Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus (Review)

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ABSTRACT

Background
Short acting insulin analogue use for diabetic patients is still controversial, as reflected in many scientific debates.

Objectives
To assess the effects of short acting insulin analogues versus regular human insulin.

Search strategy
The Cochrane Library (Issue 3, 2005), MEDLINE, EMBASE until September 2005.

Selection criteria
Randomised controlled trials with an intervention duration of at least 4 weeks.

Data collection and analysis
Trial selection and evaluation of study quality was done independently by two reviewers.

Main results
Altogether 8274 participants took part in 49 randomised controlled studies. Most studies were of poor methodological quality.
In patients with type 1 diabetes, the weighted mean difference (WMD) of HbA1c was -0.1% (95% CI: -0.2 to -0.1) in favour of insulin analogue, whereas in patients with type 2 diabetes the WMD was 0.0% (95% CI: -0.1 to 0.0).
In subgroup analyses of different types of interventions in type 1 diabetic patients, the WMD in HbA1c was -0.2% (95% CI: -0.3 to -0.1) in favour of insulin analogue in studies using continuous subcutaneous insulin injections (CSII), whereas for conventional intensified insulin therapy (IIT) studies the WMD in HbA1c was -0.1% (95% CI: -0.1 to 0.0).
The WMD of the overall mean hypoglycaemic episodes per patient per month was -0.2 (95% CI: -1.1 to 0.7) and -0.2 (95% CI: -0.5 to 0.1) for analogues in comparison to regular insulin in patients with type 1 diabetes and type 2 diabetes, respectively.
For studies in type 1 diabetes patients the incidence of severe hypoglycaemia ranged from 0 to 247.3 (median 21.8) episodes per 100 person-years for insulin analogues and from 0 to 544 (median 46.1) for regular insulin, in type 2 the incidence ranged from 0 to 30.3 (median 0.3) episodes per 100 person-years for insulin analogues and from 0 to 50.4 (median 1.4) for regular insulin.
No study was designed to investigate possible long term effects (e.g. mortality, diabetic complications), in particular in patients with diabetes related complications.

Authors' conclusions
Our analysis suggests only a minor benefit of short acting insulin analogues in the majority of diabetic patients treated with insulin. Until long term efficacy and safety data are available we suggest a cautious response to the vigorous promotion of insulin analogues. For safety purposes, we need a long-term follow-up of large numbers of patients and well designed studies in pregnant women to determine the safety profile for both the mother and the unborn child.

PLAIN LANGUAGE SUMMARY

Short acting insulin analogues in diabetes mellitus

Short acting insulin analogues (Lispro, Aspart, Glulisine) act more quickly than regular human insulin. It can be injected immediately before meals and leads to lower blood sugar levels after food intake. Our analysis showed that short acting insulin analogues were almost identically effective to regular human insulin in long term glycaemic control and were associated with similar episodes of low blood sugar (hypoglycaemia). No information on late complications such as problems with the eyes, kidneys or feet are existing. Until long term safety data are available we suggest a cautious response to the vigorous promotion of insulin analogues.

BACKGROUND

Diabetes mellitus is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. This in turn leads to chronic hyperglycaemia (that is elevated levels of plasma glucose) with disturbances of carbohydrate, fat and protein metabolism. Long-term complications of diabetes mellitus include retinopathy, nephropathy, neuropathy and increased risk of cardiovascular disease. For a detailed overview of diabetes mellitus, please see 'Additional information' in the information on the Metabolic and Endocrine Disorders Group in *The Cochrane Library* (see 'About The Cochrane Collaboration', 'Cochrane Review Groups (CRGs)'). For an explanation of methodological terms, see the main Glossary in *The Cochrane Library*.

Despite improved purity and stability of the available insulin preparations, it has become apparent that the pharmacokinetics following subcutaneous injection of the currently available structurally unchanged regular insulin preparations make it difficult to achieve day-long normoglycaemia (Zinman 1989). In the last decade, considerable attention has been devoted to the development of insulin analogues with pharmacokinetic profiles that differ from those of existing insulin preparations. Compared to regular human insulin, lysine at position 28 and proline at position 29 of the B-region were interchanged in the short acting insulin analogue Lispro (HumalogR). In the short acting insulin analogue Aspart (NovoRapidR), proline at position 29 of the B-region was replaced by aspartic acid and in the short acting insulin analogue Glulisine (ApidraR), the amino acid asparagine was replaced by lysine at position 3 and lysine with glutamic acid at position 29 of the B-chain. Plasma insulin concentrations peak from two to four hours after injection of regular insulin, unlike the much earlier plasma insulin peak in non-diabetic individuals after meal ingestion. This low rise to peak insulin concentration is likely to account for much of the observed hyperglycaemia following meals in people with diabetes. The delay in the absorption of subcutaneously administered regular insulin is due to the fact that in this preparation, insulin tends to associate in 'clusters' of six molecules (hexamers), and time is needed after injection for these clusters to dissociate to single molecules which can be used by the body (Mosekilde 1989). Short acting insulin analogues with less tendency toward self-association are therefore absorbed more quickly, achieving peak plasma concentrations about twice as high and within approximately half the time compared to regular insulin (Howey 1994; Torlone 1994).

This pharmacokinetic profile leads to lower glucose levels after meals (Howey 1994; Heinemann 1996) and should improve overall glycaemic control. It has been proposed that lower postprandial glucose may be associated with a lower risk of cardiovascular complications in diabetes (Haffner 1998). One suggested advantage of short acting insulin analogues is the possibility to inject insulin immediately before meals, even if in daily life most diabetic patients seem to use short or even no injection-meal interval (Heinemann 1995). Further proposed advantages in terms of quality of life are changes in injection modes with the possibility of injecting short acting insulin analogues after meals without deterioration of prandial glycaemic control (Brunner 2000; Schernthaner 1998).

Treatment with the three short acting insulin analogues (Lispro - HumalogR, Aspart - Novo RapidR, Glulisine - ApidraR) available on the market is currently promoted with purported advantages with respect to metabolic control or reduced incidence of hypoglycaemic episodes for patients with diabetes mellitus (Ahmed 1998; Anderson 1997b; Anderson 1997c; Holleman 1997; Martin 1994; Vignati 1997). On the other hand, several studies failed to show a positive effect on overall blood glucose levels when short acting insulin analogues were compared with regular insulin (Anderson 1997a; Gale 2000; Garg 1996; Holleman 1997; Jacobs 1997; Pfuetzner 1996). Insulin treatment strategies, where short acting insulin analogues can be used, include intensified insulin therapy (short acting insulin before meals, basal insulin at bedtime or twice daily, including adjustment of insulin dose based on carbohydrate intake) or conventional insulin therapy (basal or premixed insulin up to three times daily with or without oral hypoglycaemic agents). Only patients treated with continuous subcutaneous insulin infusion (CSII) performing intensified insulin therapy regime showed a significant decrease in HbA1c when short acting insulin analogues were used (Melki 1998; Zinman 1997). In the case of hypoglycaemic episodes, two published meta-analyses also reported contradictory results with respect to hypoglycaemic episodes (Brunelle 1998; Davey 1997). Insulin analogues are more expensive than regular insulin and in the year 2000, Lispro and Aspart had a 30% share of the market for short acting insulins in most developed countries.

Structural homology of insulin analogues to insulin-like-growth-factor-I (IGF-I) has caused concern regarding the progression of diabetic late complications and potential mitogenic (induction of cell division) effects, especially with long-term use of insulin analogues. IGF-I may affect the progression of retinopathy (Grant 1993; King 1985) and certain modified insulin analogues have shown a carcinogenic effect in the mammary glands in female rats (Jørgensen 1992) or mitogenic potency in osteosarcoma cells (Kurtzhals 2000). Despite these potentially adverse properties of insulin analogues, only very limited data on long term safety are currently available, mainly because patients with clinically relevant microvascular complications have been excluded from most clinical studies.

As only a few reviews (Bolli 1999; Brunelle 1998; Colquitt 2003; Davey 1997; Shukla 1999) are currently available, we present a systematic review on possible advantages of treatment with short acting insulin analogues to provide adequate information for medical personnel and patients. In contrast to the only systematic review, which investigated the effect of short acting insulin analogues in patients with type 1 diabetes using CSII (Colquitt 2003), this meta-analyses covers all patient groups with different subcutaneous injection regimen.

This review is an update of the original review first published in Issue 4, 2004.

A highly sensitive search applying the same search strategy as used for the original review was performed from 01/10/2003 to 21/09/2005: 386 potentially relevant abstracts were identified and screened for retrieval. 375 of these were excluded by consensus. Eleven publications were potentially appropriate to be included in the analysis, of which further four were excluded by consensus because of not being randomised, no comparable insulin regimen were used or analogues were not compared with regular insulin. Finally, seven new studies fulfilled the criteria to be included into this systematic review. For further details see additional Figure 01 presenting the flow chart according the QUOROM statement.

OBJECTIVES

To assess the effects of short acting insulin analogues in comparison to regular human insulin.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All randomised controlled trials (blinded and open, parallel and cross-over design) with a treatment duration of four weeks or more, designed to compare diabetic patients who were treated with the currently on the market available short acting insulin analogues Lispro, Aspart or Glulisine versus regular human insulin were included in the review, regardless of dose or schedule, if insulin was injected subcutaneously via syringe, pen or pump. Only a small number of blinded studies were available, because in most cases different injection schedules were used for insulin analogues and human regular insulin.

Types of participants

People of any age or sex with type 1 or type 2 diabetes on insulin, and diabetic pregnant women (including gestational diabetes), mostly using the diagnostic criteria valid at the time of beginning the trial (ADA 1997; WHO 1985).

Types of intervention

We considered all diabetic patients receiving a short acting insulin analogue treatment (intervention group) in comparison to patients receiving treatment with regular human insulin (control group), whether the short acting insulin treatment was used with or without other long- or intermediate acting insulin, as long as any additional treatment was given equally to both groups.

Types of outcome measures

Primary outcomes:
(1) glycaemic control (for example glycated haemoglobin, fasting plasma glucose, 24 hour glucose profile);
(2) number of overall, severe (for example requiring third party help) and non-severe hypoglycaemic episodes (subdivided by time of day of occurrence);
(3) quality of life assessment, ideally using a validated instrument like the Diabetes Treatment Satisfaction Questionnaire (Bradley 1990).

Secondary outcomes:
(1) number and severity of adverse events (for example local reactions, ketoacidosis, carcinogenicity);
(2) diabetic complications (nephropathy, retinopathy, neuropathy, other diabetes related complications);
(3) diabetes related mortality (death from myocardial infarction, stroke, peripheral vascular disease, renal disease, hyperglycaemia, hypoglycaemia, sudden death);
(4) total mortality;
(5) costs.

Timing of outcome measurement

Outcome measurement was evaluated in the short term (less than or equal to three months) and the long term (more than three months).

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Metabolic and Endocrine Disorders Group methods used in reviews.

Electronic searches from 1990 to September 2005
Published studies were identified through a literature search using *The Cochrane Library* (Issue 3, 2005), MEDLINE and EMBASE. We used the standard search strategies provided by the Cochrane Metabolic and Endocrine Disorders Group and search terms for short acting insulin analogues which are shown in the MEDLINE search strategy below. The search strategies were adapted for the other databases. For a detailed search strategy see under 'Additional Tables'.

The general search strategy consisted of:
(1) short acting insulin analogues;
(2) diabetes mellitus (see search strategy of the Cochrane Metabolic and Endocrine Disorders Group in *The Cochrane Library* (see 'About the Cochrane Collaboration', 'Collaborative Review Groups');
(3) systematic reviews/meta-analyses (see search strategy of the Cochrane Metabolic and Endocrine Disorders Group in *The Cochrane Library* (see 'About the Cochrane Collaboration', 'Collaborative Review Groups');
(4) randomised/controlled trials (see search strategy of the Cochrane Metabolic and Endocrine Disorders Group in *The Cochrane Library* (see 'About the Cochrane Collaboration', 'Collaborative Review Groups');
(5) economic studies (see search strategy of the Cochrane Metabolic and Endocrine Disorders Group in *The Cochrane Library* (see 'About the Cochrane Collaboration', 'Collaborative Review Groups').

and was combined as follows in the field of insulin analogues:
(1) #1 and #2 and #3 for systematic reviews/meta-analyses;
(2) #1 and #2 and #4 for randomised controlled trials;
(3) #1 and #2 and #5 for economic studies.

For a detailed search strategy see under 'Additional Tables' (Table 01).

Additional search
Additional searching was done by using cross-references from original articles and reviews, and by screening of abstracts of major diabetology meetings (European Association for the Study of Diabetes, American Diabetes Association) ongoing from 1992 and articles of diabetes journals (Diabetologia, Diabetic Medicine, Diabetes Care, Diabetes) until December 2003.

With the help of the International Register of Clinical Trials Registers at (http://www.trialscentral.org) and the register of Current Science at (http://www.controlled-trials.com) we looked for ongoing trials.

Inquiries were also directed to the three main pharmaceutical companies producing short-acting insulin analogues (Aventis, Eli Lilly, Novo Nordisk). We contacted experts and approval agencies (the European Agency for the Evaluation of Medicinal Products (EMEA), the U.S. Food and Drug Administration (FDA), the Medicines Control Agency (MCA), the Therapeutic Goods Administration (TGA)).

With regards to economic analyses, we additionally contacted the Pharmaceutical Evaluation Section of the Pharmaceutical Benefits Branch of the Commonwealth Department of Health and Aged Care of Australia.

The bibliography of standard textbooks (Diabetes Annual, 12. Elsevier Science B.V. (Marshall 1999); Praxis der Insulintherapie (Berger 2001), Evidence-based Diabetes Care (Gerstein 2001)) were also reviewed.

METHODS OF THE REVIEW

Selection of studies
Two reviewers independently screened the title, abstract and key words of each reference identified by the search and applied the inclusion criteria. Inter-rater agreements were calculated using the kappa-statistic (Cohen 1960). Articles that appeared to fulfil the inclusion criteria were retrieved in full. Where differences in opinion existed, the differences were resolved by a third party.

Assessment of methodological quality of included studies
Trials fulfilling the review inclusion criteria were assessed independently for methodological quality by two reviewers. Interrater agreements were calculated using the kappa-statistic. In cases of disagreement, the rest of the group was consulted and a judgement was made based on consensus. Assessment for methodological quality was done using a modification of the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* and the criteria of Schulz and Jadad (Schulz 1995; Jadad 1996).

(1) Minimisation of selection bias - a) was the randomisation procedure adequate? b) was the allocation concealment adequate?
(2) Minimisation of performance bias - a) were the patients and people administering the treatment blind to the intervention?
(3) Minimisation of attrition bias - a) were withdrawals and dropouts completely described? b) was analysis done by intention-to-treat?
(4) Minimisation of detection bias - a) were outcome assessors blind to the intervention?

Based on these criteria, studies were broadly subdivided into the following three categories (see C*ochrane Handbook for Systematic Reviews of Interventions*):
A - all quality criteria met: low risk of bias;
B - one or more of the quality criteria only partly met: moderate risk of bias;
C - one or more criteria not met: high risk of bias.

For the purpose of the analysis in this review, trials were classified into categories according to criteria A, B or C (Cochrane

Handbook for Systematic Reviews of Interventions) (Higgins 2005) (see also sensitivity analysis below).

Data collection

Data from each included study were extracted by two independent reviewers using our data extraction form. Differences in data extraction were resolved by consensus, referring back to the original article. When necessary, information was sought from the authors of the primary studies. Our data extraction form was headed by the identification of the trial, the name of the first author, the year in which the trial was first published and the quality assessment criteria. The following data were extracted, checked and recorded:

General Information

The general information included the publication status (published or unpublished), the possibility of a duplicate publication, the sponsor of trial (known or not defined), the language of publication, the country of publication, the geographical area (urban or rural) and the setting where the trial was carried out (hospital inpatient, hospital outpatient, physicians office).

Methods Section

The information about the methods summarized the characteristics of the trial, the characteristics of participants, the characteristics of interventions and the outcome measures used and reported in the publication.

Characteristics of the trial

The items covered the design and the duration of the trial, the randomisation (and method), the allocation concealment (and method), the blinding (patients, people administering treatment, outcome assessors) and the check of blinding.

Characteristics of participants

Information about the participants included the number of participants in each group, how the participants were selected (random, convenience), the exclusion criteria used and the general characteristics (for example age, gender, nationality, ethnicity). Disease related information concerning duration of diabetes and late complications such as retinopathy, nephropathy, neuropathy and foot complications was extracted. The similarity of groups at baseline was checked as well as the reports about withdrawals and losses to follow-up (reasons / description). If subgroup analysis was done, the reported reasons and the method was noted.

Characteristics of interventions

The relevant extracted information to extract was the time of intervention, the length of follow-up (in days), the types of insulin (analogues versus common), the dose and route of administration and the schedule of administration.

Characteristics of outcome measures

The measures mentioned in the outcome section and any other outcomes measured in the study were extracted.

Data analysis

Weighted mean differences (WMD) were calculated for the percentage of glycated haemoglobin and a random effects model was used for the meta-analysis.

We tried to incorporate the two different study designs used, cross-over and parallel studies, into the meta-analysis (Curtin 2002; Elbourne 2002). To make use of the cross over design, one prerequisite is that the mean difference (or the difference between means) of the treatments is available. In addition, the standard deviation (SD), standard error (SE) or a confidence interval (CI) for the within-person differences must be given. In some of the studies, these estimates were provided whereas for other studies we had to estimate the SE from the test-statistic or from P-values. If no SE for the within-person differences could 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 unpaired analyses and a fixed effects model. Heterogeneity between trials was assessed by the χ^2 -test and small study bias was tested for by a funnel plot and Eggers' test. The WMD was calculated for overall hypoglycaemic episodes per patient per month using unpaired analysis. The number of severe hypoglycaemic episodes per 100 patient-years was computed by dividing the number of severe hypoglycaemic episodes by the years of exposure and then multiplying by 100.

Subgroup analyses

We performed subgroup analyses for patients with type 1 diabetes in order to explore effect size differences as follows:

(1) different interventions;

(2) duration of intervention;

(3) different types of insulin analogues (Lispro versus Aspart versus Glulisine).

Sensitivity analyses

We performed sensitivity analyses in order to explore the influence of the following factors on effect size:

(1) different study design (parallel versus cross-over);

(2) repeating the analysis taking into account study quality, as specified above ((A + B) versus C);

(3) repeating the analysis taking different diagnostic criteria into account;

(4) repeating the analysis excluding studies using the: source of funding as a filter.

As we found no unpublished studies, only three studies had a double blind design and 93% of studies were written in English sensitivity analyses was not performed for these prespecified items of the protocol. Because of various methods in studies looking at quality of life measurements a sensitivity analyses was not appropriate.

The analyses were carried out using RevMan Analyses 1.0.2 in RevMan 4.2.8 (Cochrane Software) and STATA.

DESCRIPTION OF STUDIES

Studies identified

The electronic search using the search strategy described yielded 1529 studies. No additional trials were retrieved through inquiries addressed to EMEA, FDA, MCA and TGA, all three major insulin manufacturing companies and the experts in this field. No further information on full published studies was obtained by reviewing the abstracts, the textbooks, the cross references of original articles and the results of the register of ongoing trials. For further details see additional Figure 01 presenting the flow chart according the QUOROM statement.

After investigation of the abstracts, 1445 articles were excluded by consensus. Reasons for exclusions were: for example no RCTs, narrative reviews, methodology papers of published and ongoing trials, no comparison between analogues and regular insulin, no comparable insulin regimens, non clinical studies, no diabetic patients included in the study. In four articles differences in opinion existed (Akalin 1997; Kadiri 2001; Ronnemaa 1998; Schmauss 1998) and were resolved by a third party. Three were excluded and one included in the analysis (Schmauss 1998). Inter-observer agreement was 99.7% (kappa = 0.97; 95% CI 0.94 to 1.0).

Therefore 80 RCTs were potentially appropriate to be included in meta-analysis.

The majority of primarily considered publications (94%) was written in English, but we also found two trials published in Polish (Krzymien 2001; Loba 2001), two in German (Laube 1996; Petersen 1995) and one study in Japanese (Iwamoto 2001). The Polish and Japanese papers were translated and assessed in cooperation with the translators.

Excluded studies

Overall thirty-one studies were excluded upon further scrutiny. Reasons for exclusion of studies are given in the 'Table of Excluded Studies'. The main reasons for exclusion were: no comparable interventions, non-randomised trial design, part and duplicate publication of a multi centre trial comprising no additional information according to our predefined endpoint, an intervention duration of less than one month.

