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Fullerton B, Siebenhofer A, Jeitler K, Horvath K, Semlitsch T, Berghold A, Gerlach FM

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[Intervention Review]

Short-acting insulin analogues versus regular human insulin for adult, non-pregnant persons with type 2 diabetes mellitus

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ABSTRACT

Background

The use of short-acting insulin analogues (insulin lispro, insulin aspart, insulin glulisine) for adult, non-pregnant people with type 2 diabetes is still controversial, as reflected in many scientific debates.

Objectives

To assess the effects of short-acting insulin analogues compared to regular human insulin in adult, non-pregnant people with type 2 diabetes mellitus.

Search methods

For this update we searched CENTRAL, MEDLINE, Embase, the WHO ICTRP Search Portal, and ClinicalTrials.gov to 31 October 2018. We placed no restrictions on the language of publication.

Selection criteria

We included all randomised controlled trials with an intervention duration of at least 24 weeks that compared short-acting insulin analogues to regular human insulin in the treatment of people with type 2 diabetes, who were not pregnant.

Data collection and analysis

Two review authors independently extracted data and assessed the risk of bias. We assessed dichotomous outcomes by risk ratios (RR), and Peto odds ratios (POR), with 95% confidence intervals (CI). We assessed continuous outcomes by mean differences (MD) with 95% CI. We assessed trials for certainty of the evidence using the GRADE approach.

Main results

We identified 10 trials that fulfilled the inclusion criteria, randomising 2751 participants; 1388 participants were randomised to receive insulin analogues and 1363 participants to receive regular human insulin. The duration of the intervention ranged from 24 to 104 weeks, with a mean of about 41 weeks. The trial populations showed diversity in disease duration, and inclusion and exclusion criteria. None of the trials were blinded, so the risk of performance bias and detection bias, especially for subjective outcomes, such as hypoglycaemia, was high in nine of 10 trials from which we extracted data. Several trials showed inconsistencies in the reporting of methods and results.

None of the included trials defined all-cause mortality as a primary outcome. Six trials provided Information on the number of participants who died during the trial, with five deaths out of 1272 participants (0.4%) in the insulin analogue groups and three deaths out of 1247 participants (0.2%) in the regular human insulin groups (Peto OR 1.66, 95% CI 0.41 to 6.64; P = 0.48; moderate-certainty evidence). Six trials, with 2509 participants, assessed severe hypoglycaemia differently, therefore, we could not summarise the results with a meta-analysis. Overall, the incidence of severe hypoglycaemic events was low, and none of the trials showed a clear difference between the two intervention arms (low-certainty evidence).

The MD in glycosylated haemoglobin A1c (HbA1c) change was -0.03% (95% CI -0.16 to 0.09; P = 0.60; 9 trials, 2608 participants; low-certainty evidence). The 95% prediction ranged between -0.31% and 0.25%. The MD in the overall number of non-severe hypoglycaemic episodes per participant per month was 0.08 events (95% CI 0.00 to 0.16; P = 0.05; 7 trials, 2667 participants; very low-certainty evidence). The 95% prediction interval ranged between -0.03 and 0.19 events per participant per month. The results provided for nocturnal hypoglycaemic episodes were of questionable validity. Overall, there was no clear difference between the two short-acting insulin analogues and regular human insulin. Two trials assessed health-related quality of life and treatment satisfaction, but we considered the results for both outcomes to be unreliable (very low-certainty evidence).

No trial was designed to investigate possible long term effects (all-cause mortality, microvascular or macrovascular complications of diabetes), especially in participants with diabetes-related complications. No trial reported on socioeconomic effects.

Authors' conclusions

Our analysis found no clear benefits of short-acting insulin analogues over regular human insulin in people with type 2 diabetes. Overall, the certainty of the evidence was poor and results on patient-relevant outcomes, like all-cause mortality, microvascular or macrovascular complications and severe hypoglycaemic episodes were sparse. Long-term efficacy and safety data are needed to draw conclusions about the effects of short-acting insulin analogues on patient-relevant outcomes.

PLAIN LANGUAGE SUMMARY

Short-acting insulin analogues versus regular human insulin for type 2 diabetes mellitus

Review question

Are short-acting insulin analogues better than regular human insulin for adult, non-pregnant people with type 2 diabetes?

Background

Short-acting insulin analogues act more quickly than regular human insulin. They can be injected immediately before meals and lead to lower blood sugar levels after food intake. Whether people with diabetes really profit from these newer insulins is debated.

Study characteristics

We found 10 randomised controlled trials (clinical studies where people are randomly put into one of two or more treatment groups) comparing the short-acting insulin analogues insulin lispro, insulin aspart, or insulin glulisine to regular human insulin in 2751 participants. The people in the included trials were monitored (followed) for 24 to 104 weeks.

This evidence is up to date as of 31 October 2018.

Key results

We are uncertain whether short-acting insulin analogues are better than regular human insulin for long-term blood glucose control or for reducing the number of times blood sugar levels drop below normal (hypoglycaemic episodes). The studies were too short to reliably investigate death from any cause. We found no clear effect of insulin analogues on health-related quality of life. We found

no information on late diabetes complications, such as problems with the eyes, kidneys, or feet. No study reported on socioeconomic effects, such as costs of the intervention and absence from work.

Certainty of the evidence

The overall certainty of the included studies was low or very low for most outcomes, mainly because all studies were carried out in an open-labelled fashion (study participants and study personnel knew who was getting which treatment). Several studies also showed inconsistencies in the reporting of methods, and results were imprecise.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Short-acting insulin analogues compared to regular human insulin for adults with type 2 diabetes mellitus

Patients: adults with type 2 diabetes mellitus
Setting: outpatients
Intervention: short-acting insulin analogues
Comparison: regular human insulin

