues), and these achieve peak plasma concentrations about twice as high and within approximately half the time compared with regular insulin [3, 4]. Despite the theoretical superiority of SAI analogues over regular insulin, the efficacy of SAI analogues in the treatment of diabetic patients is still unclear. Some studies have reported improved metabolic control and reduced hypoglycaemic episodes [5, 6, 7, 8, 9, 10, 11, 12, 13], whereas others failed to show a positive effect [14, 15, 16].

In this study we performed a systematic review and meta-analysis of studies that compared SAI analogues with regular insulin either in continuous subcutaneous insulin infusion (CSII) or intensified insulin therapy (IIT) according to the Quality of Reporting of Meta-analyses (QUOROM) statement [17] of controlled and randomised trials. This was carried out in order to evaluate the possible advantages of SAI analogues in terms of glycaemic control and the numbers of overall and severe hypoglycaemic episodes.

Subjects and methods

Identification and selection of trials. We performed a highly sensitive search for randomised controlled trials combined with key terms for identifying studies comparing SAI analogues with regular insulin using the Cochrane Library (issue 4, 2003) [18], Medline (1966 to December 2003), Embase (1974 to December 2003). We also hand-searched reference lists and abstract books from major diabetology meetings from 1992 to 2003, contacted the three main pharmaceutical companies (Aventis [Strasbourg, France], Eli Lilly [Indianapolis, Ind., USA], Novo Nordisk [Bagsvaerd, Denmark]) and checked textbooks and bibliographies. Forty-seven authors and experts were contacted, and 16 (34%) responded to our queries.

All randomised controlled trials in which adult type 1 diabetic patients (excluding pregnant women and children) receiving the two SAI analogue treatments available on the market (aspart, lispro) were compared with patients receiving regular insulin treatment were considered. Intervention duration had to be 4 weeks or more, and insulin had to be injected subcutaneously either via CSII or IIT with short-acting insulin before meals. Studies in which any additional treatment was given were included as long as this was administered equally to both groups.

Outcome measures. We assessed glycaemic control measured

by percentage of HbA_{1c} and numbers of overall and severe hypoglycaemic episodes. Table 1 describes the classification and threshold blood glucose levels for hypoglycaemia. The heterogeneity of reporting only allowed a statistical analysis of overall hypoglycaemic events to be made.

Study selection, collection and quality assessment. Two reviewers independently screened the title, abstract and keywords of each reference identified by the search. Where there were differences of opinion, these were resolved by a third party. Only full papers were considered for the systematic review. Data from each study included were extracted by the two independent reviewers using a structured data extraction form. The methodological quality of each trial was assessed using modifications of the criteria given in the Cochrane Handbook and the criteria of Jadad [19] and Schulz [20]. We used three categories such that assessment A means that plausible bias is unlikely to seriously affect the results, assessment B means that plausible bias raises some doubt about the results and assessment C means that plausible bias seriously weakens confidence in the results.

Statistical analysis. Weighted mean differences were calculated for the percentage of glycosylated haemoglobin, and a random effects model was used for the meta-analysis.

We tried to incorporate the two different study designs used (crossover and parallel) into the meta-analysis [21, 22]. One of the prerequisites for using a crossover study is that the mean difference (or the difference between means) of the treatments is available. Additionally, the standard deviation, standard error or a confidence interval for the within-person differences must be given. These estimates were provided for some of the studies, whereas for other studies we had to estimate the SE from the test statistic or from *p* values. In cases where the SE for the within-person differences could not be extracted from a trial, the correlation between treatment outcomes was approximated using the lowest observed correlation among the other studies ($r=0.69$). The robustness of the results was assessed by repeating the analysis using a fixed-effects model. Heterogeneity between trials was assessed by the chi square test. A funnel plot and Egger's test were used to test for publication bias. The standardised mean difference was calculated for overall hypoglycaemic episodes per patient per month using unpaired analysis. The number of severe hypoglycaemic episodes per 100 patient-years was calculated by dividing the number of severe hypoglycaemic episodes by the years of exposure and then multiplying by 100.