Designs of included studies

Finally, 49 RCTs were determined to be potentially appropriate for inclusion in the meta-analysis. Details of the characteristics of the included studies are shown in the 'Table of Included Studies'. Seventeen of the 42 included randomised studies were of parallel design, the others had a crossover design. The multi centre design was the dominating setting (59%) but single centre studies were also common (38%). For two studies the setting was not reported. All trials were published after 1995, 76% could be clearly identified as industry sponsored. All authors were contacted for personal communications and 21% replied to our questionnaire.

Participants of included studies

Altogether 8274 participants took part in the 49 randomised controlled studies. 6184 type 1 diabetic patients, 2028 type 2 diabetic patients and 107 women with gestational diabetes were investigated.

Twenty-seven of the 49 included randomised studies were performed with type 1 diabetes patients, eight with type 2 diabetic patients and six studies had a combined type 1 and type 2 diabetic study population. Further four studies were performed with children (Deeb 2001; Ford-Adams 2003; Tubiana-Rufi 2004; Tupola 2001), one with adolescents (Holcombe 2002), one with pregnant type 1 diabetic patients (Persson 2002) and two study with patients with gestational diabetes (Jovanovic 1999, Mecacci 2003). The weighted mean age of adult type 1 diabetic participants in the parallel trials was 38.1 versus 37.7 years for analogue versus regular insulin, the diabetes duration 16.1 versus 15.6 years, and the body mass index 25.5 versus 25.3 kg/m^2. Type 1 diabetic participants of crossover studies were slightly younger (35.3 years), had a shorter diabetes duration (13.6 years) and a body mass index of 24.5 kg/m^2. The weighted mean age of type 2 diabetic participants in the parallel trials was 57.7 versus 57.5 years for analogue versus regular insulin, the diabetes duration 11.3 versus 11.2 years, and the body mass index 28.9 versus 28.8 kg/m^2. Type 2 diabetic participants of crossover studies had a mean age of 58.4 years, a diabetes duration of 12.6 years and a body mass index of 29.3 kg/m^2. All but one study investigated the effects in both sexes (Home 1998, only men).

Interventions of included studies

Thirty-seven studies used Lispro, 10 used Aspart, one study used Glulisine and one study used Lispro and Aspart as short acting insulin analogues. Duration of intervention ranged from one to 12 months with a mean follow-up of 3.6 months. Approximately 78% of the trials had an initial phase lasting from two weeks to two months in order to achieve stable metabolic conditions. Diagnostic criteria for entry into the study were specified in 84% of trials. Most studies tried to achieve a comparable insulin regimen throughout the investigation period, and treating physicians tried to achieve optimisation of therapy together with their patients, usually by means of flexible insulin therapy in order to achieve metabolic targets of heterogeneously defined 'good control'. One study with cross-over design used a wash out period before switching to the other treatment (Heller 2004).

METHODOLOGICAL QUALITY

Forty-three studies (88%) were of poor methodological quality ('C'), 12% of the studies were of higher quality ('B') and described methodological issues in some detail (for example randomisation and allocation method, flow of participants, blinding of outcome assessment). Inter-observer calculation of key elements of study quality revealed an observed agreement of 90.7% (kappa = 0.69; 95% CI 0.41 to 0.97).

Randomisation

Twelve studies mentioned the method of randomisation (Annuzzi 2001; Bode 2001; Bode 2002a; Boehm 2002; Hedman 2001; Heller 1999; Heller 2004; Holleman 1997; Johansson 2000; Jovanovic 1999; Persson 2002; Tupola 2001) and 14 studies mentioned allocation concealment (Annuzzi 2001; Bode 2001; Bode 2002a; Boehm 2002; Ford-Adams 2003; Hedman 2001; Heller 1999; Holleman 1997; Johansson 2000; Jovanovic 1999; Persson 2002; Tupola 2001, Heller 2004, Gallagher 2005).

Blinding

The stated method of blinding was open in 44 studies and double-blind in five studies (Gale 2000; Home 1998; Zinman 1997; Heller 2004; Gallagher 2005). None of these studies reported checking of blinding conditions in patients and health care providers. Although they were double blind, the study quality was poor with quality assessment "C". Blinding of outcome assessors was not described in a single case.

Description of withdrawals and losses to follow-up and intention-to-treat analysis

Seventy-six per cent of studies reported drop-outs in some detail. Analysis by intention-to-treat analysis could be clearly identified in 18 studies.

Covariates, confounders and effect-modifiers

Disease severity was rarely reported: In 18% pre-existing late complications such as retinopathy, nephropathy or neuropathy were described in some detail at baseline (Chan 2004; Ciofetta 1999; Del Sindaco 1998; Hedman 2001; Heller 1999; Persson 2002; Raskin 2000; Ross 2001; Zinman 1997). Co-medication during intervention was never mentioned at all. Compliance as an important effect modifier especially for introduction of new therapeutic modalities was not investigated in any study.

RESULTS

Metabolic control

For verification of metabolic control HbA1c values were available in most studies. No standardised assessment for fasting, postprandial and 24 hour glucose profile was found throughout the data collection process. In some trials values were based on a single measurement, in others on mean values of several, sometimes weekly or even daily blood glucose readings. Postprandial period varied from one to three hours after meals and the time record of night glucose values differed substantially. Therefore, no calculation for these parameters was performed.

HBA1C

From 49 potentially to be included studies, we had to exclude a further 24 studies from this analysis for the following reasons: Two studies (Heller 1999; Schmauss 1998) reported carry-over effects and the statistical combination with the other studies was not possible. Six further studies did not report any HbA1c baseline or follow up data (Altuntas 2003; Bretzel 2004; Del Sindaco 1998; Herz 2002a; Herz 2003; Home 1998) and another three trials provided no measure of variability (Chan 2004; Roach 1999a; Roach 1999b). Two studies performed with type 1 and type 2 diabetic patients did not show separate analysis (Boehm 2002, Skrha 2002) and two further studies reported quality of life data (Bott 2003; Kotsanos 1997) of previously published studies.

Studies performed in prepubertal children with type 1 diabetes mellitus (Deeb 2001; Ford-Adams 2003, Tubiana-Rufi 2004; Tupola 2001), adolescents (Holcombe 2002), prepubertal children and adults (Jacobs 1997) and pregnant women with type 1 (Persson 2002) and gestational diabetes (Jovanovic 1999, Mecacci 2003) are described separately and were not included in the meta analyses.

In one study (Garg 2005) one subgroup where patients were treated with Glulisine after meal was excluded because of the difference in study design comparing all other studies were analogues were applicated before meal.

HbA1c - type 1 diabetic patients

In 22 studies of type 1 diabetic patients, data on post treatment HbA1c could be extracted. The weighted mean difference of HbA1c was estimated to be -0.1% (95% CI -0.2 to -0.1) in favour of insulin analogue compared to regular insulin. The test of heterogeneity gave a P value of 0.01.

In the main analysis we incorporated the studies with parallel and crossover design taking into account the two different study designs (Elbourne 2002).

In 6 of 13 crossover studies paired analysis had to be approximated by assuming correlation of 0.69 between HbA1c values. Sensitivity analyses were performed to assess the impact of the assumed correlation on the outcome of the meta analysis by repeating the analysis ignoring the crossover design and treating the results of the studies as if they had all come from a parallel design. The pooled result using unpaired analyses from each trial was very similar compared to the main analyses (-0.1%; 95% CI -0.2 to -0.1). For parallel group trials, only an investigation of the changes from baseline revealed similar results (-0.1%; 95% CI -0.2 to -0.0; heterogeneity was not significant).The funnel plot did not indicate publication bias with Eggers' test yielding non-significant results (P = 0.41).

HbA1c - type 1 diabetic patients - subgroup analyses

The studies used different types of interventions. In seven studies continuous subcutaneous insulin injections (CSII) and in 15 studies conventional intensified insulin therapy (IIT) with short acting insulin injections before meals were administered. Basal insulin was used once or twice daily in most cases.

For studies using CSII the WMD in HbA1c was -0.2% (95% CI -0.3 to -0.1) comparing analogues with regular insulin whereas for IIT studies the WMD in HbA1c was -0.1% (95% CI -0.1 to 0.0). The CSII studies showed no significant heterogeneity (P = 0.6), but for the IIT studies the test showed evidence of heterogeneity (P = 0.04).

In studies with a duration of three months or less, the WMD in HbA1c was -0.1% (95% CI -0.2 to -0.0) comparing analogues with regular insulin, in studies of long term duration (more than three months) the WMD in HbA1c was -0.1% (95% CI -0.2 to -0.1). There was no evidence of heterogeneity among long term studies (P = 0.62), however, significant heterogeneity could be observed in studies with short duration (P < 0.01).
In six studies Aspart was compared to regular insulin (-0.1%; 95% CI -0.2 to -0.0, heterogeneity P = 0.3). Five of these studies were performed with a parallel group design. Out of 16 studies comparing Lispro and to regular insulin, twelve used a crossover and four a parallel design (-0.1%; 95% CI -0.2 to -0.0). These trials showed significant heterogeneity (P = 0.02).

HbA1c - type 1 diabetic patients - sensitivity analyses
For studies using a parallel design the WMD in HbA1c was -0.1% (95% CI -0.2 to -0.0) comparing analogues with regular insulin whereas for studies with cross-over design the WMD in HbA1c was -0.1% (95% CI -0.2 to 0.0). The parallel studies showed no significant heterogeneity (P = 0.3), but for the cross-over studies the test showed evidence of heterogeneity (P < 0.01).
For studies with quality assessment B the WMD in HbA1c was 0.0% (95% CI -0.2 to 0.2, heterogeneity P = 0.04) comparing analogues with regular insulin whereas for studies with quality assessment C the WMD in HbA1c was -0.1% (95% CI -0.2 to -0.1, heterogeneity P = 0.03).
For studies using any diagnostic criteria for inclusion the WMD in HbA1c was -0.1% (95% CI -0.2 to -0.1, heterogeneity P = 0.03) comparing analogues with regular insulin whereas for studies without criteria for diabetes diagnosis the WMD in HbA1c was -0.2% (95% CI -0.3 to -0.1, heterogeneity P = 0.9).
For trials with pharmaceutical funding the WMD in HbA1c was -0.1%; 95% CI -0.2 to 0.0, heterogeneity P = 0.16, for Novo Nordisk sponsored and -0.1%; 95% CI -0.2 to 0.0, heterogeneity P < 0.01, for Eli Lilly sponsored trials whereas for trials without or unclear industry sponsoring the WMD HbA1c was -0.1%; 95% CI -0.3 to 0.0, heterogeneity P = 0.6).

HbA1c - type 2 diabetic patients
In five studies HbA1c was mentioned in type 2 diabetic patients (see table of 'Included studies').
The weighted mean difference of HbA1c was estimated to be 0.0% (95% CI -0.1 to 0.0). None of the five studies showed any significant difference of HbA1c values between insulin analogues and regular insulin.

HbA1c - children, adolescents, pregnant type 1 diabetic patients, patients with gestational diabetes
The four existing studies in prepubertal children (Deeb 2001; Ford-Adams 2003; Tubiana-Rufi 2004; Tupola 2001) and the study with adolescents (Holcombe 2002) with type 1 diabetes mellitus did not show any significant reduction in HbA1c. In pregnant women with type 1 diabetes, a similar reduction in HbA1c was obtained comparing the analogue and regular group (Persson 2002). No significant difference was found in patients with gestational diabetes (Jovanovic 1999, Mecacci 2003).

Hypoglycaemic episodes - overall; severe and nocturnal
Overall and severe hypoglycaemic episodes were mentioned in most studies. In case of hypoglycaemic events, various studies reported different time intervals of hypoglycaemic events and the episodes were counted per patient per month, overall and sometimes as a percentage per patient. Furthermore, different definitions of hypoglycaemic episodes were chosen: some used criteria between less than 36 mg/dl (2 mmol/L) and less than 70 mg/dl (3.9 mmol/L), others symptoms of different severity from sickness to coma. In terms of severe hypoglycaemic episodes, the definition ranged from third party help to coma and/or application of glucagon or glucose. We performed a meta-analysis for overall hypoglycaemic events only, counted as episodes per patient per month.

Overall hypoglycaemic episodes
From 49 potentially included studies, we had to exclude 36 studies from this analysis for the following reasons:
Unclear definition of hypoglycaemia (Bode 2001), reporting hypoglycaemic events during only a part of the study period (Jacobs 1997; Johansson 2000; Zinman 1997), carry-over effect (Heller 1999), discrepancy in reporting of the numbers of hypoglycaemia in the published paper (Holleman 1997; Annuzzi 2001), unclear measure of variability (Bretzel 2004;Herz 2003). One study was not designed to consider hypoglycaemia (Hedman 2001). Eight studies only mentioned overall hypoglycaemic events during the whole study period (Boehm 2002; Home 1998; Home 2000; Iwamoto 2001; Provenzano 2001; Raskin 2000; Raskin 2001; Roach 1999b), three studies reported episodes per week or year only (Ford-Adams 2003, Heller 2004; Recasens 2003) or information was provided only in percentage per patient (Roach 1999a, Skrha 2002). For one study the reference value was unclear (Altuntas 2003). After personal communication additional information on severe hypoglycaemic events was obtained (Gallagher 2005). One study performed with type 1 and type 2 diabetic patients did not present separate analysis (Chan 2004).
For lack of homogeneity of the trials included, studies performed with prepubertal children (Ford-Adams 2003; Deeb 2001; Tubiana-Rufi 2004; Tupola 2001), adolescents (Holcombe 2002) and pregnant women with type 1 (Persson 2002) or gestational diabetes (Jovanovic 1999; Mecacci 2003) were excluded from analysis, but are described below. One further study was excluded from analysis because of the different inclusion criteria compared to the other studies (Ferguson 2001).

Overall hypoglycaemic episodes - type 1 diabetic patients
Ten studies mentioned mean episodes per patient per month. The weighted mean difference of the overall mean hypoglycaemic episodes per patient per month was -0.2 (95% CI -1.1 to 0.7) for analogues in comparison to regular insulin. In these selected ten studies distinct heterogeneity has been observed (P < 0.001)

(high variation in included studies, such as numbers of participants ranged from 11 to 1008, intervention length varied from 60 to 360 days and definition of hypoglycaemia ranged from less than 2 mmol to less than 3.9 mmol with or without symptoms).

Overall hypoglycaemic episodes - type 2 diabetic patients

The weighted mean difference of the overall mean hypoglycaemic episodes per patient per month was -0.2 (95% CI -0.5 to 0.1, heterogeneity: P = 0.8) for analogues in comparison to regular insulin.

Overall hypoglycaemic episodes- children, adolescents pregnant type 1 diabetic patients, patients with gestational diabetes and type 1 diabetic patients with hypoglycaemia unawareness

The overall rate of hypoglycaemic episodes per patient per 30 days was reported in two studies and did not significantly differ in prepubertal children (Deeb 2001; Tupola 2001). In the study with adolescents (Holcombe 2002) the event rate of overall hypoglycaemia per patient per 30 days was significantly reduced with the insulin analogue (P = 0.02). In pregnant women (Persson 2002) the event rate regarding biochemical hypoglycaemia was significantly higher in the analogue group compared to the regular group (P < 0.05). In one study with women with gestational diabetes, the total number of hypoglycaemic events did not differ between the groups (Jovanovic 1999), while the other trial did not report data on hypoglycaemic episodes (Mecacci 2003). The study investigating effects of analogues on hypoglycaemic unawareness (Ferguson 2001) found no significant difference of the overall hypoglycaemic rates between the analogue and regular insulin group.

Severe hypoglycaemic episodes

From 49 potentially included studies, we had to exclude 21 studies from this analysis for the following reasons:

No information on severe hypoglycaemic episodes (Bode 2001; Bretzel 2004, Johansson 2000; Renner 1999; Anderson 1997c; Ross 2001; Herz 2002a, Skrha 2002, Herz 2003, Altuntas 2003), report on only a part of the study period (Jacobs 1997) or no separate data were presented for type 1 or type 2 diabetic patients (Chan 2004).

For homogeneity of the trials included, studies performed with prepubertal children (Tupola 2001; Deeb 2001; Ford-Adams 2003, Tubiana-Rufi 2004), adolescents (Holcombe 2002), pregnant women with type 1(Persson 2002) and gestational diabetes (Jovanovic 1999, Mecacci 2003) and one study including patients with hypoglycaemic unawareness (Ferguson 2001) were excluded from this analysis.

Severe hypoglycaemic episodes - type 1 diabetic patients

The incidence of severe hypoglycaemia ranged from 0 to 247.3 (median 21.8) episodes per 100 person-years for insulin analogues and from 0 to 544 (median 46.1) for people treated with regular insulin.

Severe hypoglycaemic episodes - type 2 diabetic patients

The incidence of severe hypoglycaemia ranged from 0 to 30.3 (median 0.3) episodes per 100 person-years for insulin analogues and from 0 to 50.4 (median 1.4) for people treated with regular insulin.

Severe hypoglycaemic episodes - children, adolescents, pregnant type 1 diabetic patients, patients with gestational diabetes and type 1 diabetic patients with hypoglycaemia unawareness

Two studies with prepubertal children presented the rate of severe hypoglycaemic episodes which did not differ (Deeb 2001; Ford-Adams 2003) nor in the study with adolescents (Holcombe 2002). Of the pregnant women, two patients treated with regular insulin had four episodes of severe hypoglycaemia (Persson 2002). In one trial with women with gestational diabetes, no severe hypoglycaemia occurred in either group (Jovanovic 1999), while the other trial did not report data on severe hypoglycaemic episodes (Mecacci 2003). In the study including patients with hypoglycaemia unawareness, there was a trend towards a higher number of severe hypoglycaemic events in the group treated with regular insulin (Ferguson 2001).

Nocturnal hypoglycaemic episodes

In seven studies nocturnal hypoglycaemic episodes were mentioned for type 1 diabetic patients (Gale 2000; Heller 1999; Heller 2004, Holleman 1997; Home 2000; Raskin 2000; Roach 1999a). Three studies were excluded because of a discrepancy in reporting of the numbers of hypoglycaemic events in the published paper (Heller 1999, Heller 2004; Holleman 1997). Overall nocturnal hypoglycaemia was presented in two studies (Gale 2000; Roach 1999a), with one (Gale 2000) showing a significantly reduced event rate with analogue treatment from midnight to 06.00 A.M., whereas no statistically significant difference was observed in the other trial (Roach 1999a) from median bedtime to median breakfast time. In the two other studies severe nocturnal hypoglycaemic episodes were presented. One study (Home 2000) reported no statistically significant difference in third party assistance but significantly less nocturnal hypoglycaemic events requiring glucose or glucagons during a nocturnal time interval from median bedtime to median breakfast. For the second study (Raskin 2000), no information on absolute numbers of severe nocturnal episodes was provided. The percentage of patients who experienced nocturnal hypoglycaemic episodes was significantly lower in the analogue treatment group from midnight to 06.00 A.M.

For type 2 diabetic patients, three studies reported on overall nocturnal hypoglycaemia (Anderson 1997a; Roach 1999a; Ross 2001) from midnight to 06.00 A.M. with diverging results. One study showed significantly less nocturnal hypoglycaemia in the analogue group (Anderson 1997a) and two reported no statistically significant difference between the treatment arms (Roach 1999a; Ross 2001).

The rate of overall nocturnal hypoglycaemic episodes did not statistically significant differ in prepubertal children 11.00 P.M. to 06.00 A.M. (Tupola 2001); bedtime to 07.00 A.M. (Ford-Adams 2003)) and was significantly reduced in adolescents treated with

analogues (Holcombe 2002) from midnight to 06.00 A.M. In the study including patients with hypoglycaemia unawareness, there was a trend of a higher number of nocturnal hypoglycaemic events (midnight to 08.00 A.M.) in the group treated with regular insulin (Ferguson 2001).

Quality of life assessment

Quality of life and treatment satisfaction were assessed in twelve publications. Seven studies (64%) used the Diabetes Treatment Satisfaction Questionnaire, DTSQ (Bradley 1990). In addition, within these seven studies, the Well-Being Questionnaire, WBQ (Bradley 1994) was applied in two trials, the Hypoglycaemia Fear Survey, HFS (Cox 1987) and the Diabetes-Specific Quality of Life Scale, DSQoLS (Bott 1994) in one study each. One publication (Kotsanos 1997) reported the results of the diabetes quality of life clinical trial questionnaire, DQLCTQ, which was validated particularly for this trial. In another trial (Holleman 1997) quality of life was evaluated by having patients complete a patient self-evaluation questionnaire, PEQ (20 questions on 5-point scales). One study in type 2 diabetic patients used a questionnaire developed for the DCCT, DQOL (DCCT 1988). For two studies the instrument used for validation were not mentioned (Schmauss 1998; Tubiana-Rufi 2004). One of these studies (Tubiana-Rufi 2004) was performed with children and the questionnaire was completed by the parents. Main outcomes are summarized in Table 02.
With the most used instrument, the DTSQ, three studies (one double blind, two open design) found no significant difference between the treatment arms, while four studies observed improvement in the analogue group. Detailed information on DTSQ domains in these trials are displayed in Table 03.