Outcomes	Risk with RHI	Risk with short-acting insulin analogues	Relative effect (95% CI)	№ of participants (trials)	Certainty of the evidence (GRADE)	Comments
All-cause mortality (N) Follow-up: 24-104 weeks	**2 per 1000**	**4 per 1000** (1 to 16)	**Peto OR 1.66** (0.41 to 6.64)	2519 (6)	⊕⊕⊕◯ **moderate**[a]	Low event rate
Macrovascular or microvascular complications	Not reported					
Severe hypoglycaemic episodes (N) Follow-up: 24-52 weeks	See comment	See comment	-	2509 (6)	⊕⊕◯◯ **low**[b]	Reporting of results too diverse to allow a meta-analysis; small number of events. The effects of short-acting insulin analogues compared with regular human insulin for this outcome are uncertain
Adverse events other than severe hypoglycaemic episodes (all non-severe hypoglycaemic episodes) (Events per participant per month) Follow-up:	All non-severe hypoglycaemic episodes ranged across RHI groups from 0.6 to 2.5 events per participant per month	The mean difference in non-severe hypoglycaemic episodes in short-acting insulin analogue groups was **0.08 events per participant per month higher**	-	2667 (7)	⊕◯◯◯ **very low**[c]	The 95% prediction interval ranged between -0.03 events per participant per month and 0.19 events per participant per month

24-52 weeks		(0.00 lower to 0.16 higher)				
HbA1c (%) Follow-up: 24-104 weeks	The mean change in HbA1c levels across RHI groups ranged from -0.1% to -2.3%	The mean change in HbA1c levels across short-acting insulin analogue groups **was 0.03% lower** (0.16% lower to 0.09% higher)	-	2608 (9)	⊕⊕◯◯ **low**[d]	The 95% prediction interval ranged between -0.31% and 0.25%
Health-related quality of life (different scales used) Follow-up: 24-52 weeks	See comment		-	Unclear (2)	⊕◯◯◯ **very low**[e]	Health-related quality of life was either assessed in subpopulations of 2 trials, or insufficiently reported. The effects of short-acting insulin analogues compared with regular human insulin for this outcome are uncertain
Socioeconomic effects	Not reported					

CI: confidence interval; **HbA1c:** glycosylated haemoglobin A1c; **N**: number; **OR**: odds ratio; **RHI**: regular human insulin

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

[a] Downgraded by one level because of imprecision - see Appendix 15
[b] Downgraded by two levels because of serious risk of bias (performance and detection bias) - see Appendix 15
[c] Downgraded by two levels because of serious risk of bias (performance and detection bias), and by one level because of inconsistency (non-consistent direction of effects, 95% prediction interval ranging from benefit to harm), and indirectness (surrogate outcome) - see Appendix 15

[d]Downgraded by one level because of inconsistency (non-consistent direction of effect, 95% prediction interval ranging from benefit to harm), and by one level because of imprecision (CI consistent with benefit and harm) - see Appendix 15
[e]Downgraded by two levels because of serious risk of bias (performance bias, detection bias, attrition bias), and by one level because of imprecision (small number of trials) - see Appendix 15

BACKGROUND

Description of the condition

Type 2 diabetes mellitus is a chronic metabolic disease characterised by a combination of insulin resistance of peripheral tissues, and insufficient insulin secretion from the pancreas, which results in chronic hyperglycaemia (elevated levels of plasma glucose) with disturbances of the carbohydrate, fat, and protein metabolism. Long-term complications of diabetes mellitus include retinopathy, nephropathy, neuropathy, and increased risk of cardiovascular disease. Type 2 diabetes is the most common form of diabetes, with the number of people affected rising rapidly worldwide (Wild 2004).

Description of the intervention

The main treatment goal for most people with type 2 diabetes is to reduce the risk of diabetic complications and hypoglycaemia. While initially, the disease can often be treated with dietary and behavioural changes alone, or in combination with non-insulin antidiabetic drugs, eventually, many people require additional insulin therapy (ADA 1997). Different insulin regimens are possible for people with type 2 diabetes. Usually, insulin therapy for people with type 2 diabetes is initiated using basal insulin preparations to correct for fasting hyperglycaemia. However, with the progression of beta-cell deficiency, additional insulin injections before one or several meals are often necessary to achieve sufficient glycaemic control. Alternatively, insulin therapy can be initiated or intensified with the application of twice-daily pre-mixed insulin, whereby the insulin mixture consists of a short-acting and a medium- or long-acting insulin component (Meneghini 2013).

Insulin preparations used for prandial application or the fast-acting component of pre-mixed insulin can either be regular human insulin (RHI) or short-acting insulin analogues. In contrast to human endogenous insulin, insulin analogues have a slightly modified molecular structure, resulting in different pharmacokinetic profiles. When regular human insulin is injected subcutaneously, the plasma insulin concentration peaks about two to four hours after injection, unlike the much earlier plasma insulin peak in non-diabetic people after meal ingestion. This low rise to peak insulin concentration makes it difficult to mimic physiologic temporal insulin profiles, and is likely to account for much of the observed hyperglycaemia following meals in people with type 2 diabetes (Zinman 1989). 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 that can be used by the body (Mosekilde 1989). Short-acting insulin analogues with less tendency toward self-association are absorbed more quickly, achieving peak plasma concentrations about twice as high, and within approximately half the time as regular insulin (Howey 1994; Torlone 1994).

Currently, there are three different short-acting insulin analogues available: insulin aspart, insulin glulisine, and insulin lispro. Compared to regular human insulin, insulin aspart has aspartic acid instead of proline at position 28 of the B-region; in glulisine, the amino acid asparagine was replaced by lysine at position 3, and lysine with glutamic acid at position 29 of the B-chain; and in lispro, proline at position 28 and lysine at position 29 of the B-region were interchanged.

Adverse effects of the intervention

The key risk associated with any insulin therapy is the occurrence of hypoglycaemic episodes. While insulin analogues have been promoted as lowering the risk of hypoglycaemia, the evidence needs to be carefully evaluated, considering different patient subgroups and methodological challenges associated with the assessment of hypoglycaemia in clinical trials. For example, Singh 2009 pointed out that several trials on insulin analogues have excluded participants with a history of severe hypoglycaemia. Open-label designs, combined with measurements of hypoglycaemia that rely solely on participants' reports, make many results at high risk for bias. Overall, previous meta-analyses suggested that the risk of serious hypoglycaemic episodes were similar for regular human insulin and short-acting insulin analogues in participants with type 2 diabetes (Mannucci 2009; Singh 2009).

Another potential adverse effect of insulin therapy is weight gain. In general, improvement in glycaemic control through insulin therapy is frequently associated with weight gain, which in turn, can have negative consequences on blood pressure and lipid profiles. Especially for people with type 2 diabetes struggling with obesity, this adverse effect could have consequences for compliance. To date, there are no trials that have reported a relevant difference in weight gain between short-acting insulin analogues and regular human insulin in people with type 2 diabetes.