This manuscript presents part of the results of a systematic review "Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus" by the Metabolic and Endocrine Disorders Group of the Cochrane Collaboration, which will be published in the Cochrane Library (issue 2, 2004).

Results

The initial search using the search strategy described yielded 1143 studies. After initial investigation of the abstracts, 1071 articles were excluded by consensus. There were differences of opinion on four further articles, and these were resolved by a third party; three were excluded and one was included in the analysis. Therefore, 69 randomised controlled trials were potentially appropriate for inclusion in the meta-analysis (Fig. 1).

Table 1. Characteristics of the different randomised controlled trials

Study	Methods	Participants / interventions	Definition of hypoglycaemia
CSII studies			
Bode 2001 [38]	<i>Design:</i> parallel <i>Follow-up:</i> 49 days <i>Q-assessment:</i> C <i>Sponsor:</i> Novo Nordisk	Aspart vs. Regular 19 vs 10 Type 1 diabetic patients <i>Mean age:</i> 38 vs 34 years <i>Diabetes duration:</i> unknown	<i>Overall:</i> <2.5 mmol/l without an appropriate explanation <i>Severe:</i> not defined
Hedman 2001 [14]	<i>Design:</i> crossover <i>Follow-up:</i> 84 days <i>Q-assessment:</i> B <i>Sponsor:</i> not defined	Lispro vs Regular 12 Type 1 diabetic patients <i>Mean age:</i> 48 years <i>Diabetes duration:</i> 31 years	<i>Overall:</i> not defined <i>Severe:</i> third-party help
Johansson 2000 [5]	<i>Design:</i> crossover <i>Follow-up:</i> 120 days <i>Q-assessment:</i> B <i>Sponsor:</i> Eli Lilly	Lispro vs Regular 41 Type 1 diabetic patients <i>Mean age:</i> 42 years <i>Diabetes duration:</i> 21 years	<i>Overall:</i> <3 mmol/l and/or symptoms <i>Severe:</i> third-party help
Raskin 2001 [7]	<i>Design:</i> crossover <i>Follow-up:</i> 168 days <i>Q-assessment:</i> C <i>Sponsor:</i> Eli Lilly	Lispro vs Regular 59 Type 1 diabetic patients <i>Mean age:</i> 40 years <i>Diabetes duration:</i> 18 years	<i>Overall:</i> <3 mmol/l and/or symptoms <i>Severe:</i> i. v. glucose
Renner 1999 [6]	<i>Design:</i> crossover <i>Follow-up:</i> 240 days <i>Q-assessment:</i> C <i>Sponsor:</i> Eli Lilly	Lispro vs Regular 113 Type 1 diabetic patients <i>Mean age:</i> 37 years <i>Diabetes duration:</i> 19 years	<i>Overall:</i> <3.5 mmol/l and/or symptoms <i>Severe:</i> not defined