Additional outcomes

56% of the studies provided at least some information on adverse events. Overall, frequency and type of adverse events are reported to be comparable for the two treatment groups. Most of the events were mild in severity, such as respiratory tract infections, headaches, flu symptoms or accidental injuries and were not considered to be related to one of the treatments. In most cases, the reasons for withdrawal from trial drug treatment were not considered to be related to the investigational medication. No statistically significant difference in discontinuation rate was seen between the treatments throughout the trials. Six trials reported on local site reactions and found no differences.

Events of ketoacidosis, which were distributed in equal proportions between both treatment groups, were described in 8% of trials. No trial provided information on eventual carcinogenicity. Furthermore, no clinically significant differences were noted for vital signs, physical parameters, results of electrocardiography or clinical laboratory findings.

Whilst in 18% of the studies pre-existing late complications such as retinopathy, nephropathy or neuropathy were described in some detail at baseline, outcome data on these complications under trial drug treatment was only reported in one trial dealing with pregnancy (Persson 2002).

Studies were not planned to investigate mortality. In four trials mortality data were reported. One patient died after a prolonged seizure that was possibly related to hypoglycaemia, while taking regular insulin (Heller 1999). One death from myocardial infarction was reported during analogue treatment (Home 2000) and one from ischaemic heart disease (Holleman 1997) with unknown treatment group assignment. One study reported that no deaths occurred (Garg 2005).

Regarding costs no data were found in the publications.

DISCUSSION

This meta-analysis included 49 studies. In adults with type 1 diabetes the analysis resulted in a small, but statistically significant decrease in HbA1c using short acting insulin analogues. In patients with type 2 diabetes no superiority in HbA1c was observed. In terms of overall hypoglycaemia, the results obtained with short acting insulin analogues and regular insulin were comparable.
The heterogeneous design of the studies, often of poor methodological quality, allows only a cautious interpretation of the results. In addition, only a small percentage of authors submitted the requested original data and therefore the study quality assessment could not be substantially improved after this communication process. Considering only full published trial for this review publication bias can not be excluded.
In subgroup analyses we found a more pronounced effect on HbA1c in favour of analogues for patients using CSII and for studies with an intervention period longer than 3 months. The almost identical results for trials with Aspart Lispro or Glulisine are in accordance with controlled clinical clamp studies (Homko 2003; Plank 2002). In the sensitivity analysis trials with higher quality (B) revealed no improvement for insulin analogues on HbA1c in contrast to trials of lower quality (C).
No study designed to investigate possible long term effects was found. Therefore, it remains unclear to what extent the effect of improved glycaemic control, which was observed in analogue treatment (overall minus 0.1% HbA1c), affects the development and progression of microvascular complications compared to results obtained with regular insulin.
In the DCCT over a period of 6.5 years, a decrease in HbA1c of about 2% resulted in an absolute risk reduction in the development of retinopathy of 20% and of 17% in the progression of retinopathy, which yields numbers needed to treat per year of 32 and 39 (DCCT 1993). Assuming that a reduction in HbA1c with insulin analogues would result in a similar relative benefit, approximately 650 patients would have to be treated with analogues for one year to prevent the development of retinopathy in one patient and approximately 765 patients treated to prevent a single case of progression of diabetic retinopathy. However, in DCCT the

beneficial effect of improved glycaemic control on microvascular complications was not seen before three years of treatment.
For overall hypoglycaemic episodes, the results of our analysis are in line with a previously published meta analysis (Davey 1997). There were no significant differences in overall hypoglycaemia when analogues were compared with regular insulin. The estimation that an average type 1 diabetic patient experiences from six to eight mild episodes of hypoglycaemia per month (Pramming 1990; DCCT 1991) implies that the reduction of hypoglycaemic episodes with analogues was clinically negligible.
For severe hypoglycaemia, we expressed the numbers of overall episodes per 100 person-years as median and range. Severe hypoglycaemia occurred less often in the analogue group than in the regular group. The wide range of severe hypoglycaemia in IIT studies resulted mostly from the inclusion of one study with a very short duration (Home 1998). In this study the definition for severe hypoglycaemia was third party help and the inclusion criteria for patients did not differ from the other included studies. The extraordinarily high number of severe hypoglycaemic episodes may have been caused by the use of the strict dosage algorithm for hyper- and hypoglycaemia. However, the interpretation of the results of the frequency of severe hypoglycaemia in the studies 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 result in more reliable data (Muehlhauser 1998). Also, based on the available evidence 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 (Cryer 2002).

Thirteen trials reported data on quality of life. Various instruments and open study design hardly allow an objective interpretation of the data reported in type 1 diabetic patients. When the mostly used instrument, the DTSQ, showed significant improvement for analogues, it was mainly due to changes in the convenience, flexibility and continuation of treatment. According to the study protocols in the open label studies patients were advised to inject regular insulin in average 30 minutes before meal. One may hypothesize, the difference in injection time (analogues: immediately versus regular: ~ 30 minutes before meals) is a major underlying reason for treatment satisfaction improvements in analogues.
Even in daily life most patients seem to use short or even no injection meal interval (Heinemann 1995). The hypothesis of suggesting a time injection interval for intensified insulin therapy is only based on poorly performed trials and never proven on the basis of controlled studies (see comments Chanteleau E). The only study using a double design (Gale 2000) did not find an improvement in any quality of life item, metabolic control and overall hypoglycaemia. In type 2 diabetic studies with open label design no difference was observed (Kotsanos 1997, Ross 2001).

Owing to the maximum observation period of 12 months and the exclusion of patients with clinically relevant microvascular complications, the overall picture with regard to adverse events did not indicate any substantial difference between analogue and regular insulin treatment. Regarding potentially adverse properties, such as mitogenic effects with possible progression of microvascular complications or development of carcinogenic effects under insulin analogue treatment, this meta-analysis cannot provide any further guidance.

The inclusion criteria for further updates of this review will be changed to studies with a treatment duration of at least 24 weeks. This reflects our efforts to emphasise long-term treatment effects on the outcome measures mentioned above.

AUTHORS' CONCLUSIONS

Implications for practice

Our analysis suggests only a minor clinical benefit of short acting insulin analogues in the majority of diabetic patients treated with insulin. Until long term efficacy and safety data are available, we suggest a cautious response to the vigorous promotion of insulin analogues.

Implications for research

For safety purposes, we need a long-term follow-up of large numbers of patients who use short acting insulin analogues. Due to fears of potentially carcinogenic and proliferative effects, most studies to date have excluded patients with advanced diabetic complications. Furthermore, we need well designed studies in pregnant women to determine the safety profile for both the mother and the unborn child.
For economic analysis, we need to collect cost data in future RCTs.

FEEDBACK

Comment to the review by Siebenhofer

Summary

The review concluded that the "patients who received insulin analogues were more satisfied with the treatment mainly due to greater convenience in the timing of injections"(p4).
This relates to the peculiarity of the study designs of many analog studies: in the control (human insulin) regular groups, an interval of at least 30 minutes was prescribed between injection and meal intake. However, this interval has never been established on the basis of controlled trials, nor has it been based on insulin pharmacokinetics of regular insulin in relation to gastrointestinal physiology (meal carbohydrate absorption).
Heinemann (1995) has mentioned that many patients do not use a fixed injection-meal- interval of30 min; moreover, many patients

adapt the length of an injection-meal-interval to the premeal blood glucose level.

Papers concerning injection-meal-interval are scarce, e.g. Sackey AH, Jefferson IG: Interval between insulin injection and breakfast in diabetes. Arch Dis Child 1994;71 :248-250. The patients in this study were in twice daily injections of NPH/Regular mixtures; only 2/64 patients were on intensified insulin therapy using regular and long acting insulin separately. As a result, the authors found that before breakfast a prolonged injection-meal-interval was advisable (because of the high prebreakfast blood glucose, due to insufficient insulin dosage during the night). For supper, no such interval was required.

In another study (Kinmonth AL, Baum ill: Timing of pre-breakfast insulin injection and postprandial metabolic control in diabetic children. Br Med J 1980; i: 604-606) children were investigated on once-daily injection of Monotard + Actrapid before breakfast, starting their day with a pre-breakfast blood glucose of 180 mg/dl! Again, the recommendation to have a 30 min interval between insulin injection and eating is related only to the breakfast meal (there is no other meal tested), is further related to non-intensive insulin therapy, and is not related to the speed of regular insulin absorption (as suggested by the promoters of insulin analogues 25 years later).

The same holds true for the study by Lean: t\...:1EJ, Ng LL and Tennison BR: Interval between insulin injection and eating in relation to blood glucose control in adult diabetics. Br Med J 1985; i: 105-108. Again the study participants were not giving regular insulin separately from basal insulin, but were using twice daily injections of a mixture of regular and basal (NPH) insulin. The study quality is limited because 225 study patients were studied only by questionnaire, and 11 patients were studied only at breakfast. The latter showed 1 h pp blood glucose increments between 3.5 and 4.9 mmol/l , and corresponding 2h pp blood glucose increments between 0.56-1.88 mmol/l, with injection-meal-intervals between 15 and 45 min. Hence, the author's recommendation that "increasing the interval between insulin injection and eating to 45 minutes would significantly improve control for at least those patients, who currently delay 15 min or less" is unfounded.

On the contrary, as Orre-Petterson AC, Lindstrom T, Bergmark Vand Arnqvist HJ (The snack is critical for the blood glucose profile during treatment with regular insulin pre-prandially. Journal Intern Med 1999; 245:41-45) have shown, "the recommended interval of30 min between insulin injection and meal may be too long".

Finally, Schemthaner et al. have recently demonstrated that HbAlc deteriorates when analogues are given postprandially (Diabetic Medicine 2004, published just before the completion of the Siebenhofer-Cochrane review).

Why has the Nielsen B 10Asp study (Diabetologia 1995) not been quoted: this is the only study on insulin analogs (except for Gale et a1. 2000) that has been performed really double blinded without prescribing an injection-meal-interval- there was no greater patient satisfaction with the analogue (neither was it in the Gale study).

Finally, why has the review on hypoglycaemia by Heinemann (J Diabetes Compl.1999; 13: 105-114) not been quoted? It contains valuable information from hidden sources.

Author's reply

Many thanks for your helpful comments on this important topic.

We agree that the comment on "quality of life" in the synopsis is not appropriate and may be misleading for the general reader. There is no conclusive evidence for requirement of different injection intervals when comparing short acting insulin analogues with regular insulin. We now removed this sentence from the synopsis, because there is - as shown in table 3 - only one double blinded study (Gale) which did not find any differences in terms of quality of life. As you suggested, we have included more information on this topic in the discussion section and, for further detailed information for our readers, we used your comprehensive and detailed comment as a reference.

The study published by Nielson B10Asp. was excluded because, as this analogue is not available on the market, this study does not meet our inclusion criteria.

The review published by Heinemann was cross checked during the process of developing the manuscript. However, no additional "full published" paper could be found, and no abstracts were considered for our review.

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POTENTIAL CONFLICT OF INTEREST

The research group performed several studies in short and long acting insulin analogues with the companies Aventis, Eli Lilly, Novo Nordisk. TR Pieber was and is currently a paid consultant for these companies.

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** Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	Altuntas 2003
Methods	TRIAL DESIGN: parallel SETTING: single centre RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT:- BLINDING: open ITT: unclear SPONSOR: not defined QUALITY ASSESSMENT: C
Participants	COUNTRY: Turkey NUMBER: 40 TYPE OF DIABETES: 2 MEAN AGE [YEARS]: 55 MEAN DIABETES DURATION [YEARS]: 6 vs 10 (lispro vs. regular) OTHER CHARACTERISTICS:
Interventions	LISPRO VERSUS REGULAR LENGTH OF INTERVENTION [days]: 168 SCHEDULE: analogue: immediately; regular: 30 - 45 min.
Outcomes	1.HBA1C [%]:- 2. HYPOGLYCAEMIA: OVERALL DEFINITION: < 3.3 mmol/l or symptoms OUTCOME 0.57% vs. 0,009% (lispro vs. regular); reference base unclear) 3. HYPOGLYCAEMIA : SEVERE DEFINITION: - OUTCOME: - 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: - 6.COSTS: - 7.DROP OUTS: described - none 8. OTHERS: -
Notes	HbA1c was not shown because of inconsistent baseline HbA1c data
Allocation concealment	B – Unclear

Study	Anderson 1997a
Methods	TRIAL DESIGN: crossover SETTING: multicentre, multinational RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT: unclear BLINDING: open ITT: unclear SPONSOR: Eli Lilly

Characteristics of included studies (*Continued*)

	QUALITY ASSESSMENT: C
Participants	COUNTRY: AMERICA, EUROPE, AUSTRALIA, South Africa NUMBER: 722 TYPE OF DIABETES: 2 MEAN AGE [YEARS]: 59 MEAN DIABETES DURATION [YEARS]: 12 OTHER CHARACTERISTICS:
Interventions	LISPRO VERSUS REGULAR LENGTH OF INTERVENTION [days]: 90 SCHEDULE: analogue: immediately; regular: 30 - 45 min.
Outcomes	1.HBA1C [%]: at endpoint: 8.2 vs. 8.2 (lispro vs. regular) 2. HYPOGLYCAEMIA: OVERALL DEFINITION: < 3.5 mmol/l and/or symptoms OUTCOME[epis/pat/month]: 3.2 vs. 3.4 (lispro vs. regular) 3. HYPOGLYCAEMIA : SEVERE DEFINITION: iv glucose or glucagon OUTCOME [overall episodes]: 1 vs. 5 (lispro vs regular) 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: - 6.COSTS: - 7.DROP OUTS: described 8. OTHERS: -
Notes	
Allocation concealment	B – Unclear

Study	**Anderson 1997b**
Methods	TRIAL DESIGN: crossover SETTING: multicentre, multinational RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT: unclear BLINDING: open ITT: yes SPONSOR: Eli Lilly QUALITY ASSESSMENT: C
Participants	COUNTRY: AMERICA, EUROPE, AUSTRALIA ,South Africa NUMBER: 1008 TYPE OF DIABETES: 1 MEAN AGE [YEARS]: 33 MEAN DIABETES DURATION [YEARS]: 12 OTHER CHARACTERISTICS:
Interventions	LISPRO VERSUS REGULAR LENGTH OF INTERVENTION [days]: 90 SCHEDULE: lispro: immediately; regular: 30-45 min.
Outcomes	1.HBA1C [%]: at endpoint: 8.2 vs. 8.2 (lispro vs. regular)

	2. HYPOGLYCAEMIA: OVERALL DEFINITION: <3.5 mmol/l and/or symptoms OUTCOME [epis/pat/month]: 6.4 vs 7.2 (lispro vs. regular) 3. HYPOGLYCAEMIA: SEVERE DEFINITION: third party help OUTCOME [overall episodes]: 84 vs. 119 (lispro vs regular) 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: - 6.COSTS: - 7.DROP OUTS: described 8. OTHERS: -
Notes	
Allocation concealment	B – Unclear

Study	**Anderson 1997c**
Methods	TRIAL DESIGN: parallel SETTING: multicentre, multinational RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT: unclear BLINDING: open ITT: unclear SPONSOR: Eli Lilly QUALITY ASSESSMENT: C
Participants	COUNTRY: AUSTRALIA, USA, CANADA, EUROPE, South Africa NUMBER: I:Type 1: 162 vs. 174; II:Type 2: 145 vs. 150 Type 2 (lispro vs. regular) TYPE OF DIABETES: 1 and 2 MEAN AGE [YEARS]: Type 1: 32 vs. 32; Type 2: 56 vs. 56 (lispro vs. regular) MEAN DIABETES DURATION [YEARS]: Type 1: 13 vs. 12; Type 2: 12 vs. 12 (lispro vs. regular) OTHER CHARACTERISTICS:
Interventions	LISPRO VERSUS REGULAR LENGTH OF INTERVENTION [days]: 360 SCHEDULE: lispro: immediately vs. regular: 30 to 45 min.
Outcomes	1.HBA1C [%]: at endpoint: Type 1: 8.1 vs. 8.3; Type 2: 8.2 vs 8.4 (lispro vs. regular) 2. HYPOGLYCAEMIA: OVERALL DEFINITION: < 2 mmol/l and/or symptoms OUTCOME [epis/pat/month]: TYPE 1: 4.4 vs. 4.5; Type 2: 1.5 vs. 1.6 (lispro vs. regular) 3. HYPOGLYCAEMIA: SEVERE DEFINITION: not defined OUTCOME: not reported 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: - 6.COSTS: -

Characteristics of included studies (*Continued*)

	7.DROP OUTS: described 8. OTHERS: -
Notes	
Allocation concealment	B – Unclear

Study	**Annuzzi 2001**
Methods	TRIAL DESIGN: crossover SETTING: multicentre RANDOMISATION PROCEDURE: adequate ALLOCATION CONCEALMENT: adequate BLINDING: open ITT: unclear SPONSOR: Eli Lilly QUALITY ASSESSMENT: C
Participants	COUNTRY: Italy NUMBER: 90 TYPE OF DIABETES: 1 MEAN AGE [YEARS]: 31 MEAN DIABETES DURATION [YEARS]: 12 OTHER CHARACTERISTICS:
Interventions	LISPRO VERSUS REGULAR LENGTH OF INTERVENTION [days]: 90 SCHEDULE: lispro: immediately; regular: 30-45 min.
Outcomes	1.HBA1C [%]: at endpoint: 8.1 vs. 8.3 (lispro vs. regular) 2. HYPOGLYCAEMIA: OVERALL DEFINITION: < 3.3 mmol/l and/or symptoms OUTCOME [epis/pat/month]: 3.0 vs. 2.4 (lispro vs. regular) 3. HYPOGLYCAEMIA: SEVERE DEFINITION: third party help OUTCOME [overall episodes]: 4 vs. 6 (lispro vs. regular) 4. QUALITY OF LIFE: Preference for lispro shown by DTSQ data. 5. ADVERSE EVENTS: - 6.COSTS - 7.DROP OUTS: described 8. OTHERS: -
Notes	
Allocation concealment	A – Adequate

Study	**Bode 2001**
Methods	TRIAL DESIGN: parallel SETTING: single centre RANDOMISATION PROCEDURE: adequate

Characteristics of included studies (*Continued*)

	ALLOCATION CONCEALMENT: unclear BLINDING: open ITT: unclear SPONSOR:Novo Nordisk QUALITY ASSESSMENT: C
Participants	COUNTRY: USA NUMBER: 19 vs. 10 (aspart vs. regular) TYPE OF DIABETES: 1 MEAN AGE [YEARS]: 38 vs. 34 (aspart vs. regular) MEAN DIABETES DURATION [YEARS]: - OTHER CHARACTERISTICS: patients on CSII therapy
Interventions	ASPART VERSUS REGULAR: LENGTH OF INTERVENTION [days]: 49 days SCHEDULE: aspart: immediately; regular: 30 min.
Outcomes	1.HBA1C [%]: at endpoint: 6.9 vs. 7.1 (aspart vs. regular) 2. HYPOGLYCAEMIA: OVERALL DEFINITION: < 2.5 mmol/l without an appropriate explanation OUTCOME [patients with episodes]: 14 vs. 6 (aspart vs. regular) 3. HYPOGLYCAEMA: SEVERE DEFINITION: not defined OUTCOME: not reported 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: - 6.COSTS: - 7.DROP OUTS: described 7. OTHERS: -
Notes	
Allocation concealment	B – Unclear

Study	**Bode 2002a**
Methods	TRIAL DESIGN: parallel SETTING: multicentre RANDOMISATION PROCEDURE: adequate ALLOCATION CONCEALMENT: unclear BLINDING: open ITT: unclear SPONSOR: Novo Nordisk QUALITY ASSESSMENT: C
Participants	COUNTRY: USA NUMBER: 59 vs. 59 vs. 28 (aspart (I) vs. regular vs.lispro (II)) TYPE OF DIABETES: 1 MEAN AGE [YEARS]: 42 vs. 43 vs. 40 (aspart vs. regular vs.lispro) MEAN DIABETES DURATION [YEARS]: - OTHER CHARACTERISTICS: patients on CSII therapy
Interventions	ASPART (I) VERSUS REGULAR [VERSUS LISPRO (II)]