Finally, the 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).

How the intervention might work

Due to their faster pharmacokinetics, insulin analogues could lead to lower glucose levels after meals, and potentially also improve overall glycaemic control (Heinemann 1996; Howey 1994). Since it has been proposed by some authors that lower postprandial glu-

cose may be associated with a lower risk of cardiovascular complications in diabetes, hypothetically, treatment with short-acting insulin analogues could also result in a reduced risk for complications (Haffner 1998).

Insulin analogues might have additional beneficial effects on patients' quality of life by requiring less restrictive mealtime planning. For participants treated with RHI, insulin should be administered at least 30 minutes before meals. However, this recommendation is often not followed by patients because of its inconvenience (Overman 1999). In contrast, short-acting insulin analogues can be injected directly before meals, or even after meals, without a deterioration of prandial glycaemic control (Brunner 2000; Giugliano 2008; Schernthaner 1998).

Why it is important to do this review

Based on their pharmacokinetic profile, we might expect short-acting insulin analogues to improve the insulin therapy of people with diabetes mellitus, but at best, the evidence collected in previous reviews and meta-analyses showed only limited benefits on glycaemic control and the frequency of hypoglycaemic episodes, compared to therapy with regular human insulin (Gough 2007; Mannucci 2009; Singh 2009; WHO 2011). Furthermore, potential adverse effects of treatment with these insulin analogues have not been ruled out sufficiently, and there is a lack of evidence regarding the effects on long-term clinical outcomes (Singh 2009; WHO 2011).

Although clinical guidelines on type 2 diabetes do not give a clear preference of short-acting insulin analogues over regular human insulin (NICE 2008; NVL 2013), short-acting insulin analogues have become increasingly popular in the treatment of type 2 diabetes mellitus since their introduction to the market (Alexander 2008; Frick 2008).

Based on the results of cost effectiveness analyses (Cameron 2009; Holden 2011), this heavy use of insulin analogues promoted through aggressive marketing of the pharmaceutical industry has become a matter of political debate (Frick 2008; Gale 2011; Gale 2012; Holleman 2007; Sawicki 2011). This issue is of particular importance for low- and middle-income countries, where people still die due to the lack of affordable insulin (Cohen 2011; Gale 2011).

Considering this background, the availability of current evidence is highly relevant. The aim of this work was to systematically review the clinical efficacy and safety of the short-acting insulin analogues aspart, glulisine, and lispro in the treatment of people with type 2 diabetes mellitus, with a particular focus on long-term clinical outcomes. In contrast to the previous review, this update is restricted to trials with a follow-up duration of at least 24 weeks (Siebenhofer 2006).

OBJECTIVES

To assess the effects of short-acting insulin analogues compared to regular human insulin (RHI) in adult, non-pregnant persons with type 2 diabetes mellitus.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) with a treatment duration (follow-up) of 24 weeks or more, designed to compare participants with type 2 diabetes who were treated with the currently available short-acting insulin analogues lispro, aspart, glulisine, or with their biosimilars, compared with RHI, regardless of dose or schedule.

For mortality, macrovascular, and microvascular complications, trials with a follow-up of several years would be needed. To assess metabolic control, trials with a shorter duration could be useful, if the blood glucose lowering effect of the investigated treatments were assessed with sufficient confidence, and compared to patient-relevant outcomes (e.g. avoidance of hypoglycaemic events). Thus, we considered trials with a minimum duration of 24 weeks for inclusion in this review. This is concurrent with the requirement of the European Medicines Agency for confirmatory trials in the treatment of diabetes mellitus (EMA 2002).

Types of participants

Adults (18 years and older) with type 2 diabetes mellitus who were not pregnant.

Diagnostic criteria for type 2 diabetes mellitus

In order to be consistent with changes in the classification and diagnostic criteria of diabetes mellitus over the years, the diagnosis should have been established using the standard criteria valid at the time of the trial commencing (for example ADA 2003; ADA 2017; WHO 1999). Ideally, diagnostic criteria should have been described. We used the trial authors' definition of diabetes mellitus, if necessary. We had planned to subject diagnostic criteria to a sensitivity analysis.

Types of interventions

We considered all trials comparing treatment with short-acting insulin analogues (insulin lispro, insulin aspart, insulin glulisine, or biosimilars) to treatment with RHI, if insulin was injected subcutaneously via syringe, pen, or pump.

Combination with long- or intermediate-acting insulins was possible, as long as any additional treatment was given equally to both groups.
We planned to investigate the following comparisons of interventions versus control or comparator.

Intervention

- Short-acting insulin analogues (insulin lispro, insulin aspart, insulin glulisine, or biosimilars)

Comparison

- Regular human insulin (RHI)

Concomitant interventions had to be the same in both the intervention and comparator groups to establish fair comparisons.
If a trial included multiple arms, we included any arm that met the review inclusion criteria.

Summary of specific exclusion criteria

We excluded trials of the following category.

- Trials in participants younger than 18 years
- Trials in pregnant women
- Trials with a treatment duration (follow-up) of less than 24 weeks
- Trials where insulin was not administered subcutaneously

Types of outcome measures

Glycosylated haemoglobin A1c (HbA1c) is used in many trials as a surrogate outcome for macrovascular and microvascular endpoints. Because the incidence of such late complications rises with higher HbA1c values in a linear way in observational studies, it was assumed that lowering HbA1c would, in turn, lead to a reduction of unfavourable outcomes, such as myocardial infarction, stroke, amputation, nephropathy, retinopathy, etc (Nordwall 2009; Stratton 2000). However, in interventional trials in people with type 2 diabetes mellitus, lowering HbA1c was not consistently associated with a corresponding lowering of the incidence of the above mentioned patient-relevant outcomes, and in some instances, was even associated with a increase of such events (ACCORD 2008; Nissen 2007; Singh 2007). Therefore, we did not consider it a valid surrogate endpoint for reduction of late diabetic complications in persons with type 2 diabetes mellitus in this systematic review.
In this review, we reported HbA1c, because it is required to judge the effects of the different insulins on the occurrence of hypoglycaemic reactions. Intervention trials have shown that lowering blood glucose targets was associated with higher rates of hypoglycaemic events (ACCORD 2008; ADVANCE 2008; DCCT 1993; Duckworth 2009; UKPDS 1998). Thus, a reduction of such events in one of the comparison groups in interventional trials could be caused by a lower intensity of blood glucose reduction, and not necessarily by the effect of a specific treatment. Because of this, the rate of hypoglycaemic events has to be judged in reference to the respective blood glucose lowering effects, measured by HbA1c.