Schmauss 1998 [15]	<i>Design:</i> crossover <i>Follow-up:</i> 180 days <i>Q-assessment:</i> C <i>Sponsor:</i> Eli Lilly	Lispro vs Regular 11 Type 1 diabetic patients <i>Mean age:</i> 30 years <i>Diabetes duration:</i> 14 years	<i>Overall:</i> <3.5 mmol and/or symptoms <i>Severe:</i> i. v. glucagon or glucose
Zinman 1997 [40]	<i>Design:</i> crossover <i>Follow-up:</i> 180 days <i>Q-assessment:</i> C <i>Sponsor:</i> Eli Lilly	Lispro vs Regular 30 Type 1 diabetic patients <i>Mean age:</i> 35 years <i>Diabetes duration:</i> 18 years	<i>Overall:</i> <3 mmol/l and/or symptoms <i>Severe:</i> third-party help
Bode 2002 [39]	<i>Design:</i> parallel <i>Follow-up:</i> 112 days <i>Q-assessment:</i> C <i>Sponsor:</i> Novo Nordisk	Aspart (I) vs Regular vs Lispro (II) 59 vs 59 vs 28 Type 1 diabetic patients <i>Mean age:</i> 42 vs 43 vs 40 years <i>Diabetes duration:</i> not defined	<i>Overall:</i> symptoms <i>Severe:</i> third-party help and glucose <2.8 mmol/l
IIT studies			
Anderson 1997 [8]	<i>Design:</i> parallel <i>Follow-up:</i> 360 days <i>Q-assessment:</i> C <i>Sponsor:</i> Eli Lilly	Lispro vs Regular 336 Type 1 diabetic patients <i>Mean age:</i> 32 years <i>Diabetes duration:</i> 13 years <u>295 Type 2 diabetic patients (not analysed)</u>	<i>Overall:</i> <2 mmol/l and/or symptoms <i>Severe:</i> not defined
Anderson 1997 [12]	<i>Design:</i> crossover <i>Follow-up:</i> 180 days <i>Q-assessment:</i> C <i>Sponsor:</i> Eli Lilly	Lispro vs Regular 1008 Type 1 diabetic patients <i>Mean age:</i> 33 years <i>Diabetes duration:</i> 12 years	<i>Overall:</i> <3.5 mmol/l and/or symptoms <i>Severe:</i> third-party help
Del Sindaco 1998 [11]	<i>Design:</i> 4 groups, crossover <i>Follow-up:</i> 180 days <i>Q-assessment:</i> C <i>Sponsor:</i> not defined	I: lispro vs regular + NPH once or twice daily II: lispro vs regular + NPH 4 times daily I: 15; II: 12 Type 1 diabetic patients <i>Mean age:</i> I: 33; II: 32 years <i>Diabetes duration:</i> I: 15; II: 13 years	<i>Overall:</i> <3.3 mmol/l <i>Severe:</i> third-party help
Ferguson 2001 [41]	<i>Design:</i> crossover <i>Follow-up:</i> 336 days <i>Q-assessment:</i> C <i>Sponsor:</i> Eli Lilly	Lispro vs Regular 39 Type 1 diabetic patients <i>Mean age:</i> 46 years <i>Diabetes duration:</i> 26 years	<i>Overall:</i> <3.5 mmol/l and/or symptoms <i>Severe:</i> third-party help