	LENGTH OF INTERVENTION [days]: 112 SCHEDULE: aspart and lispro: immediately; regular: 30 min.
Outcomes	1.HBA1C [%]: at endpoint: no significant difference 2. HYPOGLYCAEMIA: OVERALL DEFINITION: symptoms OUTCOME [overall episodes]: 1580 vs. 2240 vs. 1159 (aspart vs. regular vs. lispro) 3. HYPOGLYCAEMIA: SEVERE DEFINITION: < 2.8 mmol/l and third party help OUTCOME [overall episodes]: 0 vs.1 vs.0 (aspart vs. regular vs. lispro) 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: - 6.COSTS: - 7.DROP OUTS: described 8. OTHERS: -
Notes	
Allocation concealment	B – Unclear

Study	**Bode 2002b**
Methods	Comparison II of Bode 2002 (lispro vs. regular)
Participants	
Interventions	[ASPART (I) VERSUS] REGULAR VERSUS LISPRO (II)
Outcomes	
Notes	
Allocation concealment	B – Unclear

Study	**Boehm 2002**
Methods	TRIAL DESIGN: parallel SETTING: multicentre, multinational RANDOMISATION PROCEDURE: adaequate ALLOCATION CONCEALMENT: adaequate BLINDING: open ITT: unclear SPONSOR: Novo Nordisk QUALITY ASSESSMENT: C
Participants	COUNTRY: Germany, Austria, UK, Ireland NUMBER: Type 1: 55 vs. 49; Type 2: 85 vs. 102 (premixed formulation of aspart[BiAsp 30] vs. premixed formulation of regular [BHI 30]) TYPE OF DIABETES: 1 and 2 MEAN AGE [YEARS]: Type 1: 43 vs. 46; Type 2: 63 vs. 64 (BiAsp 30 vs. BHI 30) MEAN DIABETES DURATION [YEARS]: Type 1: 15 vs. 17; Type 2: 15 vs. 14 (BiAsp 30 vs. BHI 30) OTHER CHARACTERISTICS:-
Interventions	BiAsp 30 VERSUS BHI 30 LENGTH OF INTERVENTION [days]: 84

Characteristics of included studies (*Continued*)

	SCHEDULE: BiAsp 30: 10 min.; BHI 30: 30 min.
Outcomes	1.HBA1C [%]: at endpoint type 1 and type 2: 8.1 vs. 8.2 (BiAsp 30 vs. BHI 30) 2. HYPOGLYCAEMIA: OVERALL DEFINITION: symptoms OUTCOME [overall episodes]: Type 1 and Type 2: 382 vs. 403 (BiAsp 30 vs. BHI 30) Type 1: 121 vs. 115 (BiAsp 30 vs. BHI 30) 3. HYPOGLYCAEMIA: SEVERE DEFINITION: third party help OUTCOME [overall episodes]: Type 1 and Type 2: 20 vs. 42 (BiAsp 30 vs. BHI 30) Type 1: 4 vs.14 (BiAsp 30 vs. BHI 30) 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: - 6.COSTS: - 7.DROP OUTS: - 8. OTHERS: -
Notes	Pharmacy dispensing error
Allocation concealment	A – Adequate

Study	**Bott 2003**
Methods	TRIAL DESIGN: parallel SETTING: multicentre RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT: unclear BLINDING: open ITT: unclear SPONSOR: Novo Nordisk QUALITY ASSESSMENT: C
Participants	COUNTRY: Austria, Germany, Switzerland NUMBER: 283 vs. 141 (aspart vs. regular) TYPE OF DIABETES: 1 MEAN AGE [YEARS]: 37 MEAN DIABETES DURATION [YEARS]: 13 OTHER CHARACTERISTICS: -
Interventions	ASPART VERSUS REGULAR: LENGTH OF INTERVENTION [days]: 180 SCHEDULE: aspart: immediately; regular: 30 min.
Outcomes	1.HBA1C [%]: at endpoint: 7.5 vs. 7.5 (aspart vs. regular) 2. HYPOGLYCAEMIA: OVERALL DEFINITION: symptoms OUTCOME: no difference 3. HYPOGLYCAEMIA: SEVERE DEFINITION: third party help OUTCOME [overall episodes]: no difference 4. QUALITY OF LIFE:

	significant change from baseline in favour of aspart for DSQOLS and DTSQ score 5. ADVERSE EVENTS: - 6.COSTS: - 7.DROP OUTS: - 8. OTHERS: -
Notes	Part results of german speaking participants of HOME 2000
Allocation concealment	D – Not used

Study	**Bretzel 2004**
Methods	TRIAL DESIGN: parallel SETTING: multicentre RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT: unclear BLINDING: open ITT: yes and per protocol SPONSOR: Novo Nordisk QUALITY ASSESSMENT: C
Participants	COUNTRY: Germany NUMBER: 75 vs. 80 (aspart vs. regular) TYPE OF DIABETES: 2 MEAN AGE [YEARS]: 61-62 MEAN DIABETES DURATION [YEARS]: - OTHER CHARACTERISTICS: -
Interventions	ASPART VERSUS REGULAR: LENGTH OF INTERVENTION [days]: 84 SCHEDULE: aspart and regular: preprandial
Outcomes	1.HBA1C [%]: at endpoint: - 2. HYPOGLYCAEMIA: OVERALL DEFINITION: <2.5 mmol/l and/or symptoms OUTCOME: [ep/pat/month]: 0.4 vs. 0.56 (aspart vs. regular) 3. HYPOGLYCAEMIA: SEVERE DEFINITION: - OUTCOME.- 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: - 6.COSTS: - 7.DROP OUTS: numbers given, no reason described 8. OTHERS: -
Notes	no randomisation HbA1c; third study arm no comparable intervention
Allocation concealment	B – Unclear

Characteristics of included studies (*Continued*)

Study	**Chan 2004**
Methods	TRIAL DESIGN: cross-over SETTING: unclear RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT: unclear BLINDING: open ITT: unclear SPONSOR: not defined QUALITY ASSESSMENT: C
Participants	COUNTRY: China NUMBER: Type 1: 12; Type 2: 18 TYPE OF DIABETES: 1 and 2 MEAN AGE [YEARS]: Type 1 and Type 2: mean 42 years MEAN DIABETES DURATION [YEARS]: Type 1 and Type 2: 8 years OTHER CHARACTERISTICS:-
Interventions	LISPRO VERSUS REGULAR LENGTH OF INTERVENTION [days]: 84 SCHEDULE: lispro and regular: time not reported
Outcomes	1.HBA1C [%]: at endpoint: Type 1: 6,8 vs. 6,6 (lispro vs. regular) Type 2: 7,6 vs. 7,6 (lispro vs. regular) 2. HYPOGLYCAEMIA: OVERALL DEFINITION: OUTCOME: < 3.0 mmol/l and/or symptoms[ep/pat/month]: Type 1 and Type 2: 50 vs. 38 (lispro vs. regular) HYPOGLYCAEMIA: SEVERE DEFINITION: TPH OUTCOME [overall episodes]: Type 1 and Type 2: 2 vs. 1 (lispro vs. regular) 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: - 6.COSTS: - 7.DROP OUTS: described 8. OTHERS: -
Notes	
Allocation concealment	B – Unclear

Study	**Ciofetta 1999**
Methods	TRIAL DESIGN: parallel, group 1 and 2 included SETTING: single centre RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT: unclear BLINDING: open ITT: unclear SPONSOR: not defined QUALITY ASSESSMENT: C

Characteristics of included studies (*Continued*)

Participants	COUNTRY: Italy NUMBER : 8 vs.8 (lispro vs. regular) TYPE OF DIABETES: 1 MEAN AGE [YEARS]: 33 MEAN DIABETES DURATION [YEARS]: 13 OTHER CHARACTERISTICS:-
Interventions	LISPRO VERSUS REGULAR LENGTH OF INTERVENTION [days]: 90 SCHEDULE: lispro: immediately; regular: 10-40 min.
Outcomes	1.HBA1C [%]: at endpoint: 7.0 vs. 6.8 (lispro vs. regular) 2. HYPOGLYCAEMIA: OVERALL DEFINITION: < 3.9 mmol/l OUTCOME [epis/pat/month]: 8.1 vs. 4.0 (lispro vs. regular) 3. HYPOGLYCAEMIA: SEVERE DEFINITION: third party help OUTCOME [overall epidodes]: lispro and regular: 0 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: - 6.COSTS: - 7.FOLLOW UP: not described 8. OTHERS: -
Notes	
Allocation concealment	B – Unclear

Study	**Deeb 2001**
Methods	TRIAL DESIGN: 3-period crossover SETTING: multicentre RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT: unclear BLINDING: open ITT: unclear SPONSOR: Eli Lilly QUALITY ASSESSMENT: C
Participants	COUNTRY: USA, Canada NUMBER: 60 TYPE OF DIABETES: 1 AGE [YEARS]: 8 MEAN DIABETES DURATION [YEARS]: 4 OTHER CHARACTERISTICS:-
Interventions	LISPRO PREPRANDIAL VERSUS LISPRO POSTPRANDIAL VERSUS REGULAR LENGTH OF INTERVENTION [days]: 90 SCHEDULE: lispro preprandial: 0-15 min.; lispro postprandial: directly after meals; regular: 30-45 min.
Outcomes	1.HBA1C [%]: at endpoint: 8.4 vs. 8.5 vs. 8.4 (lispro preprandial vs. lispro postprandial vs. regular) 2. HYPOGLYCAEMIA: OVERALL

	DEFINITION: <3,5 mmol/l and/or symptoms OUTCOME [epis/pat/month]: 14.7 vs. 13.6 vs. 13.8 (lispro preprandial vs. lispro postprandial vs. regular) 3. HYPOGLYCEMIA: SEVERE DEFINITION: third party help OUTCOME [overall episodes]: 2 vs. 3 vs. 6 (lispro preprandial vs. lispro postprandial vs. regular) 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: - 6.COSTS: - 7.DROP OUTS: described 8. OTHERS: -
Notes	
Allocation concealment	B – Unclear

Study	**Del Sindaco 1998**
Methods	TRIAL DESIGN: crossover, 2 (I,II) of 4 comparison groups included SETTING: single centre RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT: unclear BLINDING: open ITT: unclear SPONSOR: not defined QUALITY ASSESSMENT: C Comparison II used for analysis
Participants	COUNTRY: Italy NUMBER: I: 15 ; II: 12 TYPE OF DIABETES: 1 MEAN AGE [YEARS]: I:33; II: 32 MEAN DIABETES DURATION [YEARS]: I: 15; II: 13 OTHER CHARACTERISTICS:
Interventions	I: LISPRO+1-2x NPH VERSUS REGULAR+1-2x NPH; II: LISPRO+3-4x NPH VERSUS REGULAR+3-4x NPH LENGTH OF INTERVENTION [days]: 90 SCHEDULE: lispro: immediately ; regular: 10 - 40 min.
Outcomes	1.HBA1C [%]: I: at endpoint: no significant difference II: at endpoint: significant difference in favor of lispro 2. HYPOGLYCAEMIA: OVERALL DEFINITION: < 3.3 mmol OUTCOME [epis/pat/month]: I: 5.3 vs. 4.0; II: 4.4 vs. 11 3. HYPOGLYCAEMIA: SEVERE DEFINITION: third party help OUTCOME [overall episodes]: I+II: 0 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: - 6.COSTS: - 7.DROP OUTS: not described 8. OTHERS: -
Notes	
Allocation concealment	B – Unclear

Study	**Ferguson 2001**
Methods	TRIAL DESIGN: crossover SETTING: single centre RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT: unclear BLINDING: open ITT: no SPONSOR: Eli Lilly QUALITY ASSESSMENT: C
Participants	COUNTRY: UK NUMBER: 39 TYPE OF DIABETES: 1 MEAN AGE [YEARS]: 46 MEAN DIABETES DURATION [YEARS]: 26

	OTHER CHARACTERISTICS: patients with impaired hypoglycemia awareness, patients on multiple injections and twice daily insulin therapy
Interventions	LISPRO VERSUS REGULAR LENGTH OF INTERVENTION [days]: 168 SCHEDULE: lispro: immediately; regular: 30 min.
Outcomes	1.HBA1C [%]: at endpoint: 9.1 vs. 9.3 (lispro vs. regular) 2. HYPOGLYCAEMIA: OVERALL DEFINITION: 3.5 mmol/l and/or symptoms OUTCOME [overall episodes]: 1156 vs. 1115 (lispro vs. regular) 3. HYPOGLYCAEMIA: SEVERE DEFINITION: third party help OUTCOME [overall episodes]: 55 vs. 84 (lispro vs. regular) 4. QUALITY OF LIFE: DTSQ and HFS: no significant difference 5. ADVERSE EVENTS: - 6.COSTS: - 7.DROP OUTS: described, post hoc exclusion of 1 patient 8. OTHERS -
Notes	
Allocation concealment	B – Unclear

Study	**Ford-Adams 2003**
Methods	TRIAL DESIGN: crossover SETTING: multicentre RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT: adequate BLINDING: open ITT: yes SPONSOR: Eli Lilly QUALITY ASSESSMENT: B
Participants	COUNTRY: UK NUMBER: 23 TYPE OF DIABETES: 1 MEAN AGE [years]: 9 MEAN DIABETES DURATION [years]: not known OTHER CHARACTERISTICS:
Interventions	LISPRO VERSUS REGULAR LENGTH OF INTERVENTION [days]: 112 SCHEDULE: not defined
Outcomes	1.HBA1C [%]: at endpoint: no significant difference 2. HYPOGLYCAEMIA: OVERALL DEFINITION: symptoms OUTCOME [overall episodes]: 556 vs. 604 (lispro vs. regular) 3. HYPOGLYCAEMIA : SEVERE DEFINITION: convulsions and/or glucagon

	OUTCOME [overall episodes]: 2 vs. 1 (lispro vs. regular) 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: - 6.COSTS: - 7. DROP OUTS: described 8. OTHERS: -
Notes	
Allocation concealment	A – Adequate

Study	**Gale 2000**
Methods	TRIAL DESIGN: crossover SETTING: multicentre RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT: unclear BLINDING: double-blind IIT: yes SPONSOR: Eli Lilly QUALITY ASSESSMENT: C
Participants	COUNTRY: UK NUMBER: 93 TYPE OF DIABETES: 1 MEAN AGE [YEARS]: 35 MEAN DIABETES DURATION [YEARS]: 13 OTHER CHARACTERISTICS:
Interventions	LISPRO VERSUS REGULAR LENGTH OF INTERVENTION [days]: 84 SCHEDULE: lispro and regular: immediately
Outcomes	1.HBA1C [%]: at endpoint: at endpoint: 7,5% vs. 7,4% (lispro vs. regular) 2. HYPOGLYCAEMIA: OVERALL DEFINITION: - OUTCOME:- 3. HYPOGLYCAEMIA: SEVERE DEFINITION: coma and/or iv glucose or glucagon OUTCOME [overall episodes]: 3 vs. 10 (lispro vs. regular) 4. QUALITY OF LIFE: no significant difference in DTSQ, WBQ 5. ADVERSE EVENTS: - 6.COSTS: - 7. DROP OUTS: described 8. OTHERS -
Notes	
Allocation concealment	B – Unclear

Characteristics of included studies (*Continued*)

Study	**Gallagher 2005**
Methods	TRIAL DESIGN: crossover SETTING: single centre RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT: third party contact BLINDING: double-blind IIT: unclear SPONSOR: NOVO Nordisk QUALITY ASSESSMENT: C
Participants	COUNTRY: UK NUMBER: 21 TYPE OF DIABETES: 2 MEAN AGE [YEARS]: 66 MEAN DIABETES DURATION [YEARS]: 11 OTHER CHARACTERISTICS:
Interventions	ASPART VERSUS REGULAR LENGTH OF INTERVENTION [days]: 42 SCHEDULE: aspart and regular: 5 minutes before meals
Outcomes	1.HBA1C [%]: at endpoint: 7.0 vs. 7.2 (aspart vs. regular) 2. HYPOGLYCAEMIA: OVERALL DEFINITION:- OUTCOME 3. HYPOGLYCAEMIA: SEVERE DEFINITION:- OUTCOME: 0 in both groups 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: - 6.COSTS: - 7. DROP OUTS: described - unclear if patients were withdrawn before of after randomisation 8. OTHERS
Notes	personal communication: no severe hypoglycaemic episodes
Allocation concealment	B – Unclear

Study	**Garg 2005**
Methods	TRIAL DESIGN: parallel SETTING: multicentre RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT: unclear BLINDING: open IIT: yes SPONSOR: Sanofi-Aventis QUALITY ASSESSMENT: C
Participants	COUNTRY: USA NUMBER: 286 vs. 296 vs. 278 (glu premeal vs. glu postmeal vs. regular) TYPE OF DIABETES: 1 MEAN AGE [YEARS]: 41 vs. 40 vs. 40 (glu premeal vs. glu postmeal vs. regular)

Characteristics of included studies (*Continued*)

	MEAN DIABETES DURATION [YEARS]: 20 vs. 20 vs. 19 (glu premeal vs. glu postmeal vs. regular) OTHER CHARACTERISTICS:
Interventions	GLULISINE PREMEAL VERSUS GLULISINE POSTMEAL VERSUS REGULAR LENGTH OF INTERVENTION [days]: 84 SCHEDULE: glulisine premeal: 0-15 minutes; glulisine postmeal: immediately after completing, or 20 minutes after starting the meal; regular: 30 - 45 minutes
Outcomes	1. HBA1C [%]: change from baseline to endpoint: -0.26% vs. -0.11% vs.-0.13% (glu premeal vs. glu postmeal vs. regular)2. HYPOGLYCAEMIA: OVERALL DEFINITION: symptoms OUTCOME: [epis/pat/month] 3,5 vs. 3.7 vs. 3.5 (glu premeal vs. glu postmeal vs. regular) 3. HYPOGLYCAEMIA: SEVERE DEFINITION: TPH OUTCOME: [epis/pat/month] 0.05 vs. 0.05 vs. 0.13 (glu premeal vs. glu postmeal vs. regular) 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: described - 6.COSTS: - 7. DROP OUTS:described, but not separately for the treatment groups. OTHERS: -
Notes	
Allocation concealment	B – Unclear

Study	**Hedman 2001**
Methods	TRIAL DESIGN: crossover SETTING: single centre RANDOMISATION PROCEDURE: adequate ALLOCATION CONCEALMENT: adequate BLINDING: open IIT: yes SPONSOR: not defined QUALITY ASSESSMENT: B
Participants	COUNTRY: Sweden NUMBER: 12 TYPE OF DIABETES: 1 MEAN AGE [YEARS]: 48 MEAN DIABETES DURATION [YEARS]: 31 OTHER CHARACTERISTICS: patients on CSII therapy
Interventions	LISPRO VERSUS REGULAR LENGTH OF INTERVENTION[days]: 42 SCHEDULE: lispro: immediately; regular: 20 min.
Outcomes	1.HBA1C [%]: at endpoint: at endpoint 7,7 vs. 7,7 (aspart vs. regular) 2. HYPOGLYCAEMIA: OVERALL DEFINITION: - OUTCOME: - 3. HYPOGLYCAEMIA: SEVERE

	DEFINITION: third party help OUTCOME [overall episodes]: lispro and regular: 0 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: - 6.COSTS: - 7.DROP OUTS: described 8. OTHERS: -
Notes	
Allocation concealment	B – Unclear

Study	**Heller 1999**
Methods	TRIAL DESIGN: crossover designed, only first treament period because of period and treatment period interactions analyzed SETTING: multicentre RANDOMIZATION PROCEDURE: adequate ALLOCATION CONCEALMENT: adequate BLINDING: open ITT: yes SPONSOR: Eli Lilly QUALITY ASSESSMENT: B
Participants	COUNTRY: UK NUMBER: 68 vs. 67 (lispro vs. regular) TYPE OF DIABETES:1 MEAN AGE [YEARS]: 37 vs. 39 (lispro vs. regular) MEAN DIABETES DURATION [YEARS]: 16 vs. 17(lispro vs. regular) OTHER CHARACTERISTICS:-
Interventions	LISPRO VERSUS REGULAR LENGTH OF INTERVENTION [days]: 120 SCHEDULE: lispro: immediately; regular: 30 min.
Outcomes	1.HBA1C [%]: at endpoint of period 1: 6.0 vs. 6.2 (lispro vs. regular) 2. HYPOGLYCAEMIA: OVERALL-Period 1 DEFINITION: <3mmol/l and/or symptoms OUTCOME [overall epidoses]: 724 vs. 1072 (lispro vs. regular) 3. HYPOGLYCAEMIA: SEVERE-Period 1 DEFINITION: third party help OUTCOME [overall episodes]: 8 vs. 12 (lispro vs. regular) 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: 1 patient died after prolonged seizure that was possible related to hypoglycaemia during the second phase of the study 6.COSTS: - 7.DROP OUTS: described