Primary outcomes

- All-cause mortality
- Macrovascular and microvascular complications
- Severe hypoglycaemic episodes

Secondary outcomes

- Glycaemic control (HbA1c)
- Adverse events other than severe hypoglycaemic episodes
- Health-related quality of life
- Socioeconomic effects

Method of outcome measurement

- All-cause mortality: death from any cause
- Macrovascular complications: nonfatal and fatal myocardial infarction and stroke
- Microvascular complications: manifestation and progression of retinopathy, nephropathy, neuropathy, and end-stage renal disease
- Severe hypoglycaemic episodes: number of participants with at least one severe hypoglycaemic episode
- Glycaemic control: measured by HbA1c in percent or mmol/mol
- Adverse events other than severe hypoglycaemic episodes: number of non-severe overall hypoglycaemic episodes, number of participants who experienced at least one episode of ketoacidosis, weight gain, or other adverse events
- Health-related quality of life: evaluated with a validated instrument, such as the 36-item Short Form Health Survey (SF-36) or the EuroQol Instument (EQ-5D), and measured at the latest measurement time point during follow-up
- Socioeconomic effects: costs of the intervention, absence from work, medication consumption, etc

Timing of outcome measurement

We included outcomes that were measured after a time interval of shorter than 12 months (short-term), or longer than 12 months (long-term).

Search methods for identification of studies

Electronic searches

This review is an update of the former review 'Short-acting insulin analogues versus regular human insulin in patients with diabetes mellitus', which was withdrawn and split into two Cochrane Reviews on short-acting insulin analogues versus regular human insulin for type 1 and type 2 diabetes mellitus.

The review teams carried out the electronic search in two steps. The first search was conducted from inception until April 2015 in the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL, 2015, issue 3), in the Cochrane Library (March 2015).
- MEDLINE Ovid, MEDLINE In-process & Other Non-indexed Citations Ovid, MEDLINE Daily Ovid, and OLDMEDLINE Ovid (1946 to 14 April 2015);
- Embase Ovid (1988 to 2015, Week 15);

A second search was conducted from 1 January 2015 to the specified date in the following sources:

- Cochrane Central Register of Controlled Trials (CENTRAL) via Cochrane Register of Studies Online (CRSO; searched on 31 October 2018);
- MEDLINE Ovid (Epub Ahead of Print, In-Process & Other Non-indexed Citations, MEDLINE Daily and OLDMEDLINE (1 January 2015 to 31 October 2018);
- Embase Ovid (1 January 2015 to 5 October 2017).

We did not update the Embase search after 2017, as RCTs indexed in Embase are now prospectively added to CENTRAL via a highly sensitive screening process (CENTRAL creation details).

We searched the following clinical trial registers from inception to the specified date:

- ClinicalTrials.gov (www.clinicaltrials.gov; searched on 31 October 2018);
- WHO International Clinical Trials Registry Platform (ICTRP; apps.who.int/trialsearch/; searched on 31 October 2018).

For detailed search strategies, see Appendix 1. We placed no restrictions on the language of publication when searching the electronic databases or reviewing reference lists of identified trials.

Searching other resources

In addition to the electronic search, we reviewed references from original articles and reviews.

For the original review, we screened abstracts of major diabetology meetings (European Association for the Study of Diabetes, American Diabetes Association) from 1992, and articles of diabetes journals (Diabetologia, Diabetic Medicine, Diabetes Care, Diabetes) until December 2003.

We directed inquiries to the three main pharmaceutical companies producing short-acting insulin analogues (Aventis, Eli Lilly, Novo Nordisk). In addition, we searched the company's trial registers (Lilly; Novo Nordisk; Sanofi).

We contacted experts and approval agencies (the European Agency for the Evaluation of Medicinal Products (EMA), the US Food and Drug Administration (FDA), the Medicines Control Agency (MCA), the Therapeutic Goods Administration (TGA); Hart 2012**;** Schroll 2015).

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

We also reviewed the bibliography of standard textbooks (Diabetes Annual, 12 (Marshall 1999); Praxis der Insulintherapie (Berger 2001), Evidence-based Diabetes Care (Gerstein 2001)).

We considered additional information, based on original trial reports, which was published in a report by the German Institute for Quality and Efficiency in Health Care (IQWIG 2005). Therefore, this report was cited as an additional source. If we encountered inconsistency between journal publications and the IQWIG 2005, we used data from the IQWiG report, since these data were based on original trial reports, and therefore deemed more reliable.

Data collection and analysis

Selection of studies

Two review authors (BF or MS, KH or TS) independently scanned the abstract, title, or both, of every record retrieved by the literature searches, to determine which trials we should assess further. We resolved any disagreements through consensus, or by recourse to a third review author (AS). If resolving disagreement was not possible, we categorised the trial as 'awaiting classification', and contacted the trial authors for clarification. We presented an adapted PRISMA flow-diagram to shown the process of trial selection (Liberati 2009). We listed all articles excluded after full-text assessment in the 'Characteristics of excluded studies' table, and provided the reasons for exclusion.

Data extraction and management

For trials that fulfilled the inclusion criteria, two review authors (BF and MS) independently extracted relevant population and intervention characteristics. We reported data on efficacy outcomes and adverse events using standardised data extraction sheets from the Cochrane Metabolic and Endocrine Disorders (CMED) Group. We resolved any disagreements by discussion, or if required, we consulted a third review author (AS). For details, see Characteristics of included studies; Table 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6; Appendix 7; Appendix 8; Appendix 9; Appendix 10; Appendix 11; Appendix 12; Appendix 13; Appendix 14; Appendix 15.

We provided information about potentially-relevant ongoing trials, including trial identifier, in the 'Characteristics of ongoing studies' table, and in the Appendix 7 'Matrix of study endpoints'.