Table 1 (continued)

Study	Methods	Participants / interventions	Definition of hypoglycaemia
Gale 2000 [16]	<i>Design:</i> crossover <i>Follow-up:</i> 168 days <i>Q-assessment:</i> C <i>Sponsor:</i> Eli Lilly	Lispro vs Regular 93 Type 1 diabetic patients <i>Mean age:</i> 35 years <i>Diabetes duration:</i> 13 years	<i>Overall:</i> <2.5 mmol/l and/or symptoms <i>Severe:</i> coma and/or i. v. glucose or glucagon
Heller 1999 [42]	<i>Design:</i> crossover <i>Follow-up:</i> 240 days <i>Q-assessment:</i> B <i>Sponsor:</i> Eli Lilly	Lispro vs Regular 68 vs 67 Type 1 diabetic patients <i>Mean age:</i> 37 vs 39 years <i>Diabetes duration:</i> 16 vs 17 years	<i>Overall:</i> <3 mmol/l and /or symptoms <i>Severe:</i> third-party help
Holleman 1997 [10]	<i>Design:</i> crossover <i>Follow-up:</i> 84 days <i>Q-assessment:</i> C <i>Sponsor:</i> Eli Lilly	Lispro vs Regular 199 Type 1 diabetic patients <i>Mean age:</i> 35 years <i>Diabetes duration:</i> 13 years	<i>Overall:</i> <3 mmol/l and/or symptomatic <i>Severe:</i> third-party help
Home 1998 [43]	<i>Design:</i> crossover <i>Follow-up:</i> 56 days <i>Q-assessment:</i> C <i>Sponsor:</i> Novo Nordisk	Aspart vs Regular 104 Type 1 diabetic patients <i>Mean age:</i> 34 years <i>Diabetes duration:</i> 15 years	<i>Overall:</i> symptoms <i>Severe:</i> third-party help
Home 2000 [44]	<i>Design:</i> parallel <i>Follow-up:</i> 180 days <i>Q-assessment:</i> C <i>Sponsor:</i> Novo Nordisk	Aspart vs. Regular 707 vs 358 Type 1 diabetic patients <i>Mean age:</i> 38 years <i>Diabetes duration:</i> 15 years	<i>Overall:</i> symptoms <i>Severe:</i> third-party help
Iwamoto 2001 [45]	<i>Design:</i> parallel <i>Follow-up:</i> 168 days <i>Q-assessment:</i> C <i>Sponsor:</i> Novo Nordisk	Aspart vs Regular 143 vs 64 Type 1 diabetic patients <i>Mean age:</i> 34 vs 32 years <i>Diabetes duration:</i> 11 years	<i>Overall:</i> symptoms <i>Severe:</i> not defined
Provenzano 2001 [46]	<i>Design:</i> crossover <i>Follow-up:</i> 336 days <i>Q-assessment:</i> C <i>Sponsor:</i> not defined	Lispro vs Regular 12 Type 1 diabetic patients <i>Mean age:</i> 28 years <i>Diabetes duration:</i> 12 years	<i>Overall:</i> symptoms <i>Severe:</i> glucagon, glucose, coma
Raskin 2000 [49]	<i>Design:</i> parallel <i>Follow-up:</i> 180 days and 180 days extension <i>Q-assessment:</i> C <i>Sponsor:</i> Novo Nordisk	Aspart vs Regular 596 vs 286 Type 1 diabetic patients <i>Mean age:</i> 39 vs 40 years <i>Diabetes duration:</i> 16 years	<i>Overall:</i> <2.5 mmol/l and/or symptoms <i>Severe:</i> third-party help
Vignati 1997 [52]	<i>Design:</i> crossover <i>Follow-up:</i> 120 days <i>Q-assessment:</i> C <i>Sponsor:</i> Eli Lilly	Lispro vs Regular 379 Type 1 diabetic patients <i>Mean age:</i> 39 years <i>Diabetes duration:</i> 13 years <u>328 Type 2 diabetic patients (not analysed)</u>	<i>Overall:</i> <3.5 mmol/l <i>Severe:</i> glucagon
Ciofetta 1999 [47]	<i>Design:</i> parallel <i>Follow-up:</i> 90 days <i>Q-assessment:</i> C <i>Sponsor:</i> No sponsor	Lispro vs Regular 16 Type 1 diabetic patients <i>Mean age:</i> 33 years <i>Diabetes duration:</i> 13 years	<i>Overall:</i> <3.9 mmol/l <i>Severe:</i> third-party help
Annuzzi 2001 [48]	<i>Design:</i> crossover <i>Follow-up:</i> 180 days <i>Q-assessment:</i> C <i>Sponsor:</i> Eli Lilly	Lispro vs Regular 90 Type 1 diabetic patients <i>Mean age:</i> 31 years <i>Diabetes duration:</i> 12 years	<i>Overall:</i> <3.3 mmol/l and/or symptoms <i>Severe:</i> third-party help
Roach 1999 [51]	<i>Design:</i> crossover <i>Follow-up:</i> 180 days <i>Q-assessment:</i> C <i>Sponsor:</i> Eli Lilly	Lispro vs Regular 37 Type 1 diabetic patients <i>Mean age:</i> 40 years <i>Diabetes duration:</i> 13 years <u>63 Type 2 diabetic patients (not analysed)</u>	<i>Overall:</i> <3 mmol/l and/or symptoms <i>Severe:</i> coma, i. v. glucagon or glucose

Table 1 (continued)