	8.OTHERS: -
Notes	
Allocation concealment	A – Adequate

Study	**Heller 2004**
Methods	TRIAL DESIGN: crossover SETTING: multicentre RANDOMIZATION PROCEDURE: adequate ALLOCATION CONCEALMENT: adequate BLINDING: double-blind ITT: no SPONSOR: Novo Nordisk QUALITY ASSESSMENT: C
Participants	COUNTRY: UK NUMBER: 156 TYPE OF DIABETES:1 MEAN AGE [YEARS]: 36 MEAN DIABETES DURATION [YEARS]: - OTHER CHARACTERISTICS:-
Interventions	ASPART VERSUS REGULAR LENGTH OF INTERVENTION [days]: 112 SCHEDULE: aspart and regular: immediately before meals
Outcomes	1.HBA1C [%]: at endpoint 7,7 vs. 7,7 (aspart vs. regular) 2. HYPOGLYCAEMIA: OVERALL DEFINITION: symptoms OUTCOME 3. [ep/pat/year]: 35,8 vs. 38,2 (aspart vs. regular) HYPOGLYCAEMIA: SEVERE- DEFINITION: third party help OUTCOME: [ep/pat/year]: 0,85 vs. 1,12 (aspart vs. regular) 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: 6.COSTS: - 7.DROP OUTS: unclear 8.OTHERS:
Notes	Discrepancies in reporting of major nocturnal hypoglycaemia within publication and between congress posters and publication.
Allocation concealment	A – Adequate

Study	**Herz 2002a**
Methods	TRIAL DESIGN: crossover SETTING: single centre RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT: unclear BLINDING: open ITT: yes SPONSOR: Eli Lilly

Characteristics of included studies (*Continued*)

	QUALITY ASSESSMENT: C
Participants	COUNTRY: Croatia NUMBER: 37 TYPE OF DIABETES: 2 MEAN AGE [YEARS]: 55 vs. 56 (premixed formuation of lispro [Mix 25]-premixed formulation of regular [BHI 30] vs. BHI 30-Mix 25 treatment sequence MEAN DIABETES DURATION [YEARS]: 8.9 vs. 7.5 (Mix 25-BHI 30 vs. BHI 30 - Mix 25 treatment sequence) OTHER CHARACTERISTICS:
Interventions	MIX 25 VERSUS BHI 30 LENGTH OF INTERVENTION [days]: 28 SCHEDULE: MIX 25: 5 min.; BHI 30: 30 min.
Outcomes	1.HBA1C [%]: - 2. HYPOGLYCAEMIA: OVERALL DEFINITION: <3 mmol/l and/or symptoms OUTCOME [pat/month]: 0.7 vs. 1.2 (Mix 25 vs. BHI 30) 3. HYPOGLYCAEMIA: SEVERE DEFINITION: - OUTCOME: - 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: - 6.COSTS: - 7.DROP OUTS: described 8. OTHERS -
Notes	
Allocation concealment	B – Unclear

Study	**Herz 2003**
Methods	TRIAL DESIGN: crossover SETTING: single centre RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT: unclear BLINDING: open ITT: yes SPONSOR: Eli Lilly QUALITY ASSESSMENT: C
Participants	COUNTRY: South Africa NUMBER: 25 TYPE OF DIABETES: 2 MEAN AGE [YEARS]: 55 vs. 54 (premixed formuation of lispro [Mix 25]-premixed formulation of regular [BHI 30] vs. BHI 30-Mix 25 treatment sequence MEAN DIABETES DURATION [YEARS]: - OTHER CHARACTERISTICS: -
Interventions	MIX 25 VERSUS BHI 30 LENGTH OF INTERVENTION [days]: 28 SCHEDULE: MIX 25: 5 min.; BHI 30: 5 min.
Outcomes	1.HBA1C [%]: - 2. HYPOGLYCAEMIA: OVERALL DEFINITION: <3 mmol/l and/or symptoms OUTCOME [epis/pat/month]: 0.049 vs. 0.10 (Mix 25 vs. BHI 30) 3. HYPOGLYCAEMIA: SEVERE DEFINITION: - OUTCOME: - 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: - 6.COSTS: - 7.DROP OUTS: described 8. OTHERS -
Notes	
Allocation concealment	D – Not used

Study	**Holcombe 2002**
Methods	TRIAL DESIGN: crossover

Characteristics of included studies (*Continued*)

	SETTING: multicentre, multinational RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT: unclear BLINDING: open IIT: unclear SPONSOR: Eli Lilly QUALITY ASSESSMENT: C
Participants	COUNTRY: NORTH AMERICA; AUSTRALIA, EUROPE, South Africa NUMBER: 463 TYPE OF DIABETES: 1 MEAN AGE [YEARS]: 15 MEAN DIABETES DURATION [YEARS]: 6 OTHER CHARACTERISTICS: all patients had reached Tanner stage 2 at inclusion
Interventions	LISPRO VERSUS REGULAR LENGTH OF INTERVENTION [days]: 120 SCHEDULE: lispro: immediately; regular: 30-45 min.
Outcomes	1.HBA1C [%]: at endpoint: 8.7 vs. 8.7 (lispro vs. regular) 2. HYPOGLYCAEMIA: OVERALL DEFINITION: < 3mmol/l and/or symptoms OUTCOME [epis/pat/month]: 4.0 vs. 4.3 (lispro vs. regular) 3. HYPOGLYCAEMIA: SEVERE DEFINITION: third party help OUTCOME [overall episodes]: 6 vs. 5 (lispro vs. regular) 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: - 6.COSTS: - 7.DROP OUTS: described 8. OTHERS: -
Notes	
Allocation concealment	B – Unclear

Study	**Holleman 1997**
Methods	TRIAL DESIGN: crossover SETTING: multicentre, multinational RANDOMISATION PROCEDURE: adequate ALLOCATION CONCEALMENT: adequate BLINDING: open ITT: yes SPONSOR: Eli Lilly QUALITY ASSESSMENT: C
Participants	COUNTRY: UK, Netherlands, Belgium NUMBER: 199 TYPE OF DIABETES: 1 MEAN AGE [YEARS]: 35 MEAN DIABETES DURATION [YEARS]: 13

Characteristics of included studies (*Continued*)

	OTHER CHARACTERISTIC:
Interventions	LISPRO VERSUS REGULAR LENGTH OF INTERVENTION [days]: 84 SCHEDULE: lispro: immediately ; regular: 30 min.
Outcomes	1.HBA1C [%]: at endpoint: 7.6 vs. 7.5 (lispro vs. regular) 2. HYPOGLYCAEMIA: OVERALL DEFINITION: <3 mmol/l and/or symptoms OUTCOME [overall episodes]: 2249 vs. 2344 (lispro vs. regular) 3. HYPOGLYCAEMIA: SEVERE DEFINITION: third party help OUTCOME [overall episodes]: 36 vs. 58 (lispro vs. regular) 4. QUALITY OF LIFE: 20 questions to rate on a 5 point scales, favouring insulin lispro. 5. ADVERSE EVENTS: 1 person died from ischemic heart disease, no group assignement mentioned 6.COSTS: - 7.DROP OUTS: described 8. OTHERS: -
Notes	
Allocation concealment	A – Adequate

Study	**Home 1998**
Methods	TRIAL DESIGN: crossover SETTING: multicentre RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT: unclear BLINDING: double-blind ITT: yes SPONOR: Novo Nordisk QUALITY ASSESSMENT:C
Participants	COUNTRY: UK NUMBER: 104 TYPE OF DIABETES: 1 AGE MEAN [YEARS]: 34 MEAN DURATION [YEARS]: 15 OTHER CHARACTERISTIC: all participants male
Interventions	ASPART VERSUS REGULAR LENGTH OF INTERVENTION [days]: 28 SCHEDULE: aspart and regular: immediately
Outcomes	1.HBA1C [%]: - FRUCTOSAMINE [mmol/l]: at endpoint: 3.8 vs. 3.8 (aspart vs. regular) 2. HYPOGLYCAEMIA:OVERALL: DEFINITION: symptoms OUTCOME [overall episodes]: 567 vs. 615 (aspart vs. regular)

Characteristics of included studies (*Continued*)

	3. HYPOGLYCAEMIA: SEVERE DEFINITION: third party help OUTCOME [overall episodes]: 20 vs. 44 (aspart vs regular) 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: - 6.COSTS: - 7.DROP OUTS: - 8. OTHERS: -
Notes	
Allocation concealment	B – Unclear

Study	**Home 2000**
Methods	TRIAL DESIGN: parallel SETTING: multicentre, multinational RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT: unclear BLINDING: open ITT: unclear SPONSOR: Novo Nordisk QUALITY ASSESSMENT: C
Participants	COUNTRY: EUROPE NUMBER: 707 vs. 358 (aspart vs. regular) TYPE OF DIABETES: 1 MEAN AGE [YEARS]: 38 MEAN DIABETES DURATION [YEARS]: 15 OTHER CHARACTERISTICS: -
Interventions	ASPART VERSUS REGULAR: LENGTH OF INTERVENTION [days]: 180 SCHEDULE: aspart: immediately; regular: 30 min.
Outcomes	1.HBA1C [%]: at endpoint: 7.9 vs. 8.0 (aspart vs. regular) 2. HYPOGLYCAEMIA: OVERALL DEFINITION: symptoms OUTCOME [overall episodes]: 10427 vs. 4474 (aspart vs. regular) 3. HYPOGLYCAEMIA: SEVERE DEFINITION: third party help OUTCOME[overall episodes]: 314 vs. 152 (aspart vs. regular) 4. QUALITY OF LIFE: at endpoint: DTSQ 32.0 vs. 29.7 (aspart vs regular) 5. ADVERSE EVENTS: 1 death in aspart group (myocardial infarction) 6.COSTS: - 7.DROP OUTS: described

	8. OTHERS: -
Notes	
Allocation concealment	D – Not used

Study	**Iwamoto 2001**
Methods	TRIAL DESIGN: parallel SETTING: multicentre RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT: unclear BLINDING: open ITT: unclear SPONSOR: Novo Nordisk QUALITY ASSESSMENT: C
Participants	COUNTRY: Japan NUMBER: 143 vs. 64 (aspart vs. regular) TYPE OF DIABETES: 1 MEAN AGE [YEARS]: 34 vs. 32 (aspart vs. regular) MEAN DIABETES DURATION [YEARS]: 11 OTHER CHARACTERISTICS:
Interventions	ASPART VERSUS REGULAR LENGTH OF INTERVENTION [days]: 168 SCHEDULE: aspart and regular: previous practice
Outcomes	1.HBA1C [%]: at endpoint: 7.4 vs. 7.6 (aspart vs. regular) 2. HYPOGLYCAEMIA: OVERALL DEFINITION: symptoms OUTCOME [overall episodes]: 550 vs. 261 (aspart vs. regular) 3. HYPOGLYCAEMIA: SEVERE DEFINITION: - OUTCOME: - 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: - 6.COSTS: - 7.FOLLOW UP: described 8. OTHERS: -
Notes	
Allocation concealment	D – Not used

Study	**Jacobs 1997**
Methods	TRIAL DESIGN: crossover SETTING: single centre RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT: unclear BLINDING: open

Characteristics of included studies (*Continued*)

	ITT: unclear SPONSOR: ELi Lilly QUALITY ASSESSMENT: C
Participants	COUNTRY: Netherlands NUMBER: 12 TYPE OF DIABETES: 1 MEAN AGE [YEARS]: 18 MEAN DIABETES DURATION [YEARS]: - OTHER CHARACTERISTICS: including patients from 7 to 34 years of age
Interventions	LISPRO VERSUS REGULAR LENGTH OF INTERVENTION [days]: 28 SCHEDULE: lispro: immediately; regular: 15 - 30 min.
Outcomes	1.HBA1C [%] significant improvement in favor of regular during treatment phase 3. HYPOGLYCAEMIA: OVERALL DEFINITION: <3.5 mmol/l and/or symptoms OUTCOME [epis/pat/2 weeks]: 6.5 vs 6.7 (lispro vs.regular) 3. HYPOGLYCAEMIA: SEVERE DEFINITION: third party help OUTCOME [overall episodes in last 2 weeks]: lispro and regular: 0 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: - 6.COSTS: - 7.DROP OUTS: not described 8. OTHERS: -
Notes	
Allocation concealment	B – Unclear

Study	**Johansson 2000**
Methods	TRIAL DESIGN: crossover SETTING: multicentre RANDOMISATION PROCEDURE: adequate ALLOCATION CONCEALMENT: adequate BLINDING: open ITT: yes SPONSOR: Eli Lilly QUALITY ASSESSMENT: B
Participants	COUNTRY: Sweden NUMBER: 41 TYPE OF DIABETES: 1 MEAN AGE [YEARS]: 42 MEAN DIABETES DURATION [YEARS]: 21 OTHER CHARACTERISTICS: patients on CSII therapy
Interventions	LISPRO VERSUS REGULAR LENGTH OF INTERVENTION [days]: 60

Characteristics of included studies (*Continued*)

	SCHEDULE: lispro: 5 min.; regular: 30 min.
Outcomes	1.HBA1C [%]: at endpoint: 7.4 vs 7.6 (lispro vs. regular) 2. HYPOGLYCAEMIA: OVERALL DEFINITION: < 3 mmol/l and/or symptoms OUTCOME [epis/pat/month]: 9.7 vs. 8.0 (lispro vs. regular) 3. HYPOGLYCAEMIA: SEVERE DEFINITION: third party help OUTCOME: lispro and regular: 0 4. QUALITY OF LIFE: WBQ and DTSQ no signifiant difference 5. ADVERSE EVENTS: one episode of ketoacidosis in lispro group due to pump failure 6.COSTS: - 7.DROP OUTS: described 8. OTHERS: -
Notes	
Allocation concealment	A – Adequate

Study	**Jovanovic 1999**
Methods	TRIAL DESIGN: parallel SETTING: single centre RANDOMIZATION PROCEDURE: adequate ALLOCATION CONCEALMENT: adequate BLINDING: open ITT: yes SPONSOR: Eli Lilly QUALITY ASSESSMENT: B
Participants	COUNTRY: USA NUMBER: 19 vs. 23 (lispro vs. regular) TYPE OF DIABETES: gestational diabetes MEAN AGE [YEARS]: 34 vs. 30 (lispro vs. regular) MEAN DIABETES DURATION [YEARS]:- OTHER CHARACTERISTICS: ethnicity: mainly hispanic, enrollment after dietary therapy failure and exercise failure beginning at gestational week 21, mean enrollment gestational week 27 vs 26 (lispro vs. regular)
Interventions	LISPRO VERSUS REGULAR LENGTH OF INTERVENTION: up to delivery SCHEDULE: lispro: 5 min. ; regular: 30 min.
Outcomes	1.HBA1C [%]: 6 weeks after enrollment: 5.1 vs. 5.2 (lispro vs. regular) 2. HYPOGLYCEMIA: OVERALL DEFINITION: <3.1 mmol OUTCOME: total: no difference 4. HYPOGLYCAEMIA: SEVERE- DEFINITION: third party help OUTCOME [overall episodes]: lispro and regular: 0

	4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: - 6.COSTS: - 7.DROP OUTS: described 8.OTHERS: no differences in fetal or maternal outcome, no macrosomic newborn in either group, no intrauterine growth restriction, comparable antibody formation to regular insulin
Notes	
Allocation concealment	B – Unclear

Study	**Kotsanos 1997**
Methods	TRIAL DESIGN: crossover SETTING: multicentre, multinational RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT: unclear BLINDING: open ITT: unclear SPONSOR: Eli Lilly QUALITY ASSESSMENT: C
Participants	COUNTRY: AMERICA, EUROPE, AUSTRALIA, South Africa NUMBER: Type 1:468; Type 2: 474 TYPE OF DIABETES: 1 and 2 MEAN AGE [YEARS]: Type 1: 34; Type 2: 58 MEAN DIABETES DURATION [YEARS]: Type 1: 13; Type 2: 13 OTHER CHARACTERISTICS:
Interventions	LISPRO VERSUS REGULAR LENGTH OF INTERVENTION [days]: 90 SCHEDULE: analogue: immediately; regular: 30 - 45 min.
Outcomes	1.HBA1C [%]: - 2. HYPOGLYCAEMIA: OVERALL DEFINITION: < 3.5 mmol/l and/or symptoms OUTCOME: - 3. HYPOGLYCAEMIA : SEVERE DEFINITION: iv glucose or glucagon OUTCOME: - 4. QUALITY OF LIFE: type 1: improvement in 3 of 34 domains of health-related quality of life in favour of lispro type 2: no significant differences for any domain 5. ADVERSE EVENTS: - 6.COSTS: - 7.DROP OUTS: - 8. OTHERS: -
Notes	Quality of life results of a subset of patients of ANDERSON 1997 A and ANDERSON 1997 B
Allocation concealment	D – Not used

Study	**Mecacci 2003**
Methods	TRIAL DESIGN: parallel

	SETTING: single centre RANDOMIZATION PROCEDURE: unclear ALLOCATION CONCEALMENT: unclear BLINDING: open ITT: not SPONSOR: not defined QUALITY ASSESSMENT: C
Participants	COUNTRY: Italy NUMBER: 32 vs. 33 (lispro vs. regular) TYPE OF DIABETES: gestational diabetes MEAN AGE [YEARS]: 35 MEAN DIABETES DURATION [YEARS]:- OTHER CHARACTERISTICS: ethnicity: caucasian, week of gestation at diagnosis: 28 median, range 25-32; week of gestation at start of insulin 29, range 27-32
Interventions	LISPRO VERSUS REGULAR LENGTH OF INTERVENTION: up to delivery SCHEDULE: lispro: immediately; regular: 15 min.
Outcomes	1.HBA1C [%]: at enrollment: 5.5 vs. 5.4; final: 5.2 vs. 5.1(lispro vs. regular) 2. HYPOGLYCEMIA: OVERALL DEFINITION: not reported OUTCOME: not reported 4. HYPOGLYCAEMIA: SEVERE DEFINITION: not reported OUTCOME: not reported 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: - 6.COSTS: - 7.DROP OUTS: overall 16 (25%) women were lost to follow up: 7 lispro and 9 regular treated: 4 discontinued SBGM, 4 received betamimetics or corticosteroids, five did not deliver at trial center, 3 had a spontanoeus pre-term delivery 8.OTHERS: no statistically difference between the groups in neonatal outcome and anthropometric characteristics; however, the rate of infants with a cranial-thoracic circumference (CC/CT) ratio between the 10th and 25th percentile was signifiantly higher in the group treated with regular in a post hoc analyses
Notes	no differences in fetal or maternal outcomes, no statistical difference in newborn large for gestational age
Allocation concealment	B – Unclear

Study	**Persson 2002**
Methods	TRIAL DESIGN: parallel SETTING: multicentre RANDOMIZATION PROCEDURE: adequate ALLOCATION CONCEALMENT: adequate BLINDING: open ITT: yes SPONSOR: not defined QUALITY ASSESSMENT: B
Participants	COUNTRY: Sweden NUMBER: 16 vs. 17 (lispro vs. regular) TYPE OF DIABETES: 1 MEAN AGE [YEARS]: 31 vs. 30 (lispro vs. regular) MEAN DIABETES DURATION [YEARS]: 15 vs. 12 (lispro vs. regular) OTHER CHARACTERISTICS: women were recruited at gestational week 6-8, treated with regular and NPH and were thereafter randomised at week 15
Interventions	LISPRO VERSUS REGULAR LENGTH OF INTERVENTION [days]: until delivery SCHEDULE: lispro: immediately; regular: 30 min.
Outcomes	1.HBA1C [%]: last before delivery: 5.2 vs. 5.0 (lispro vs. regular) 2. HYPOGLYCAEMIA: OVERALL DEFINITION: <3mmol/l OUTCOME [epis/pat/month]: 1.2 vs. 0.8 (lispro vs. regular) 3. HYPOGLYCAEMIA: SEVERE