We tried to find the protocol of each included trial, either in databases of ongoing trials, in publications of study designs, or both, and specified data in Appendix 7.
We sent an email request to authors of included trials to enquire whether they were willing to answer questions regarding their trials. Appendix 13 shows the results of this survey. If they agreed, we sought relevant missing information on the trial from the primary trial author(s), if required.

Dealing with duplicate publications and companion papers

We maximised our yield of information by collating all available data from duplicate publications, companion documents, or multiple reports of a primary trial, as available. In case of doubt, we gave priority to the publication reporting the longest follow-up associated with our primary or secondary outcomes.
We listed any duplicate publications, companion documents, multiple reports of a primary trial, and trial documents of included trials (such as trial registry information) as secondary references under the study identifier (ID) of the included trial. We also listed duplicate publications, companion documents, multiple reports of a trial, and trial documents of excluded trials (such as trial registry information) as secondary references under the study ID of the excluded trial.

Data from clinical trials registers

If data from included trials were available as study results in clinical trials registers, such as ClinicalTrials.gov or similar sources, we made full use of this information and extracted the data. If there was also a full publication of the trial, we collated and critically appraised all available data. If an included trial was marked as a completed study in a clinical trials register, but no additional information (study results, publication or both) was available, we added this trial to the 'Characteristics of studies awaiting classification' table.

Assessment of risk of bias in included studies

Two review authors (BF, TS, or KH) independently assessed the risk of bias of each included trial. We resolved any disagreements by consensus, or by consulting a third review author (KH). In the cases of disagreement, we consulted the remainder of the review author team, and made a judgement based on consensus. If adequate information was unavailable from the trials, trial protocols, or other sources, we contacted the trial authors to request more details or missing data on 'Risk of bias' items.
We used the Cochrane 'Risk of bias' assessment tool, and assigned assessments of low, high, or unclear risk of bias; for details see Appendix 2; Appendix 3. We evaluated individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions,* according to the criteria and associated categorisations contained therein*(*(Higgins 2011; Higgins 2017).

Summary assessment of risk of bias

We presented a 'Risk of bias' graph and a 'Risk of bias' summary figure.
We distinguished between self-reported, investigator-assessed, and adjudicated outcome measures.
We considered the following outcomes to be self-reported.

- Macrovascular or microvascular complications
- Severe hypoglycaemic episodes
- Adverse events other than severe hypoglycaemic episodes
- Health-related quality of life

We considered the following outcomes to be investigator-assessed.

- All-cause mortality
- Macrovascular or microvascular complications
- Severe hypoglycaemic episodes
- Glycaemic control (HbA1c)
- Adverse events other than severe hypoglycaemic episodes
- Socioeconomic effects

Risk of bias for a trial across outcomes: some risk of bias domains, such as selection bias (sequence generation and allocation sequence concealment), affect the risk of bias across all outcome measures in a trial. In cases of high risk of selection bias, we marked all endpoints investigated in the associated trial as being at high risk. Otherwise, we did not performed a summary assessment of the risk of bias across all outcomes for a trial.
Risk of bias for an outcome within a trial and across domains: we assessed the risk of bias for an outcome measure by including all entries relevant to that outcome (i.e. both trial-level entries and outcome-specific entries). We considered low risk of bias to denote a low risk of bias for all key domains, unclear risk to denote an unclear risk of bias for one or more key domains, and high risk to denote a high risk of bias for one or more key domains.
Risk of bias for an outcome across trials and across domains: these are the main summary assessments that we incorporated into our judgments about the quality of evidence in the 'Summary of findings' tables. We defined outcomes as at low risk of bias when most information came from trials at low risk of bias, unclear risk when most information came from trials at low or unclear risk of bias, and high risk when a sufficient proportion of information came from trials at high risk of bias.

Measures of treatment effect

When at least two included trials were available for a comparison and a given outcome, we tried to express dichotomous data as a risk ratio (RR) or Peto odds ratio (POR) with 95% confidence intervals (CIs). For continuous outcomes measured on the same scale (e.g. weight loss in kg), we estimated the intervention effect using the mean difference (MD) with 95% CIs. For continuous outcomes that measured the same underlying concept (e.g. health-related quality of life) but used different measurement scales, we calculated the standardised mean difference (SMD). We had planned

to express time-to-event data as a hazard ratio (HR) with 95% CIs.

Unit of analysis issues

We took into account the level at which randomisation occurred, such as cross-over trials, cluster-randomised trials, and multiple observations for the same outcome.

If more than one comparison from the same trial was eligible for inclusion in the same meta-analysis, we either combined groups to create a single pair-wise comparison, or appropriately reduced the sample size so that the same participants did not contribute multiple data (splitting the 'shared' group into two or more groups). While the latter approach offers some solution to adjusting the precision of the comparison, it does not account for correlation arising from the same set of participants being in multiple comparisons.

We wanted to re-analyse cluster-RCTs that did not appropriately adjust for potential clustering of participants within clusters in their analyses. We planned to inflate the variance of the intervention effects by a design effect. Calculation of a design effect involves estimation of an intra-cluster correlation (ICC). We would have obtained estimates of ICCs through contact with the trial authors, imputed them using estimates from other included trials that reported ICCs, or using external estimates from empirical research (e.g. Bell 2013). We had planned to examine the impact of clustering using sensitivity analyses.

Dealing with missing data

If possible, we obtained relevant missing data from the authors of the included trials. We carefully evaluated important numerical data, such as screened, randomised, assigned participants, as well as intention-to-treat (ITT), as-treated, and per-protocol populations. We investigated attrition rates (e.g. dropouts, losses to follow-up, withdrawals), and we critically appraised issues of missing data and imputation methods (e.g. last observation carried forward).

Where included trials did not report means and standard deviations (SDs) for outcomes and we did not receive the necessary information from trial authors, we imputed these values by estimating the mean and variance from the median, range, and the size of the sample (Hozo 2005).

We planned to investigate the impact of imputation on meta-analyses by performing sensitivity analyses and we reported per outcome, which trials were included with imputed SDs.

Assessment of heterogeneity

In the event of substantial clinical or methodological heterogeneity, we did not report trial results as the pooled effect estimate in a meta-analysis.

We identified heterogeneity (inconsistency) by visual inspection of the forest plots, and by using a standard Chi² test with a significance level of $\alpha = 0.1$. In view of the low power of this test, we also considered the I^2 statistic, which quantifies inconsistency across trials to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003).