Study	Methods	Participants / interventions	Definition of hypoglycaemia
Boehm 2002 [53]	<i>Design:</i> parallel <i>Follow-up:</i> 84 days <i>Q-assessment:</i> C <i>Sponsor:</i> Novo ND	Aspart vs Regular 104 Type 1 diabetic patients <i>Mean age:</i> 45 years <i>Diabetes duration:</i> 16 years <u>187 Type 2 diabetic patients</u> (not separately analysed)	<i>Overall:</i> symptoms <i>Severe:</i> third-party help
Recasens 2003 [50]	<i>Design:</i> parallel <i>Follow-up:</i> 360 days <i>Q-assessment:</i> C <i>Sponsor:</i> not defined	Lispro vs Regular 22 vs 23 Type 1 diabetic patients <i>Mean age:</i> 23 vs 24 years <i>Diabetes duration:</i> new onset	<i>Overall:</i> <3.3 mmol/l and/or symptoms <i>Severe:</i> third-party help
Skrha 2002 [54]	<i>Design:</i> crossover <i>Follow-up:</i> 60 days <i>Q-assessment:</i> C <i>Sponsor:</i> Eli Lilly	Lispro vs Regular 55 Type 1 diabetic patients <i>Mean age:</i> 36 years <i>Diabetes duration:</i> 11 years <u>7 Type 2 diabetic patients</u> (not separately analysed)	<i>Overall:</i> <3.5 mmol/l and/or symptoms <i>Severe:</i> not defined

NPH: neutral protamine Hagedorn insulin; Q-assessment, quality assessment

Twenty-seven studies were excluded upon further scrutiny. The main reasons for exclusion were: (i) interventions not comparable; (ii) partial and duplicate publications of a multicentre study; (iii) study duration of less than 4 weeks; or (iv) reporting of data for only one study period. A further 15 studies were excluded from this analysis. Of these, five were performed with patients with type 2 diabetes [23, 24, 25, 26, 27], three were performed with children [28, 29, 30], one with adolescents [31], one with children and adults [32], one with pregnant type 1 diabetic patients [33], two with patients with gestational diabetes [34, 35] and two duplicate publications did not provide further information on prespecified outcome measures [36, 37]. We ultimately identified 27 randomised controlled trials that compared SAI analogues with regular insulin using either CSII or IIT as injection regimens. Of these, 22 studies were performed with type 1 diabetic patients [5, 6, 7, 10, 11, 12, 14, 15, 16, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50] and five studies had a combined study population of type 1 and type 2 diabetic patients [8, 51, 52, 53, 54].

Table 1 summarises the characteristics of the trials included in our analysis. The comprehensive data collection sheet is available from the authors. Of the eight trials in which CSII was used, six had a crossover design and two had a parallel design. A total of 707 subjects took part in the CSII trials. The unweighted mean age was 39 years for patients treated with SAI analogues and 38 years for patients treated with regular insulin. Diabetes duration was 20 years for both treatment groups. Trial duration ranged from 42 to 120 days, with a mean follow-up period of 84 days. The quality of six studies was assessed to be in category C. Two studies were of higher quality (category B) and described methodological issues in some

detail (e.g. method of randomisation, flow of participants, blinding of outcome assessment).

There were 19 IIT trials, 12 of which had a crossover design and seven a parallel design. Altogether, 7975 individuals participated in the IIT trials. Both treatment groups had an unweighted mean age of 36 years and a diabetes duration of 14 years. Trial duration ranged from 28 to 360 days, with a mean follow-up period of 122 days. The quality of 15 studies was assessed to be in category C and only three studies were of higher quality (category B).

Glycaemic control – HbA_{1c}. Post-treatment HbA_{1c} levels were assessed in 20 studies. The CSII and IIT studies were analysed separately. For studies using CSII (two parallel, five crossover), the weighted mean difference in HbA_{1c} percentages between SAI analogues and regular insulin was -0.19% (95% CI: -0.27 to -0.12) (Fig. 2a), whereas for IIT studies (six parallel, seven crossover) the weighted mean difference in HbA_{1c} percentages was -0.08% (95% CI: -0.15 to -0.02) (Fig. 2b). Although the CSII studies showed no significant variation ($p=0.6$), the chi square test showed some evidence of heterogeneity among the IIT studies ($p=0.09$). The robustness of the results was evaluated using different statistical models. The estimates from the fixed-effects model were similar for both treatment regimens. The funnel plots did not indicate publication bias with Egger's test, yielding non-significant results for both types of administration ($p=0.5$ for CSII, $p=0.8$ for IIT).