	DEFINITION: third party help OUTCOME [overall episodes]: 0 vs. 4 (lispro vs. regular) 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: Progression of retinopathy in 3/16 and 6/17 patients in lispro and regular group, respectively. 6.COSTS: - 7.DROP OUTS: not described 8. OTHERS: complications during pregnancy or route of delivery did not differ between the groups, likewise no differences regarding gestational age at delivery, birthweight, rate of LGA infants or neonatal complications, no perinatal deaths or trauma recorded. One malformation, hypospadia, in the regular group.
Notes	
Allocation concealment	A – Adequate

Study	**Provenzano 2001**
Methods	TRIAL DESIGN: crossover SETTING: single centre RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT: unclear BLINDING: open ITT: unclear SPONSOR: not defined QUALITY ASSESSMENT: C
Participants	COUNTRY: Italy NUMBER: 12 TYPE OF DIABETES: 1 MEAN AGE [YEARS]: 28 MEAN DIABETES DURATION [YEARS]: 12 OTHER CHARACTERISTICS:
Interventions	LISPRO VERSUS REGULAR LENGTH OF INTERVENTION [days]: 168 SCHEDULE: lispro and regular: immediately
Outcomes	1.HBA1C [%]: mean levels for drug treatment: 7.6 vs. 7.8 (lispro vs. regular) 2. HYPOGLYCAEMIA: OVERALL DEFINITION: symptoms OUTCOME [overall episodes]: 58 vs. 101 episodes (lispro vs. regular) 3. HYPOGLYCAEMIA: SEVERE DEFINITION: glucagon and/or glucose and/or coma OUTCOME [overall episodes]: 2 vs. 4 (lispro vs. regular) 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: - 6.COSTS: - 7. DROP OUTS: not described

	8. OTHERS -
Notes	
Allocation concealment	B – Unclear

Study	**Raskin 2000**
Methods	TRIAL DESIGN: parallel SETTING: multicentre, multinational RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT: unclear BLINDING: open ITT: unclear SPONSOR: Novo Nordisk QUALITY ASSESSMENT: C
Participants	COUNTRY: NORTH AMERICA NUMBER: 596 vs. 286 (aspart vs. regular) TYPE OF DIABETES: 1 MEAN AGE [YEARS]: 39 vs. 40 (aspart vs. regular) MEAN DIABETES DURATION [YEARS]: 16 OTHER CHARACTERISTICS:
Interventions	ASPART VERSUS REGULAR LENGTH OF INTERVENTION [days]: 180 SCHEDULE: aspart: immediately; regular: 30 min.
Outcomes	1.HBA1C [%]: at endpoint: 7.8 vs. 7.9 (aspart vs. regular) 2. HYPOGLYCAEMIA: OVERALL DEFINITION: 2.5 mmol/l and/or symptoms OUTCOME [epis/pat/year]: 43.4 vs. 45.5 (aspart vs. regular) 3. HYPOGLYCAEMIA: SEVERE DEFINITION: third party help OUTCOME [epis/pat/year]: 0.9 vs. 1.1 (aspart vs. regular) 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: - 6.COSTS: - 7.DROP OUTS: described 8. OTHERS: -
Notes	
Allocation concealment	B – Unclear

Study	**Raskin 2001**
Methods	TRIAL DESIGN: crossover SETTING: multicentre RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT: unclear BLINDING: open

Characteristics of included studies (*Continued*)

	ITT: yes SPONSOR: Eli Lilly QUALITY ASSESSMENT: C
Participants	COUNTRY: USA NUMBER: 59 TYPE OF DIABETES: 1 MEAN AGE [YEARS]: 41 vs. 38 (lispro-regular vs. regular-lispro treatment sequence) MEAN DIABETES DURATION [YEARS]: 19 vs.17 (lispro-regular vs. regular-lispro treatment sequence) OTHER CHARACTERISTICS: patients on CSII therapy
Interventions	LISPRO VERSUS REGULAR LENGTH OF INTERVENTION [days]: 84 SCHEDULE: lispro and regular: immediately
Outcomes	1.HBA1C [%]: at endpoint: 7.4 vs. 7.7 (lispro vs. regular) 2. HYPOGLYCAEMIA: OVERALL DEFINITION: < 3mmol/l and/or symptoms OUTCOME [overall episodes]: 8 vs. 11 (lispro vs. regular) 3. HYPOGLYCAEMIA: SEVERE DEFINITION: iv. glucose OUTCOME [overall episodes]: 3 vs. 3 (lispro vs. regular) 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: - 6.COSTS: - 7.DROP OUTS: described 8. OTHERS: -
Notes	
Allocation concealment	B – Unclear

Study	**Recasens 2003**
Methods	TRIAL DESIGN: parallel SETTING: single centre RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT: unclear BLINDING: open ITT: unclear SPONSOR: not defined QUALITY ASSESSMENT: C
Participants	COUNTRY: Spain NUMBER: 22 vs. 23 (lispro vs. regular) TYPE OF DIABETES: 1 MEAN AGE [years]: 23 vs. 24 (lispro vs. regular) MEAN DIABETES DURATION [years]: new onset OTHER CHARACTERISTICS:
Interventions	LISPRO VERSUS REGULAR LENGTH OF INTERVENTION [days]: 360

	SCHEDULE: lispro: immediately; regular: 30 min.
Outcomes	1.HBA1C [%]: at endpoint: 6.2 vs. 6.3 (lispro vs. regular) 2. HYPOGLYCAEMIA: OVERALL DEFINITION: > 3.3 mmol/l and/or symptoms OUTCOME: no significant difference 3. HYPOGLYCAEMIA: SEVERE DEFINITION: third party help OUTCOME [overall episodes]: lispro and regular: 0 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: - 6.COSTS: - 7. DROP OUT: not described 8. OTHERS: -
Notes	
Allocation concealment	B – Unclear

Study	**Renner 1999**
Methods	TRIAL DESIGN: crossover SETTING: multicentre RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT: unclear BLINDING: open ITT: unclear SPONSOR: Eli Lilly QUALITY ASSESSMENT: C
Participants	COUNTRY: Germany NUMBER: 113 TYPE OF DIABETES: 1 MEAN AGE [YEARS]: 37 MEAN DIABETES DURATION [YEARS]: 19 OTHER CHARACTERISTICS: patients on CSII therapy
Interventions	LISPRO VERSUS REGULAR LENGTH OF INTERVENTION [days]: 120 SCHEDULE: lispro: immediately; regular: 30 min.
Outcomes	1.HBA1C [%]: at endpoint: 6.8 vs. 6.9 (lispro vs. regular) 2. HYPOGLYCAEMIA: OVERALL DEFINITION: < 3.5 mmol/l and/or symptoms OUTCOME [epis/pat/month]: 12.4 vs. 11.0 (lispro vs. regular) 3. HYPOGLYCAEMIA: SEVERE DEFINITION: - OUTCOME: - 4. QUALITY OF LIFE: DTSQ-score significantly improved in lispro group

	5. ADVERSE EVENTS: - 6.COSTS: - 7.DROP OUTS: not decribed 8. OTHERS: -
Notes	
Allocation concealment	B – Unclear

Study	**Roach 1999a**
Methods	TRIAL DESIGN: crossover SETTING: multicentre, multinational RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT: unclear BLINDING: open IIT: yes SPONSOR: Eli Lilly QUALITY ASSESSMENT: C
Participants	COUNTRY: Germany, Hungary, Netherlands, Switzerland, UK NUMBER: Type 1: 37; Type 2: 63 TYPE OF DIABETES: 1 and 2 MEAN AGE [YEARS]: Type 1: 42 vs. 37; Type 2: 58 vs. 60 (premixed formuation of lispro Mix 25 at breakfast and Mix 50 at dinner [Mix 25/ Mix 50] - premixed formulation of regular insulin BHI 50 and BHI 30 [BHI 50/BHI 30] sequence vs. BHI 50/BHI 30 - Mix 50/Mix 25 -sequence MEAN DIABETES DURATION [YEARS]: Type 1: 14 vs. 11; Type 2: 12 vs. 13 (Mix 50/Mix 25-BHI 50/ BHI25 vs. BHI 50/BHI 30 - Mix 50/Mix 25) OTHER CHARACTERISTICS:
Interventions	Mix 50/Mix 25 VERSUS- BHI 50/ BHI 30 LENGTH OF INTERVENTION [days]: 90 SCHEDULE: Mix 50/Mix 25: immediately; BHI 50/BHI 30: 30 to 45 min.
Outcomes	1.HBA1C [%]: at endpoint: Type 1: 7.7 vs. 7.4; Type 2: 7.7 vs. 7.7 (Mix 50/Mix25 vs. BHI 50/BHI25) 2. HYPOGLYCAEMIA: OVERALL DEFINITION: < 3 mmol/l and/or symptoms OUTCOME: Type 1 and 2: no significant difference (Mix 50/Mix25 vs. BHI 50/BHI25) 3. HYPOGLYCAEMIA: SEVERE DEFINITION: coma and/or glucagon and/or glucose OUTCOME [overall episodes]: Type : 2 vs. 4 (Mix 50/Mix25 vs. BHI 50/BHI25) Type 2: not reported 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: - 6.COSTS: - 7.DROP OUTS: described

	8. OTHERS:
Notes	
Allocation concealment	D – Not used

Study	**Roach 1999b**
Methods	TRIAL DESIGN: crossover SETTING: multicentre, multinational RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT: unclear BLINDING: open ITT: yes SPONSOR: Eli Lilly QUALITY ASSESSMENT: C
Participants	COUNTRY: Spain, South Africa, UK NUMBER: 89 TYPE OF DIABETES: 2 MEAN AGE [YEARS]: 57 MEAN DIABETES DURATION [YEARS]: ˜ 12-13 OTHER CHARACTERISTICS:
Interventions	Mixture of 25%Lispro (Mix25) VERSUS mixture of regular (BHI 30) LENGTH OF INTERVENTION [days]: 90 SCHEDULE: Mix 25: immediately; BHI 30: 20-30 min.
Outcomes	1.HBA1C [%]: at endpoint: 7.8 vs. 8.1 (Mix 25 vs. BHI 30) 2. HYPOGLYCAEMIA: OVERALL DEFINITION: < 3 mmol/l and/or symptoms OUTCOME: no significant difference 3. HYPOGLYCAEMIA: SEVERE DEFINITION: third party help OUTCOME [pat]: 1 vs. 1 (Mix 25 vs. BHI 30) 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: - 6.COSTS: - 7.DROP OUTS: described 8. OTHERS:
Notes	
Allocation concealment	B – Unclear

Study	**Ross 2001**
Methods	TRIAL DESIGN: parallel SETTING: multicentre RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT: unclear BLINDING: open ITT: yes SPONSOR: Eli Lilly

Characteristics of included studies (*Continued*)

	QUALITY ASSESSMENT: C
Participants	COUNTRY: Canada NUMBER: 70 vs. 78 (lispro vs. regular) TYPE OF DIABETES: 2 MEAN AGE [YEARS]: 59 vs. 58 (lispro vs. regular) MEAN DIABETES DURATION [YEARS]: 11 OTHER CHARACTERISTICS: patients with maximum doses of oral agents (sulphonyurea or metformin) without achieving acceptable control
Interventions	LISPRO VERSUS REGULAR LENGTH OF INTERVENTION [days]: 165 SCHEDULE: lispro: immediately ; regular: 30-45 min.
Outcomes	1.HBA1C [%]: at endpoint: 8.0 vs. 8.0 (lispro vs. regular) 2. HYPOGLYCAEMIA: OVERALL DEFINITION: < 3mmol/l and/or symptoms OUTCOME [epis/pat/month]: 1.8 vs. 1.7 (lispro vs. regular) 3. HYPOGLYCAEMIA: SEVERE DEFINITION: third party help OUTCOME: not reported 4. QUALITY OF LIFE: no overall improvment in DQOL score in 49 patients in lispro group and 53 patients of regular group, who completed questionaire 5. ADVERSE EVENTS: - 6.COSTS - 7. DROP OUTS: described 8. OTHERS: -
Notes	
Allocation concealment	B – Unclear

Study	**Schmauss 1998**
Methods	TRIAL DESIGN: crossover SETTING: single centre RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT: unclear BLINDING: open ITT: unclear SPONSOR: Eli Lilly QUALITY ASSESSMENT: C
Participants	COUNTRY: Germany NUMBER: 11 TYPE OF DIABETES: 1 MEAN AGE [YEARS]: 30 MEAN DIABETES DURATION [YEARS]: 14 OTHER CHARACTERISTICS: patients on CSII therapy
Interventions	LISPRO VERSUS REGULAR: LENGTH OF INTERVENTION [days]: 90

	SCHEDULE: lispro: immediately; regular: 30 min.
Outcomes	1.HBA1C [%]: no significant difference 2. HYPOGLYCAEMIA: OVERALL DEFINITION: < 3.5 mmol/l and/or symptoms OUTCOME [epis/pat/month]: 4 vs. 3.2 (lispro vs. regular) 3. HYPOGLYCAEMIA: SEVERE DEFINITION: glucagon and/or glucose OUTCOME [overall episodes]: lispro and regular: 0 4. QUALITY OF LIFE: "no significant difference concerning treatment satisfation", no scores/methods shown 5. ADVERSE EVENTS: - 6.COSTS: - 7.DROP OUTS: described 8. OTHERS: -
Notes	
Allocation concealment	B – Unclear

Study	**Skrha 2002**
Methods	TRIAL DESIGN: crossover SETTING: multicentre, multinational RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT: unclear BLINDING: open ITT: unclear SPONSOR: Eli Lilly QUALITY ASSESSMENT: C
Participants	COUNTRY: Czech Republic, Slovenia, Slovak Republic NUMBER: Type 1: 55; Type 2: 7; TYPE OF DIABETES: 1 and 2 MEAN AGE [YEARS]: Type 1 and Type 2: 36 MEAN DIABETES DURATION [YEARS]: Type 1 and Type 2: 11 OTHER CHARACTERISTICS:-
Interventions	LISPRO VERSUS REGULAR: LENGTH OF INTERVENTION [days]: 60 SCHEDULE: lispro: immediately; regular: 30 min.
Outcomes	1.HBA1C [%]: Type 1 and Type 2: 7.6 vs. 7.4 (lispro vs. regular) 2. HYPOGLYCAEMIA: OVERALL DEFINITION: < 3.5 mmol/l and/or symptoms OUTCOME [percent of patients]: 66 vs. 63 (lispro vs. regular) 3. HYPOGLYCAEMIA: SEVERE DEFINITION: not defined OUTCOME: not reported 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: - 6.COSTS: - 7.DROP OUTS: not described 8. OTHERS: -
Notes	
Allocation concealment	D – Not used

Study	**Tubiana-Rufi 2004**
Methods	TRIAL DESIGN: crossover SETTING: multicentre RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT: unclear BLINDING: open ITT: no SPONSOR: Eli Lilly QUALITY ASSESSMENT: C
Participants	COUNTRY: France NUMBER: 29 TYPE OF DIABETES: 1 MEAN AGE [YEARS]: 5 MEAN DIABETES DURATION [YEARS]: - OTHER CHARACTERISTICS:-
Interventions	LISPRO VERSUS REGULAR: LENGTH OF INTERVENTION [days]: 112 SCHEDULE: lispro: immediately; regular: 20-30 min.
Outcomes	1.HBA1C [%]:

	changes at end of first study period 0.2 vs. 0.1 (lispro vs. regular) 2. HYPOGLYCEMIA: OVERALL DEFINITION: OUTCOME [epis/pat/month]: 4.9 vs. 4.4 (lispro vs. regular) 3. HYPOGLYCAEMIA: SEVERE DEFINITION: unconsciousness OUTCOME [overall episodes]: 2 vs. 2 (lispro vs. regular) 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: - 6.COSTS: - 7.DROP OUTS: described 8. OTHERS:
Notes	
Allocation concealment	D – Not used

Study	**Tupola 2001**
Methods	TRIAL DESIGN: crossover SETTING: multicentre RANDOMISATION PROCEDURE: adequate ALLOCATION CONCEALMENT: adequate BLINDING: open ITT: unclear SPONSOR: Eli Lilly QUALITY ASSESSMENT: B
Participants	COUNTRY: France NUMBER: 29 TYPE OF DIABETES: 1 MEAN AGE [YEARS]: 6 MEAN DIABETES DURATION [YEARS]: 3 OTHER CHARACTERISTICS: all participants were prepubertal before and at the end of study
Interventions	LISPRO VERSUS REGULAR LENGTH OF INTERVENTION [days]: 90 SCHEDULE: lispro: no longer than 30 min. from the start of the meal; regular: 20 - 30 min.
Outcomes	1.HBA1C [%]: no significant difference 2. HYPOGLYCEMIA: OVERALL DEFINITION: <3.3 mmol/l OUTCOME [ep/pat/within LAST 30 days]: 14 vs. 11 (lispro vs. regular) 3. HYPOGLYCAEMIA: SEVERE DEFINITION: - OUTCOME- 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: ketoacidosis: 0 vs. 2 (lispro vs. regular) -

	6.COSTS: - 7.DROP OUTS: described 8. OTHERS:
Notes	HbA1c analysis: only first treatment period due to carry-over effect
Allocation concealment	A – Adequate

Study	**Vignati 1997**
Methods	TRIAL DESIGN: crossover SETTING: multicentre, multinational RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT: unclear BLINDING: open ITT: no SPONSOR: Eli Lilly ASSESSMENT: C
Participants	COUNTRY: USA ,Canada, EUROPE, AUSTRALIA, South Africa NUMBER: Type 1: 379; Type 2: 328 TYPE OF DIABETES: Type 1 and 2 MEAN AGE [YEARS]: Type 1:39; Type 2: 58 MEAN DIABETES DURATION [YEARS]: Type 1:13; Type 2: 13 OTHER CHARACTERISTICS:
Interventions	LISPRO VERSUS REGULAR LENGTH OF INTERVENTION [days]: 60 SCHEDULE: lispro: immediately; regular: previous practice
Outcomes	1.HBA1C [%]: at endpoint: Type 1: 7.8 vs. 7.9; Type 2: 8.1 vs. 8.1 (lispro vs. regular) 2. HYPOGLYCAEMIA: OVERALL DEFINITION: < 3.5 mmol/l OUTCOME [epis/pat/month]: Type 1: 4.6 vs. 4.5; Type 2: 1.9 vs. 1.9 (lispro vs. regular) 3. HYPOGLYCAEMIA: SEVERE DEFINITION: glucagon OUTCOME [pat]: Type 1: 5 vs. 5; Type 2: 0 vs. 0 (lispro vs. regular) 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: - 6.COSTS: - 7. DROP OUTS: described 8. OTHERS: -
Notes	
Allocation concealment	B – Unclear

Study	**Zinman 1997**
Methods	TRIAL DESIGN: crossover SETTING: multicentre

	RANDOMISATION PROCEDURE: unclear ALLOCATION CONCEALMENT: unclear BLINDING: double-blind ITT: unclear SPONSOR: Eli Lilly QUALITY ASSESSMENT: C
Participants	COUNTRY: CANADA NUMBER: 30 TYPE OF DIABETES: 1 MEAN AGE [YEARS]: 35 MEAN DIABETES DURATION [YEARS]: 18 OTHER CHARACTERISTICS: patients on CSII therapy
Interventions	LISPRO VERSUS REGULAR LENGTH OF INTERVENTION [days]: 90 SCHEDULE: lispro and regular: immediately: 0-5 min.
Outcomes	1.HBA1C [%]: at endpoint: 7.7 vs. 8.0 (lispro vs. regular) 2. HYPOGLYCAEMIA: OVERALL DEFINITION: < 3mmol and/or symptoms OUTCOME [epis/pat/month]: 8.6 vs. 10.8 (lispro vs. regular) 3. HYPOGLYCAEMIA: SEVERE DEFINITION: third party help OUTCOME [overall episodes]: lispro and regular: 0 4. QUALITY OF LIFE: - 5. ADVERSE EVENTS: - 6.COSTS: - 7.DROP OUTS: described 8.OTHERS: -
Notes	
Allocation concealment	B – Unclear

Characteristics of excluded studies

Study	Reason for exclusion
Bastyr 2000	no information according to our predefined endpoints
Boehm 2004	not randomised
Colombel 1999	no comparable insulin regimen in intervention and control group
Cypryk 2004	not randomised
DeVries 2003	no comparable insulin regimen in intervention and control group
Fineberg 1996	Did not provide any additional information according to our predefined endpoints
Garg 1996	including new onset type 1 diabetic patients, receiving different insulin regimen, with unclear group assignment.
Garg 2000	not randomised

Characteristics of excluded studies (*Continued*)

Heller 2002	Substudy of Heller 1999, did not provide any additional information according to our predefined endpoints
Herz 2002b	no comparable insulin regimen in intervention and control group
Janssen 2000	no comparable insulin regimen in intervention and control group
Jansson 1998	no comparable insulin regimen in intervention and control group
Kaplan 2004	No comparison between analogues and regular
Kaufman 2000	no comparable insulin regimen in intervention and control group
Kilo 2003	Included patients receiving oral antidiabetic agents
Krzymien 2001	duration of intervention less than 4 weeks
Lalli 1999	no comparable insulin regimen in intervention and control group
Laube 1996	duplicate publishing, substudy from multicentre trial (not referenced)
Loba 2001	non randomised
Martin 2003	no comparable insulin regimen in intervention and control group
McSorley 2002	duration of intervention less than 4 weeks
Melki 1998	results for only the first period of treatment available.
Nielsen 1995	insulin not available on market
Petersen 1995	duplicate publishing, substudy from multicentre trial (not referenced)
Pfuetzner 1996	duplicate publishing, substudy from multicentre trial (Anderson 1997 B)
Roach 2001	no comparable insulin regimen in intervention and control group
Sargin 2003	no comparable insulin regimen in intervention and control group
Schernthaner 2004	no comparable insulin regimen in intervention and control group
Tamas 2001	only preliminary results (week 12 of 64) shown
Tsui 1998	Substudy of Zinman 1997, did not provide any additional information according to our predefined endpoints
Velussi 2002	not randomised

ADDITIONAL TABLES

Table 01. Search strategy

Electronic searches:

An asterisk (*) stands for any character(s); exp = exploded MeSH; pt = publication type; sh = MeSH subject heading (Medline medical index term); tw = text word.
1. insulin* analog*.tw.
2. insulin* derivat*.tw.
3. short acting insulin*.tw.
4. fast acting insulin*.tw.
5. rapid acting insulin*.tw.
6. novel insulin*.tw.
7. new insulin*.tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. (Lyspro* or Lispro*).tw.
10. (B28 or LysB28 or ProB29).tw.