Had we found heterogeneity, we would have attempted to determine potential reasons for it by examining individual study and subgroup characteristics.

Assessment of reporting biases

If we included 10 or more trials that investigated a particular outcome, we had planned to use funnel plots to assess small-trial effects. Several explanations may account for funnel plot asymmetry, including true heterogeneity of effect with respect to trial size, poor methodological design (and hence bias of small trials), and publication bias. Therefore, we interpreted the results carefully (Sterne 2011).

Data synthesis

We undertook a meta-analysis only if we judged participants, interventions, comparisons, and outcomes to be sufficiently similar to ensure an answer that was clinically meaningful. Unless good evidence showed homogeneous effects across trials of different methodological quality, we primarily summarised data at low risk of bias using a random-effects model (Wood 2008). We interpreted random-effects meta-analyses with due consideration to the whole distribution of effects and presented a prediction interval (Borenstein 2017a; Borenstein 2017b; Higgins 2009). A prediction interval needs at least three trials to be calculated and specifies a predicted range for the true treatment effect in an individual study (Riley 2011). For rare events, such as event rates below 1%, we used the Peto's odds ratio (POR) method, provided that there was no substantial imbalance between intervention and comparator group sizes, and intervention effects were not exceptionally large. We performed statistical analyses according to the statistical guidelines presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2017).

Subgroup analysis and investigation of heterogeneity

We expected the following characteristics to introduce clinical heterogeneity, and we had planned to carry out the following subgroup analyses, including investigation of interactions (Altman 2003).

- Sex
- Age
- Different short-acting insulin analogues
- Additional anti-hyperglycaemic treatment
- Different methods of insulin application
- Duration of disease

- Duration of follow-up
- Hypoglycaemia unawareness

Sensitivity analysis

We planned to perform sensitivity analyses in order to explore the influence of the following factors (when applicable) on effect sizes, by restricting analysis to the following.

- Taking into account risk of bias, as specified in the Assessment of risk of bias in included studies section.
- Very long (more than 12 months) or large trials to establish how much they dominated the results.
- Using the following filters: language of publication, imputation, clustered data and source of funding (industry versus other).

We also planned to test the robustness of the results by repeating the analysis using different statistical models (fixed-effect model and random-effects model).

Certainty of evidence

We presented the overall certainty of evidence for each outcome specified under Types of outcome measures, We assessed the certainty of our findings according to the GRADE approach, which takes into account issues related to internal validity (risk of bias, inconsistency, imprecision, publication bias) and external validity (directness of results). Two review authors (BF, KH, TS) independently rated the quality of evidence for each outcome. Differences in assessment were solved by discussion, or in consultation with a third review author.

We used the 'Checklist to aid consistency and reproducibility of GRADE assessments', to help us standardise our assessments (Appendix 15; Meader 2014). If we did not complete a meta-analysis for an outcome, we presented the results in a narrative format in the 'Summary of findings' table. We justified all decisions to downgrade the quality of trials using footnotes, and we made comments to aid the reader's understanding of the Cochrane Review where necessary.

Summary of findings table

We presented a summary of the evidence in Summary of findings for the main comparison. It provides key information about the best estimate of the magnitude of the effect, in relative terms and as absolute differences, for the comparison of alternative management strategies (short-acting insulin analogues versus regular human insulin), numbers of participants and trials addressing each important outcome, and a rating of overall confidence in effect estimates for each outcome. We created the 'Summary of findings' table based on the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions,* using the Review Manager 5 table editor rather than GRADEpro GDT software (GRADEpro GDT 2015; RevMan 2014; Schünemann 2011). We reported the following outcomes, listed according to priority.

- All-cause mortality
- Macrovacular or microvascular complications
- Severe hypoglycaemic episodes
- Adverse events other than severe hypoglycaemic episodes
- Glycaemic control (HbA1c)
- Health-related quality of life
- Socioeconomic effects