Hypoglycaemic episodes. Overall hypoglycaemic episodes were reported for 26 studies. However, only nine studies mentioned mean episodes per patient per month, which was the criterion used for analysis. For

Fig. 1. Flow chart showing the numbers of randomised controlled trials identified, those excluded for various reasons and those included in the meta-analysis. RCTs, randomised controlled trials

studies using CSII (one parallel, two crossover), the standardised mean difference between SAI analogues and regular insulin was -0.07 (95% CI: -0.43 to 0.28) (Fig. 3a). For unstandardised data it is equivalent to -0.49 (95% CI: -1.9 to 0.9). For IIT studies (two parallel, four crossover) the standardised mean difference was -0.04 (95% CI: -0.24 to 0.16) (Fig. 3b). In original units it is equivalent to -0.06 (95% CI: -1.28 to 1.16).

Severe hypoglycaemic episodes were reported for 22 studies. One study was excluded from analysis due to the use of different inclusion criteria compared with the other studies [41]. In this study, which only included patients with hypoglycaemic unawareness, there was a trend toward a lower number of severe hypoglycaemic events in the analogue group compared with the regular insulin group (55 vs 84 episodes respectively, $p=0.09$). For studies using CSII, the incidence of severe hypoglycaemia ranged from 0 to 21.8 (median 0) episodes per 100 person-years for SAI analogues and from 0 to 21.8 (median 5.5) episodes per 100 person-years for regular insulin. For studies using IIT, the incidence of severe hypoglycaemia ranged from 0 to 247.3 (median 33.3) episodes per 100 person-years for SAI analogues and from 0 to 544 (median 50.5) episodes per 100 person-years for regular insulin.

Fig. 2. Weighted mean differences (95% CI) in HbA_{1c} percentage values between SAI analogues and structurally unchanged short-acting insulin administered via (a) CSII or (b) IIT. * Aspart vs regular; ** lispro vs regular

Discussion

This meta-analysis includes 27 randomised controlled trials. In adults with type 1 diabetes the use of SAI analogues in CSII only produced a relatively small

improvement in glycaemic control compared with regular insulin. This effect was negligible in patients in IIT studies. We did not differentiate between the SAI analogues lispro and aspart because it is known that both insulin analogues are equally effective at controlling prandial blood glucose fluctuations in type 1 diabetic patients [55, 56].

The heterogeneous design of the studies, often of poor methodological quality, only allows a cautious interpretation of the results to be made. In addition, only a small percentage of authors submitted the original data we requested, and therefore this communication process did not substantially improve the study quality

Fig. 3. Weighted mean differences (95% CI) in overall hypoglycaemic event rates between SAI analogues and structurally unchanged short-acting insulin administered via (a) CSII or (b) IIT. * Aspart vs regular; ** lispro vs regular; *** lispro vs regular + neutral protamine Hagedorn insulin once or twice daily; **** lispro vs regular + neutral protamine Hagedorn insulin four times daily

assessment. According to the authors who replied, some did not have direct access to original data or did not complete our questionnaire due to lack of time and funding. Any further improvement of this meta-analysis can only be made with access to the original database.

In the DCCT, over a period of 6.5 years, a decrease in HbA_{1c} of about 2% resulted in an absolute risk reduction of 20% for the development of retinopathy and of 17% for the progression of retinopathy, which yields numbers needed to treat per year of 32 and 39

respectively [57]. Assuming that a reduction in HbA_{1c} with insulin analogues would result in a similar relative benefit, 320 patients would have to be treated with SAI analogues in CSII for 1 year to prevent the development of retinopathy in one patient. Accordingly, 390 patients would need to be treated to prevent the progression of diabetic retinopathy in a single patient. For patients treated with SAI analogues in IIT, the numbers needed to treat per year would be 800 and 975 respectively. However, in the DCCT the beneficial effect of improved glycaemic control on microvascular complications was not seen until after 3 years of treatment [57]. SAI analogues have only been tested in short-term studies, and it is still uncertain whether this treatment will result in a significant long-term improvement in HbA_{1c}. Also, it remains unclear whether the beneficial effect of improved glycaemic control on the development and progression of microvascular complications achieved with regular insulin is equal to that obtained with SAI analogues [58].