Table 01. Search strategy (*Continued*)

Electronic searches:

11. Humalog*.tw.
12. 9 or 10 or 11
13. Novorapid*.tw.
14. (asp* adj B10).tw.
15. (B28-asp* or B28Asp*).tw.
16. (insulin* adj aspart*).tw.
17. 13 or 14 or 15 or 16
18. 8 or 12 or 17
19. exp INSULIN/aa [Analogs & Derivatives]
20. 18 or 19
21. exp diabetes mellitus/
22. diabet*.tw.
23. IDDM.tw.
24. NIDDM.tw.
25. MODY.tw.
26. (late onset adj diabet*).tw.
27. (maturity onset adj diabet*).tw.
28. (juvenil adj diabet*).tw.
29. exp Syndrome X/
30. (syndrome X and diabet*).tw.
31. hyperinsulin*.tw.
32. insulin sensitiv*.tw.
33. insulin* secret* dysfunc*.tw.
34. impaired glucose toleran*.tw.
35. glucose intoleran*.tw.
36. exp Glucose Intolerance/
37. insulin* resist*.tw.
38. (non insulin* depend* or noninsulin* depend* or non insulin?depend* or noninsulin?depend*).tw.
39. metabolic* syndrom*.tw.
40. (pluri metabolic* syndrom* or plurimetabolic* syndrom*).tw.
41. ((typ* 1 or typ* 2) and diabet*).tw.
42. ((typ I or typ* II) and diabet*).tw.
43. exp Insulin Resistance/
44. (insulin* depend* or insulin?depend*).tw.
45. or/21-44
46. randomized controlled trial.pt.
47. controlled clinical trial.pt.
48. randomized controlled trials.sh.
49. random allocation.sh.
50. double-blind method.sh.
51. single-blind method.sh.
52. 46 or 47 or 48 or 49 or 50 or 51
53. limit 52 to animal
54. limit 52 to human
55. 53 not 54
56. 52 not 55
57. clinical trial.pt.
58. exp clinical trials/

Table 01. Search strategy (*Continued*)

Electronic searches:

59. (clinic* adj25 trial*).tw.
60. ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind*)).tw.
61. placebos.sh.
62. placebo*.tw.
63. random*.tw.
64. research design.sh.
65. (latin adj square).tw.
66. 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65
67. limit 66 to animal
68. limit 66 to human
69. 67 not 68
70. 66 not 69
71. comparative study.sh.
72. exp evaluation studies/
73. follow-up studies.sh.
74. prospective studies.sh.
75. (control* or prospectiv* or volunteer*).tw.
76. cross-over studies.sh.
77. 71 or 72 or 73 or 74 or 75 or 76
78. limit 77 to animal
79. limit 77 to human
80. 78 not 79
81. 77 not 80
82. 56 or 70 or 81
83. 20 and 45 and 82
Search update from 01/10/2003 to 21/09/2005
same search strategy adding the following search terms for glulisine:
1. (Glulisin* or Glulysin*).ti,ab,ot.
2. (Glu*B29 or B29Glu* or (glu* adj1 B29)).ti,ab,ot.
3. Apidra*.ti,ab,ot.
4. 1 or 2 or 3

Table 02. Quality of life and treatment satisfaction

Trial	Diabetes	Method	Outcome
Kotsanos 1997	type 1	DQLCTQ	improvement in 3 of 34 domains in favour of analogue
Holleman 1997	type 1	PEQ	improvement in favour of analogue
Schmauss 1998	type 1	not reported	no difference
Johansson 1999	type 1	DTSQ, WBQ	no difference in both scores
Renner 1999	type 1	DTSQ	improvement in favour of analogue
Gale 2000	type 1	DTSQ, WBQ	no difference in both scores
Home 2000	type 1	DTSQ	improvement in favour of analogue (UK-centers)
Bott 2003	type 1	DTSQ, DSQoLS	improvement in favour of analogue (german speaking centers of Home

Table 02. Quality of life and treatment satisfaction (*Continued*)

Trial	Diabetes	Method	Outcome
			2000)
Ferguson 2001	type 1	DTSQ, HFS	no difference in both scores
Annuzzi 2001	type 1	DTSQ	improvement in subdomains in favour of analogue
Kotsanos 1997	type 2	DQLCTQ	no difference in any of the 34 domains
Ross 2001	type 2	DQOL	no difference
Tubiana-Rufi 2004	type 1 (children)	not reported	parents' questionnaire: improvements in favour of analogue

Table 03. Results of DTSQ (~ no difference, + improvements in favor of analogue treatment)

DTSQ domains	Johansson 1999	Renner 1999	Gale 2000	Home 2000	Bott 2003	Ferguson 2001	Annuzzi 2001
Satisfaction with current treatment	~	not reported	~	~	~	~	+
Unacceptably high blood sugar	~	not reported	~	~	~	~	not reported
Unacceptably low blood sugar	~	not reported	~	~	~	~	not reported
Convenience of treatment	~	not reported	~	+	+	~	+
Flexibility of treatment	~	not reported	~	+	+	~	+
Understanding of diabetes	~	not reported	~	~	~	~	not reported
Recommen-dations of treatment	~	not reported	~	~	+	~	not reported
Continuation of treatment	~	not reported	~	+	+	~	+
DTSQ TOTAL SCORE	~	+	~	+	+	~	not reported
injection interval (min.): analogue vs. regular	5 vs. 30	i vs. 30	i vs. i	i vs. 30	i vs. 30	i vs. 30	i vs. 30

ANALYSES

Comparison 01. Type 1 diabetic patients: short acting insulin anlogues versus structurally unchanged insulin

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Hba1c	22		mean difference (Random) 95% CI	-0.10 [-0.16, -0.05]
02 Hba1c by different types of interventions: CSII,. IIT	22		mean difference (Random) 95% CI	-0.10 [-0.16, -0.05]
03 Hba1c by duration of study: less than or equal to 3 months, more than 3 months	22		mean difference (Random) 95% CI	-0.10 [-0.16, -0.05]
04 Hba1c by different short acting insulin analogues: Lispro, Aspart	22		mean difference (Random) 95% CI	-0.11 [-0.16, -0.06]
05 Hba1c by different types of study design: parallel, cross-over studies	22	44	mean difference (Random) 95% CI	-0.10 [-0.16, -0.05]
06 Hypoglycaemic episodes	10	4266	Weighted Mean Difference (Random) 95% CI	-0.23 [-1.14, 0.69]

Comparison 02. Type 2 diabetic patients: short acting insulin anlogues versus structurally unchanged insulin

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Hba1c	5		mean difference (Random) 95% CI	-0.03 [-0.11, 0.04]
02 Hypoglycaemic episodes	5	2617	Weighted Mean Difference (Random) 95% CI	-0.17 [-0.46, 0.12]

INDEX TERMS

Medical Subject Headings (MeSH)

Diabetes Mellitus, Type 1 [blood; *drug therapy]; Diabetes Mellitus, Type 2 [blood; *drug therapy]; Hemoglobin A, Glycosylated [metabolism]; Hypoglycemic Agents [*therapeutic use]; Insulin [analogs & derivatives; *therapeutic use]; Randomized Controlled Trials

MeSH check words

Humans

COVER SHEET

Title Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus

Authors Siebenhofer A, Plank J, Berghold A, Jeitler K, Horvath K, Narath M, Gfrerer R, Pieber TR

Contribution of author(s)

ANDREA SIEBENHOFER: protocol development, quality assessment of trials, data extraction, development of final review, corresponding author.
JOHANNES PLANK: searching for trials, quality assessment of trials, data extraction, development of final review.
ANDREA BERGHOLD: protocol development, data analysis, development of final review.
KLAUS JEITLER: for the update of the review: searching for trials, quality assessment of trials, data extraction
KARL HORVATH: for the update of the review: quality assessment of trials, data extractions, development of final review.
GFRERER ROBERT: searching for trials, quality assessment of trials, data extraction.

	NARATH MARKUS: protocol development, correspondance and administration, searching for trials, development of final review. THOMAS R PIEBER protocol development, quality assessment of trials, development of final review.
Issue protocol first published	2001/4
Review first published	2004/2
Date of most recent amendment	22 February 2006
Date of most recent SUBSTANTIVE amendment	22 February 2006
What's New	This review is an update of the original review first published in Issue 4, 2004. A highly sensitive search applying the same search strategy as used for the original review was performed from 01/10/2003 to 21/09/2005 (adding the search terms for glulisine, which is new on the market) : 386 potentially relevant abstracts were identified and screened for retrieval. 375 of these were excluded by consensus. Eleven publications were potentially appropriate to be included in this systematic review, of which further 4 were excluded by consensus because of not being randomised, no comparable insulin regimen were used or analogues were not compared with regular insulin. Finally, seven new studies fulfilled the criteria to be included into this systematic review. For further details see figure 9 presenting the flow chart according the QUOROM statement. After including the 7 new studies in the analyses the conclusion drawn from the first systematic review remained unchanged.
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	01 September 2005
Date authors' conclusions section amended	Information not supplied by author
Contact address	Dr Andrea Siebenhofer Consultant Physician University of Medicine Leopold Auenbrugger Medical University of Graz Auenbruggerplatz 15 Graz 8036 AUSTRIA E-mail: andrea.siebenhofer@meduni-graz.at Tel: +43 316 385 6823
DOI	10.1002/14651858.CD003287.pub4
Cochrane Library number	CD003287
Editorial group	Cochrane Metabolic and Endocrine Disorders Group
Editorial group code	HM-ENDOC

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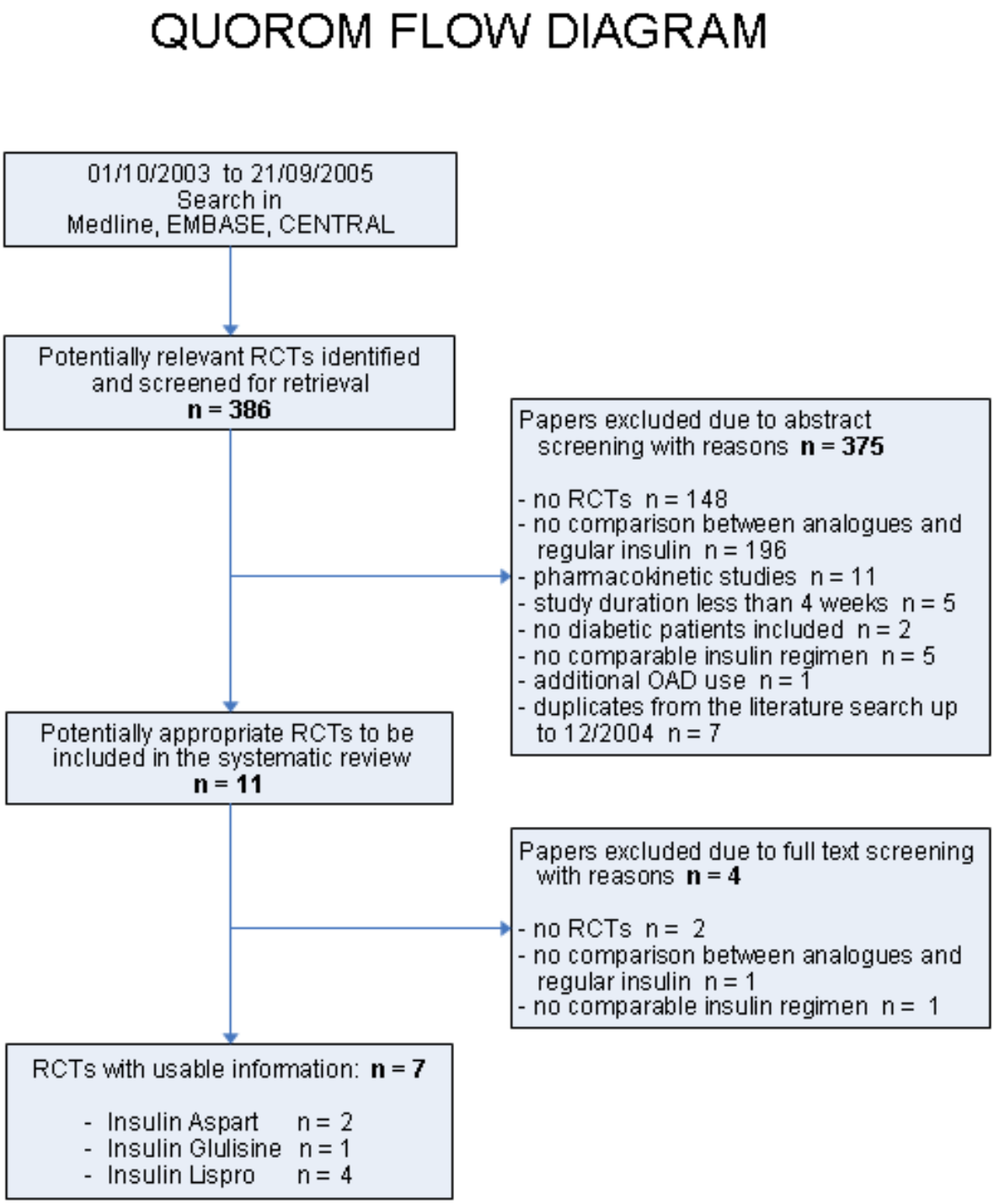
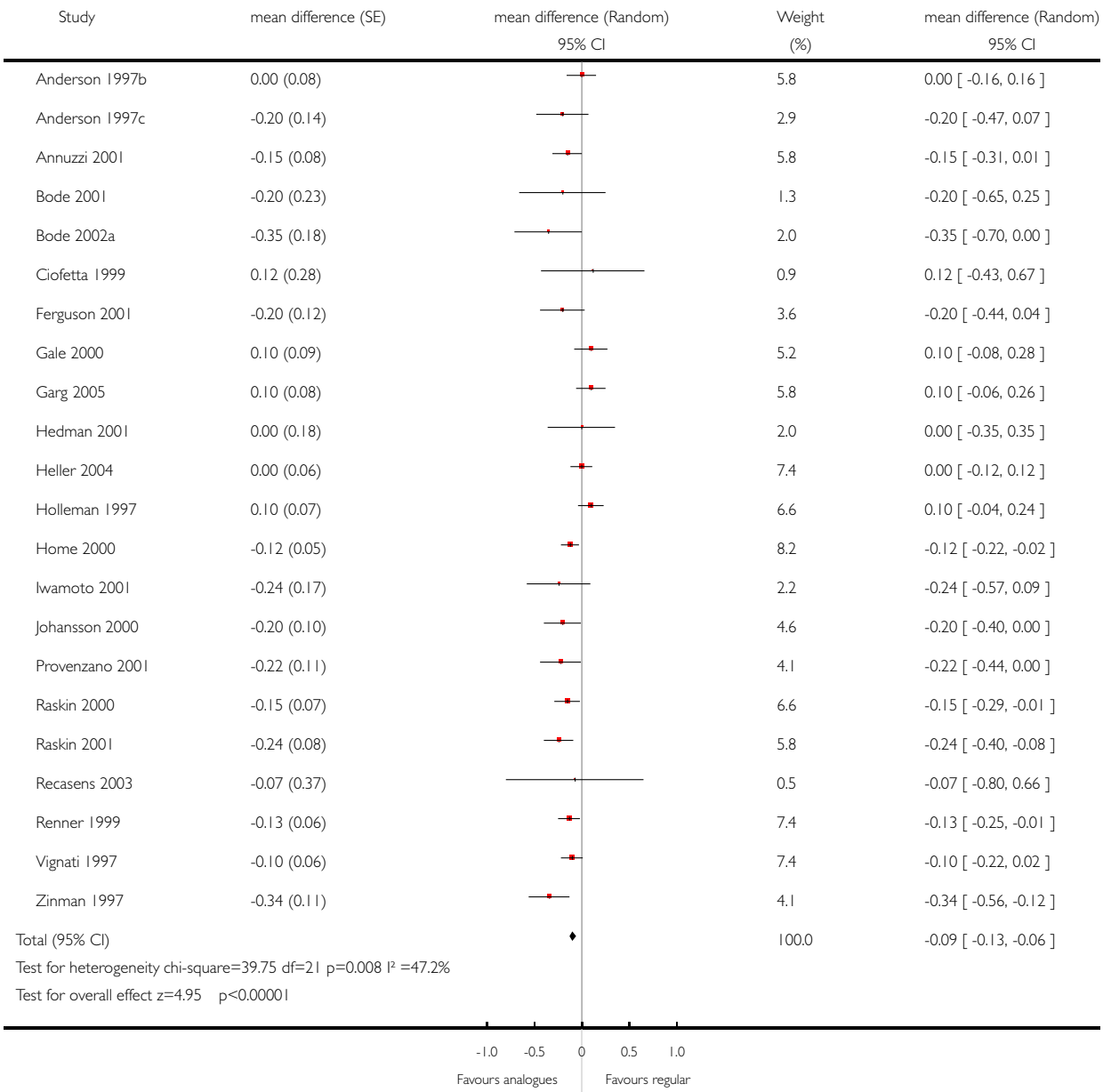


Analysis 01.01. Comparison 01 Type 1 diabetic patients: short acting insulin anlogues versus structurally unchanged insulin, Outcome 01 Hba1c

Review: Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus

Comparison: 01 Type 1 diabetic patients: short acting insulin anlogues versus structurally unchanged insulin

Outcome: 01 Hba1c



Analysis 01.02. Comparison 01 Type 1 diabetic patients: short acting insulin anlogues versus structurally unchanged insulin, Outcome 02 Hba1c by different types of interventions: CSII,. IIT

Review: Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus

Comparison: 01 Type 1 diabetic patients: short acting insulin anlogues versus structurally unchanged insulin