RESULTS

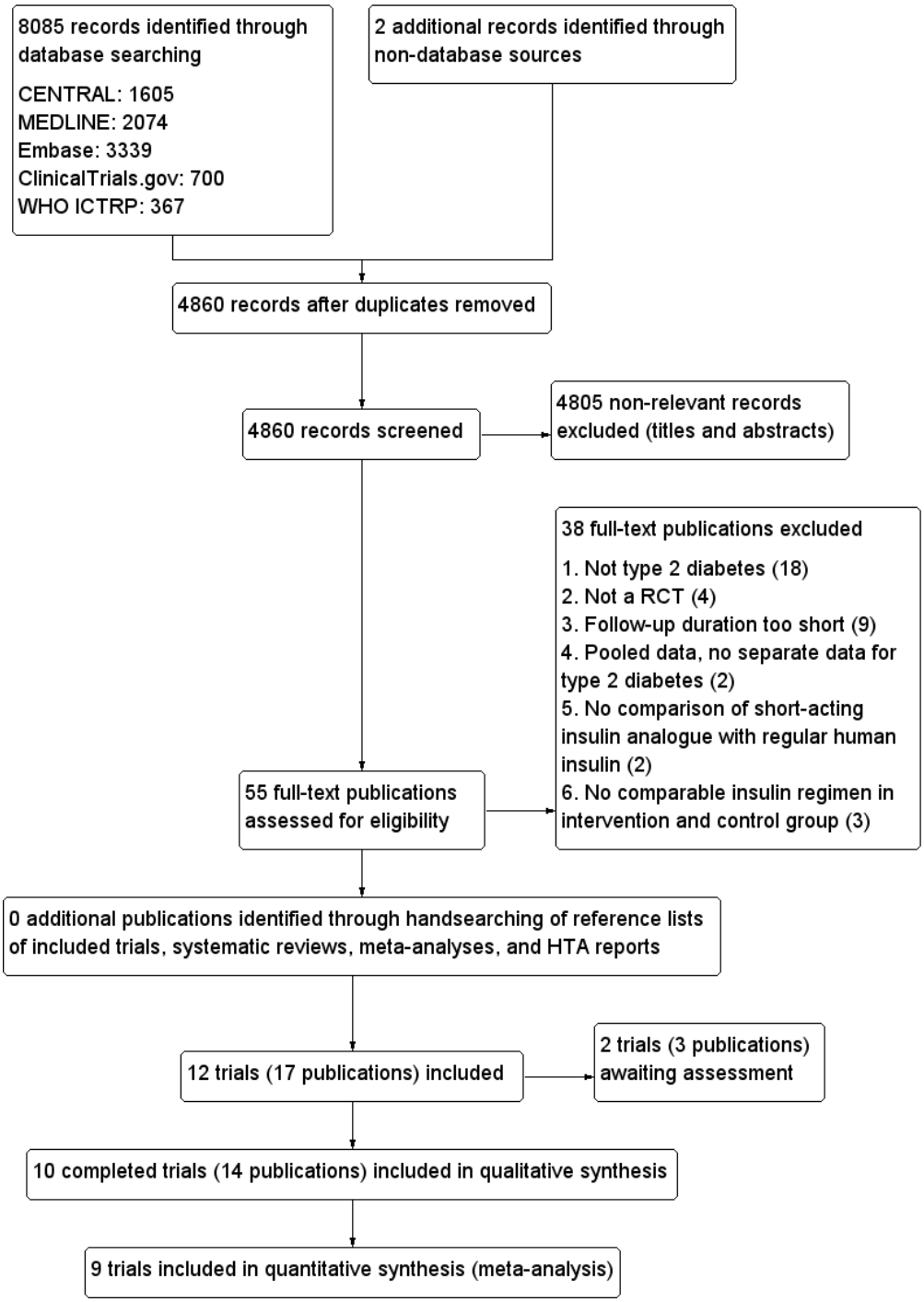
Description of studies

Results of the search

The electronic search using the search strategies described yielded 8085 references. We identified two additional records, including the IQWiG report through non-database sources (IQWIG 2005). After we removed duplicates, 4860 records remained.

After investigating these 4860 abstracts, we excluded 4805 according to our inclusion and exclusion criteria, leaving 54 for further examination. After screening the full text of these selected records, 12 trials (17 publications) met the inclusion criteria. We classified two of these trials as awaiting classification. We identified no additional trials by handsearching the reference lists of included trials, systematic reviews, meta-analyses, and HTA reports. In this review update we included 10 completed trials (14 publications). Three of these trials were included in our original review (Ross 2001; Z012 1997; Z014 1997). For further details see Figure 1.

Figure 1. Study flow diagram



Studies awaiting classification

We classified two records as awaiting classification (see Characteristics of studies awaiting classification). One trial was listed in ClinicalTrials.gov with unknown status and estimated completion date of October 2010 (NCT01500850). So far, no trial results have been reported online, and we found no publications. We contacted the trial investigator, but received no reply. For the other trial, we were unable to determine if treatment regimens were similar in both comparison groups (Farshchi 2016). We contacted the trial investigator, but received no reply.

Ongoing trials

We found no potentially relevant ongoing RCTs that investigated short-acting insulin analogues insulin aspart, insulin glulisine, insulin lispro, and their biosimilars compared to regular human insulin in adults with type 2 diabetes mellitus.

Included studies

We found 10 RCTs (described in 14 reports) to be potentially appropriate for inclusion in the meta-analysis. A detailed description of the characteristics of included studies is presented in the 'Characteristics of included studies' table. The following is a succinct overview:

Source of data

The results of the 10 trials were partially published in scientific journals between 1997 and 2013. One of these trials was only published as a conference poster (Pfützner 2013). For one of the trials, we obtained additional information from entries in clinical trials registers, and for four of the trials, we relied on additional information, based on the original study reports, which were published in a report by IQWIG (Bastyr 2000; Dailey 2004; IQWIG 2005; Z012 1997; Z014 1997). Anderson 1997 contained the combined data of two trials (Z012 1997; Z014 1997). From the publication, it was not clear that data of different two trials were combined. However, the original trial reports were available in IQWIG 2005, so we treated these trials separately in this review, using the same study names (Z012 1997; Z014 1997) as in IQWIG 2005. For one trial, information and results were only available from the entry in ClinicalTrials.gov, and from the pharmaceutical manufacturers' study reports (NCT01650129). We contacted all authors to request missing data or clarify issues about the methodology of the trial (see Appendix 13).

Comparisons

Five trials compared the insulin analogue lispro with regular human insulin (Altuntas 2003; Bastyr 2000; Ross 2001; Z012 1997; Z014 1997), two trials used the insulin analogue aspart (Hermann 2013; NCT01650129), two trials used glulisine (Dailey 2004; Rayman 2007), and one trial had three treatment arms comparing glulisine, aspart and RHI (Pfützner 2013). For details see Appendix 4.

Overview of trial populations

Overall, 2751 participants with type 2 diabetes participated in the 10 included trials; 1388 participants were randomised to the treatment arm and received a short-acting insulin analogue, 1363 participants were randomised to the control group and received regular human insulin. On average, 95% of the randomised participants participated in the trials until the end. One trial did not report the dropout rate for the treatment arms separately, but the overall attrition rate was 3% (Ross 2001). For the remaining trials, 93% (1221) of participants finished the trial in the intervention, and 93% (1195) of the participants in the comparator groups. The sample size ranged from 12 (Pfützner 2013) to 892 participants (Rayman 2007).

Trial design and setting

All included trials were RCTs with a parallel design; half of them were non-inferiority trials (see Table 1). They were all open-label trials, with no blinding of participants or investigators. The majority of the trials (70%) were carried out in multiple centres. For three trials, the setting was not reported. Two of them were likely carried out in a single centre (Altuntas 2003; Pfützner 2013), while the other was likely a multi-centre trial (Ross 2001). Five trials had study centres in multiple countries, including countries from Europe, North and South America, Australia, and Africa (Bastyr 2000; Dailey 2004; Rayman 2007; Z012 1997; Z014 1997). The other trials were carried out in Japan (NCT01650129), Turkey (Altuntas 2003), Canada (Ross 2001), and Germany (Hermann 2013). For one trial, the country was not reported, but was likely also carried out in Germany (Pfützner 2013). Two trials provided no information on the funding source (Altuntas 2003; Ross 2001). All other trials were at least partially commercially funded. The duration of the trials ranged from 22 to 104 weeks, with a mean of about 41 weeks. Four of the trials reported a run-in period that lasted from two to four weeks in order to achieve stable metabolic conditions (Dailey 2004; Rayman 2007; Z012 1997; Z014 1997). None of the trials were terminated before the planned end of follow-up.