As regards hypoglycaemic events, various studies reported these over different time intervals. The episodes were sometimes counted overall or per patient per month. The studies were also limited by the different definitions used for hypoglycaemic episodes. Some used glucose concentrations between <2 mmol/l and <3.9 mmol/l, whilst others used symptoms of different severity from unwellness to coma. In terms of severe hypoglycaemic episodes, the definition ranged from third-party help to coma and/or application of glucagon or glucose. Therefore, heterogeneity between the trials only allows a statistical analysis of overall hypoglycaemic events to be made.

For overall hypoglycaemic episodes, the results of our analysis did not confirm the often postulated advantage of reduced hypoglycaemic events with SAI analogue treatment. There were no significant differences in overall hypoglycaemia between SAI analogues and regular insulin in either injection regimen. The estimation that an average type 1 diabetic patient experiences six to eight mild episodes of hypoglycaemia per month [59, 60] implies that the non-significant reduction of hypoglycaemic episodes with SAI analogues in CSII and IIT trials that was obtained in our meta-analysis was clinically negligible.

For severe hypoglycaemia, we expressed the number of overall episodes per 100 person-years in terms of medians and ranges. The more appropriate analysis of "the number of patients with at least one severe hypoglycaemic episode" was not possible because these data were only reported by a minority of studies. Our analysis does not take into account how the likelihood of hypoglycaemic events is influenced by factors such as social status, C-peptide levels or patients' determination to reach normoglycaemia [61, 62]. Severe hypoglycaemia occurred less often in CSII studies than in IIT studies for both agents. The wide range of values for severe hypoglycaemia in IIT studies was mostly the

result of the inclusion of one study of very short duration [43]. In this study, the definition of severe hypoglycaemia was "third-party help", although the inclusion criteria for patients did not differ from the other studies analysed. The extraordinarily high number of severe hypoglycaemic episodes reported in this study may have been caused by the use of a strict dosage algorithm for hyperglycaemia and hypoglycaemia. In CSII studies and in IIT studies, the frequency of severe hypoglycaemia was lower in patients on SAI analogues. However, interpreting study results pertaining to the frequency of severe hypoglycaemia is difficult due to inconsistent and bias-prone definitions. Patients may inappropriately deny severe hypoglycaemia, and in this context "third-party help" is a soft and variable description of severity. More robust definitions, such as "injection of glucose or glucagon by another person" may produce more reliable data [62]. This definition of severe hypoglycaemia was used in only four studies, whereas five studies did not provide any definition of severe hypoglycaemia. Furthermore, based on the evidence available on this topic, it does not seem plausible that the frequency of severe hypoglycaemia can be reduced without a concomitant reduction in the frequency of overall hypoglycaemic episodes [63].

The frequency of nocturnal hypoglycaemia could not be analysed because in most cases the definition of nocturnal hypoglycaemia was either not reported, not defined or differed substantially between trials (e.g. 24.00–06.00 hours, median bedtime to median breakfast time, 23.00–06.00 hours, bedtime to 07.00 hours).

Taking into account the low quality of the trials included, our analysis suggests only a negligible benefit of SAI analogues in the majority of diabetic patients treated with insulin. We suggest a cautious response to the vigorous promotion of insulin analogues until long-term efficacy and safety data are available. More appropriately designed studies of longer duration would result in more robust findings. Because of the nature of the endpoints in studies investigating the effects of insulin treatment, such studies should be designed, performed and statistically analysed without any sponsoring bias.

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