Outcome: 02 Hba1c by different types of interventions: CSII,. IIT

Study	mean difference (SE)	mean difference (Random) 95% CI	Weight (%)	mean difference (Random) 95% CI
01 CSII				
Bode 2001	-0.20 (0.23)		1.3	-0.20 [-0.65, 0.25]
Bode 2002a	-0.35 (0.18)		2.0	-0.35 [-0.70, 0.00]
Hedman 2001	0.00 (0.18)		2.0	0.00 [-0.35, 0.35]
Johansson 2000	-0.20 (0.10)		4.6	-0.20 [-0.40, 0.00]
Raskin 2001	-0.24 (0.08)		5.8	-0.24 [-0.40, -0.08]
Renner 1999	-0.13 (0.06)		7.4	-0.13 [-0.25, -0.01]
Zinman 1997	-0.34 (0.11)		4.1	-0.34 [-0.56, -0.12]
Subtotal (95% CI)			27.1	-0.20 [-0.27, -0.12]
Test for heterogeneity chi-square=5.15 df=6 p=0.53 I^2 =0.0%				
Test for overall effect z=5.16 p<0.00001				
02 IIT				
Anderson 1997b	0.00 (0.08)		5.8	0.00 [-0.16, 0.16]
Anderson 1997c	-0.20 (0.14)		2.9	-0.20 [-0.47, 0.07]
Annuzzi 2001	-0.15 (0.08)		5.8	-0.15 [-0.31, 0.01]
Ciofetta 1999	0.12 (0.28)		0.9	0.12 [-0.43, 0.67]
Ferguson 2001	-0.20 (0.12)		3.6	-0.20 [-0.44, 0.04]
Gale 2000	0.10 (0.09)		5.2	0.10 [-0.08, 0.28]
Garg 2005	0.10 (0.08)		5.8	0.10 [-0.06, 0.26]
Heller 2004	0.00 (0.06)		7.4	0.00 [-0.12, 0.12]
Holleman 1997	0.10 (0.07)		6.6	0.10 [-0.04, 0.24]
Home 2000	-0.12 (0.05)		8.2	-0.12 [-0.22, -0.02]
Iwamoto 2001	-0.24 (0.17)		2.2	-0.24 [-0.57, 0.09]
Provenzano 2001	-0.22 (0.11)		4.1	-0.22 [-0.44, 0.00]
Raskin 2000	-0.15 (0.07)		6.6	-0.15 [-0.29, -0.01]
Recasens 2003	-0.07 (0.37)		0.5	-0.07 [-0.80, 0.66]
Vignati 1997	-0.10 (0.06)		7.4	-0.10 [-0.22, 0.02]

(*Continued . . .*)

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Study	mean difference (SE)	mean difference (Random) 95% CI	Weight (%)	mean difference (Random) 95% CI
Subtotal (95% CI)			72.9	-0.06 [-0.10, -0.02]
Test for heterogeneity chi-square=24.76 df=14 p=0.04 I² =43.5%				
Test for overall effect z=2.78 p=0.005				
Total (95% CI)			100.0	-0.09 [-0.13, -0.06]
Test for heterogeneity chi-square=39.75 df=21 p=0.008 I² =47.2%				
Test for overall effect z=4.95 p<0.00001				

Analysis 01.03. Comparison 01 Type 1 diabetic patients: short acting insulin anlogues versus structurally unchanged insulin, Outcome 03 Hba1c by duration of study: less than or equal to 3 months, more than 3 months

Review: Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus

Comparison: 01 Type 1 diabetic patients: short acting insulin anlogues versus structurally unchanged insulin

Outcome: 03 Hba1c by duration of study: less than or equal to 3 months, more than 3 months

Study	mean difference (SE)	mean difference (Random) 95% CI	Weight (%)	mean difference (Random) 95% CI
01 <= 3 months				
Anderson 1997b	0.00 (0.08)		5.8	0.00 [-0.16, 0.16]
Annuzzi 2001	-0.15 (0.08)		5.8	-0.15 [-0.31, 0.01]
Bode 2001	-0.20 (0.23)		1.3	-0.20 [-0.65, 0.25]
Ciofetta 1999	0.12 (0.28)		0.9	0.12 [-0.43, 0.67]
Gale 2000	0.10 (0.09)		5.2	0.10 [-0.08, 0.28]
Garg 2005	0.10 (0.08)		5.8	0.10 [-0.06, 0.26]
Hedman 2001	0.00 (0.18)		2.0	0.00 [-0.35, 0.35]
Holleman 1997	0.10 (0.07)		6.6	0.10 [-0.04, 0.24]
Johansson 2000	-0.20 (0.10)		4.6	-0.20 [-0.40, 0.00]
Raskin 2001	-0.24 (0.08)		5.8	-0.24 [-0.40, -0.08]
Vignati 1997	-0.10 (0.06)		7.4	-0.10 [-0.22, 0.02]
Zinman 1997	-0.34 (0.11)		4.1	-0.34 [-0.56, -0.12]
Subtotal (95% CI)			55.2	-0.06 [-0.11, -0.01]
Test for heterogeneity chi-square=29.05 df=11 p=0.002 I² =62.1%				
Test for overall effect z=2.36 p=0.02				

(*Continued* . . .)

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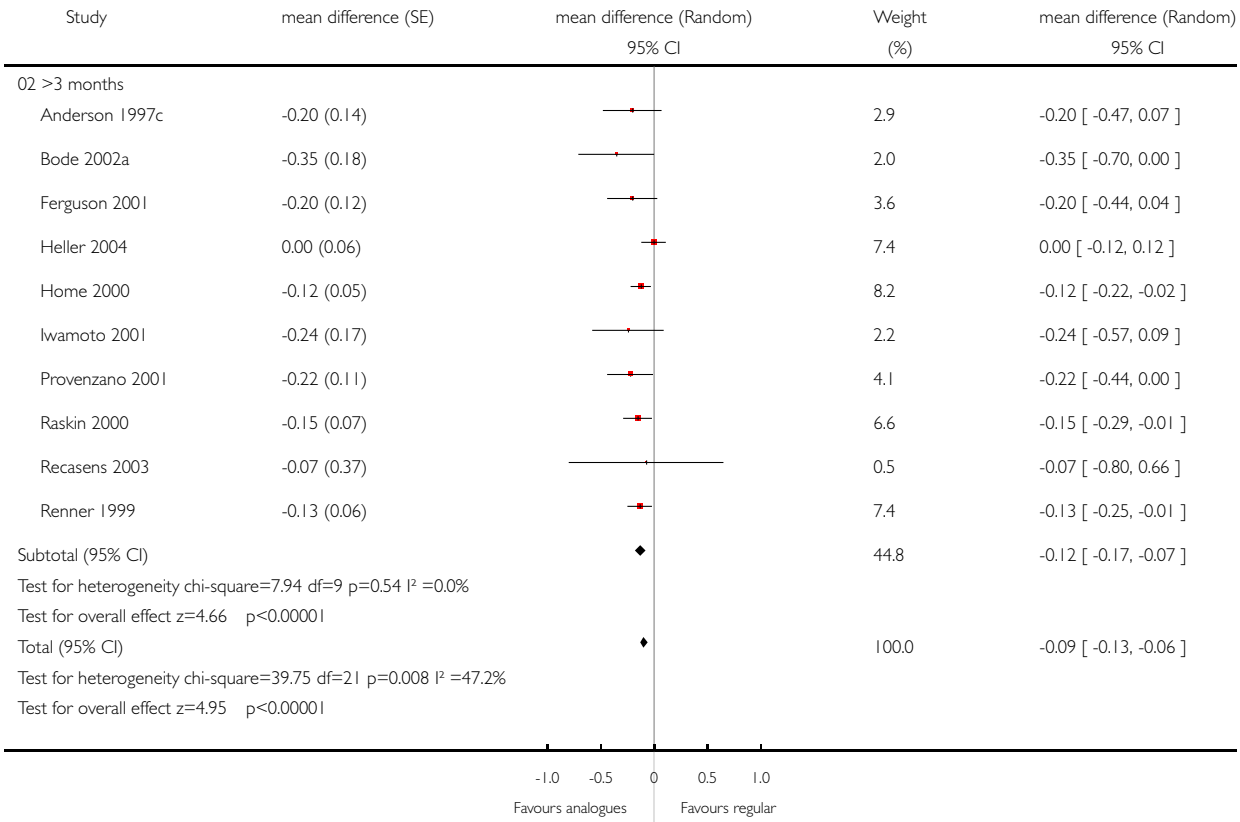
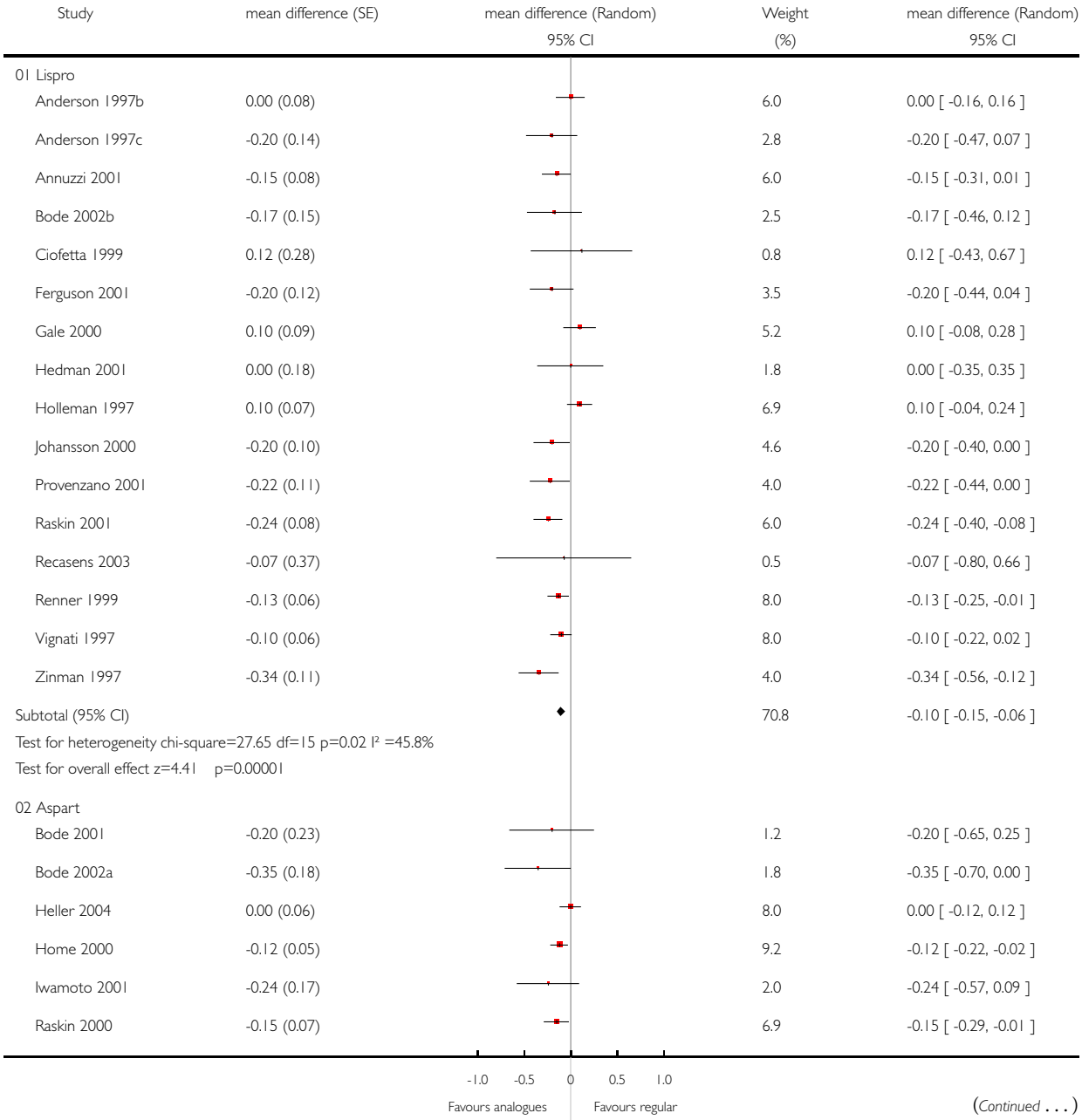


Analysis 01.04. Comparison 01 Type 1 diabetic patients: short acting insulin anlogues versus structurally unchanged insulin, Outcome 04 Hba1c by different short acting insulin analogues: Lispro, Aspart

Review: Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus

Comparison: 01 Type 1 diabetic patients: short acting insulin anlogues versus structurally unchanged insulin

Outcome: 04 Hba1c by different short acting insulin analogues: Lispro, Aspart



(*Continued . . .*)

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Study	mean difference (SE)	mean difference (Random) 95% CI	Weight (%)	mean difference (Random) 95% CI
Subtotal (95% CI)			29.2	-0.11 [-0.17, -0.04]
Test for heterogeneity chi-square=6.22 df=5 p=0.29 I² =19.6%				
Test for overall effect z=3.27 p=0.001				
Total (95% CI)			100.0	-0.10 [-0.14, -0.07]
Test for heterogeneity chi-square=33.88 df=21 p=0.04 I² =38.0%				
Test for overall effect z=5.49 p<0.00001				

Analysis 01.05. Comparison 01 Type 1 diabetic patients: short acting insulin anlogues versus structurally unchanged insulin, Outcome 05 Hba1c by different types of study design: parallel, cross-over studies

Review: Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus

Comparison: 01 Type 1 diabetic patients: short acting insulin anlogues versus structurally unchanged insulin

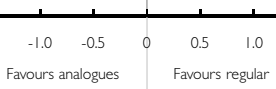
Outcome: 05 Hba1c by different types of study design: parallel, cross-over studies

Study	analogues N	regular N	mean difference (SE)	mean difference (Random) 95% CI	Weight (%)	mean difference (Random) 95% CI
01 parallel studies						
Anderson 1997c	1	1	-0.20 (0.14)		2.9	-0.20 [-0.47, 0.07]
Bode 2001	1	1	-0.20 (0.23)		1.3	-0.20 [-0.65, 0.25]
Bode 2002a	1	1	-0.35 (0.18)		2.0	-0.35 [-0.70, 0.00]
Ciofetta 1999	1	1	0.12 (0.28)		0.9	0.12 [-0.43, 0.67]
Garg 2005	1	1	0.10 (0.08)		5.8	0.10 [-0.06, 0.26]
Home 2000	1	1	-0.12 (0.05)		8.2	-0.12 [-0.22, -0.02]
Iwamoto 2001	1	1	-0.24 (0.17)		2.2	-0.24 [-0.57, 0.09]
Raskin 2000	1	1	-0.15 (0.07)		6.6	-0.15 [-0.29, -0.01]
Recasens 2003	1	1	-0.07 (0.37)		0.5	-0.07 [-0.80, 0.66]
Subtotal (95% CI)					30.4	-0.11 [-0.20, -0.02]
Test for heterogeneity chi-square=10.84 df=8 p=0.21 I² =26.2%						
Test for overall effect z=2.38 p=0.02						
02 cross-over studies						
Anderson 1997b	1	1	0.00 (0.08)		5.8	0.00 [-0.16, 0.16]
Annuzzi 2001	1	1	-0.15 (0.08)		5.8	-0.15 [-0.31, 0.01]
Ferguson 2001	1	1	-0.20 (0.12)		3.6	-0.20 [-0.44, 0.04]

(*Continued* . . .)

(. . . *Continued*)

Study	analogues N	regular N	mean difference (SE)	mean difference (Random) 95% CI	Weight (%)	mean difference (Random) 95% CI
Gale 2000	1	1	0.10 (0.09)		5.2	0.10 [-0.08, 0.28]
Hedman 2001	1	1	0.00 (0.18)		2.0	0.00 [-0.35, 0.35]
Heller 2004	1	1	0.00 (0.06)		7.4	0.00 [-0.12, 0.12]
Holleman 1997	1	1	0.10 (0.07)		6.6	0.10 [-0.04, 0.24]
Johansson 2000	1	1	-0.20 (0.10)		4.6	-0.20 [-0.40, 0.00]
Provenzano 2001	1	1	-0.22 (0.11)		4.1	-0.22 [-0.44, 0.00]
Raskin 2001	1	1	-0.24 (0.08)		5.8	-0.24 [-0.40, -0.08]
Renner 1999	1	1	-0.13 (0.06)		7.4	-0.13 [-0.25, -0.01]
Vignati 1997	1	1	-0.10 (0.06)		7.4	-0.10 [-0.22, 0.02]
Zinman 1997	1	1	-0.34 (0.11)		4.1	-0.34 [-0.56, -0.12]
Subtotal (95% CI)					69.6	-0.10 [-0.17, -0.03]
Test for heterogeneity chi-square=28.73 df=12 p=0.004 I^2 =58.2%						
Test for overall effect z=2.71 p=0.007						
Total (95% CI)					100.0	-0.10 [-0.16, -0.05]
Test for heterogeneity chi-square=39.75 df=21 p=0.008 I^2 =47.2%						
Test for overall effect z=3.62 p=0.0003						



Analysis 01.06. Comparison 01 Type 1 diabetic patients: short acting insulin anlogues versus structurally unchanged insulin, Outcome 06 Hypoglycaemic episodes

Review: Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus

Comparison: 01 Type 1 diabetic patients: short acting insulin anlogues versus structurally unchanged insulin

Outcome: 06 Hypoglycaemic episodes

Study	analogues N	analogues Mean(SD)	regular N	regular Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Anderson 1997b	1008	6.40 (6.35)	1008	7.20 (9.52)		13.9	-0.80 [-1.51, -0.09]
Anderson 1997c	162	4.40 (6.36)	174	4.50 (5.28)		11.8	-0.10 [-1.35, 1.15]
Bode 2002a	59	6.70 (5.40)	59	10.50 (8.90)		6.7	-3.80 [-6.46, -1.14]
Ciofetta 1999	8	8.10 (2.26)	8	4.00 (1.41)		9.4	4.10 [2.25, 5.95]
Del Sindaco 1998	12	4.40 (3.80)	12	11.00 (4.80)		4.8	-6.60 [-10.06, -3.14]
Gale 2000	93	2.60 (3.00)	93	3.10 (4.00)		12.7	-0.50 [-1.52, 0.52]
Garg 2005	286	3.46 (4.11)	278	3.49 (4.16)		13.9	-0.03 [-0.71, 0.65]
Renner 1999	113	12.40 (13.90)	113	11.00 (11.20)		5.1	1.40 [-1.89, 4.69]
Schmauss 1998	11	4.00 (2.98)	11	3.20 (2.32)		8.0	0.80 [-1.43, 3.03]
Vignati 1997	379	4.60 (5.50)	379	4.50 (5.00)		13.7	0.10 [-0.65, 0.85]
Total (95% CI)	2131		2135			100.0	-0.23 [-1.14, 0.69]

Test for heterogeneity chi-square=46.68 df=9 p=<0.0001 I^2 =80.7%

Test for overall effect z=0.48 p=0.6

Analysis 02.01. Comparison 02 Type 2 diabetic patients: short acting insulin anlogues versus structurally unchanged insulin, Outcome 01 Hba1c

Review: Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus

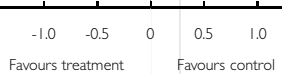
Comparison: 02 Type 2 diabetic patients: short acting insulin anlogues versus structurally unchanged insulin

Outcome: 01 Hba1c

Study	mean difference (SE)	mean difference (Random) 95% CI	Weight (%)	mean difference (Random) 95% CI
Anderson 1997a	0.00 (0.08)		24.6	0.00 [-0.16, 0.16]
Anderson 1997c	-0.20 (0.14)		8.0	-0.20 [-0.47, 0.07]
Gallagher 2005	-0.11 (0.10)		15.7	-0.11 [-0.31, 0.09]
Ross 2001	0.00 (0.14)		8.0	0.00 [-0.27, 0.27]
Vignati 1997	0.00 (0.06)		43.7	0.00 [-0.12, 0.12]
Total (95% CI)			100.0	-0.03 [-0.11, 0.04]

Test for heterogeneity chi-square=2.54 df=4 p=0.64 I^2 =0.0%

Test for overall effect z=0.84 p=0.4



Analysis 02.02. Comparison 02 Type 2 diabetic patients: short acting insulin anlogues versus structurally unchanged insulin, Outcome 02 Hypoglycaemic episodes

Review: Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus

Comparison: 02 Type 2 diabetic patients: short acting insulin anlogues versus structurally unchanged insulin

Outcome: 02 Hypoglycaemic episodes

Study	analogues		regular		Weighted Mean Difference (Random)	Weight	Weighted Mean Difference (Random)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Anderson 1997a	722	3.18 (4.30)	722	3.43 (5.11)		35.2	-0.25 [-0.74, 0.24]
Anderson 1997c	145	1.50 (3.90)	150	1.60 (3.67)		11.2	-0.10 [-0.96, 0.76]
Herz 2002a	37	0.70 (1.22)	37	1.20 (1.82)		16.8	-0.50 [-1.21, 0.21]
Ross 2001	70	1.80 (2.51)	78	1.70 (2.65)		12.1	0.10 [-0.73, 0.93]
Vignati 1997	328	1.90 (3.90)	328	1.90 (3.70)		24.7	0.00 [-0.58, 0.58]
Total (95% CI)	1302		1315			100.0	-0.17 [-0.46, 0.12]

Test for heterogeneity chi-square=1.70 df=4 p=0.79 I^2 =0.0%

Test for overall effect z=1.16 p=0.2