Participants

The mean age of participants was 57 years, ranging between 55 and 64 years across trials (see Appendix 4; Appendix 5). One trial did not provide information on the gender of the participants (Altuntas 2003). For the remaining trials, 45% of the participants were female. The average body mass index was 31 kg/m², with the trial means ranging from 23 kg/m² to 35 kg/m². Three trials did not report on the duration of diabetes in the participants (Hermann 2013; NCT01650129; Pfützner 2013).The mean duration of diabetes across the remaining seven trials ranged from 8 to 15 years, with an average duration across all participants of 13 years. The participants' average HbA1c was 8.1% at baseline, and varied between 7.1% and 10.6% across trials. Data on disease severity and comorbidities were generally scarce. Only Ross 2001 reported the prevalence of neuropathy, retinopathy, hypertension, and peripheral vascular disease in the overall trial sample. Three trials only included insulin naive participants (Altuntas 2003; Hermann 2013; Ross 2001). Six trials only included participants who were already insulin treated (Bastyr 2000; Dailey 2004; NCT01650129; Rayman 2007; Z012 1997; Z014 1997). Pfützner 2013 provided no information on pre-trial blood glucose lowering medication. While OAD co-medication was allowed in Rayman 2007 and Dailey 2004, such participants were excluded in Z012 1997 and Z014 1997. For Bastyr 2000 and NCT01650129, it remains unclear if participants had to be on insulin only. Two trials provided Information on ethnicity (Bastyr 2000; Dailey 2004). In Dailey 2004, 85% of the participants were White, 11% Black, 2% Asian, 7% Hispanic, and 1% multi-ethnic. In Bastyr 2000, 76% of the participants were White.

Criteria for entry into the individual trials are outlined in the 'Characteristics of included studies' table. Insulin pump therapy and advanced diabetic complications were major exclusion criteria.

Diagnosis

Participants were diagnosed with type 2 diabetes mellitus in all of the trials. Most trials confirmed the diagnosis of type 2 diabetes against standard diagnostic criteria; three trials used WHO 1980 criteria ((Bennett 1991) Bastyr 2000; Z012 1997; Z014 1997), one used the ADA 1997 criteria (Altuntas 2003), and one trial used the criteria of the Japanese Diabetes Association (NCT01650129). Rayman 2007 included participants who had a type 2 diabetes diagnosis documented in their medical record. The other trials provided no information regarding their diagnostic criteria (Dailey 2004; Hermann 2013; Pfützner 2013; Ross 2001).

Interventions

All trials tried to apply a comparable insulin regimen throughout the investigation period, but usually insulin therapy was left somewhat flexible, with the aim to reach optimum glycaemic control. Ninety percent of the trials defined postprandial blood glucose targets (Altuntas 2003; Bastyr 2000; Dailey 2004; Hermann 2013; Pfützner 2013; Rayman 2007; Ross 2001; Z012 1997; Z014 1997). Trials set targets of less than 135 mg/dL, or less than 180 mg/dL. Sixty percent of the trials also specified preprandial glucose targets: three trials aimed for fasting blood glucose levels of less than 140 mg/dL (Bastyr 2000; Z012 1997; Z014 1997), Hermann 2013 aimed for less than 100 mg/dL, and Dailey 2004 and Rayman 2007 sought a preprandial target range between 90 mg/dL and 120 mg/dL.

In NCT01650129, participants took either biphasic insulin aspart 50 or biphasic human insulin 50/50 twice a day (before breakfast and dinner). In Ross 2001 and Dailey 2004, the insulin analogue plus NPH insulin, or regular human insulin plus NPH insulin was taken before breakfast and dinner. Dailey 2004 allowed additional doses of analogue or human regular insulin before meals, if necessary. In all other trials, short-acting insulin was taken before each meal. Participants taking regular human insulin were instructed to take the insulin 30 to 40 minutes before the meal, whereas insulin analogues could be taken directly before eating. Most participants took an additional slower-acting insulin once or twice a day. In most trials, NPH insulin was used as the basal insulin. One trial used ultralente (Z012 1997), another allowed either NPH or ultralente (Bastyr 2000), one used detemir (Hermann 2013), and one used insulin glargine (Pfützner 2013).

Three trials did not allow additional oral antidiabetic drugs (OADs (Bastyr 2000; Z012 1997; Z014 1997)). Hermann 2013 only included participants who had been using OADs for at least the last six months, but switched to short-acting insulin as part of the trial. Two trials permitted a stable dose of OADs (Dailey 2004; Rayman 2007). The other four trials provided no information on the use of OADs (Altuntas 2003; NCT01650129; Pfützner 2013; Ross 2001).

Outcomes

Four trials clearly defined a primary study endpoint (Dailey 2004; NCT01650129; Pfützner 2013; Rayman 2007). Two trials used the change in HbA1c throughout the trial duration (Dailey 2004; Rayman 2007), one used the change in nitrotyrosine (Pfützner 2013). NCT01650129 defined two primary endpoints: the number of adverse events during the trial, and the change in HbA1c throughout the trial. Information on primary endpoints was inconsistent in three trials (Bastyr 2000; Z012 1997; Z014 1997), The original study reports referred to postprandial blood glucose levels as the primary efficacy variable, while the study protocol referred to postprandial glucose excursions and hypoglycaemia episodes in relation to glycaemic control, and metabolic control as the primary efficacy variables. The power analysis was based on the preprandial blood glucose, HbA1c, and hypoglycaemia. The remaining trials did not specify a primary study endpoint. NCT01650129 and Pfützner 2013 explicitly defined secondary outcomes.

For a summary of all outcomes assessed in each trial, see Appendix

7. For definitions of outcome measures see Appendix 9 and Appendix 10. For adverse events see Appendix 11 and Appendix 12.

Excluded studies

Overall, we excluded 38 trials upon further scrutiny of the full-text reports. We have given the reasons for excluding trials in the 'Characteristics of excluded studies' table. The main reasons for exclusion were that participants did not have type 2 diabetes and the follow-up duration too short.

Risk of bias in included studies

For details on risk of bias of included studies see the 'Characteristics of included studies' table.

For an overview of review authors' judgments about each risk of bias item for individual trials and across all trials see Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included trials (note that not all trials measured all outcomes)

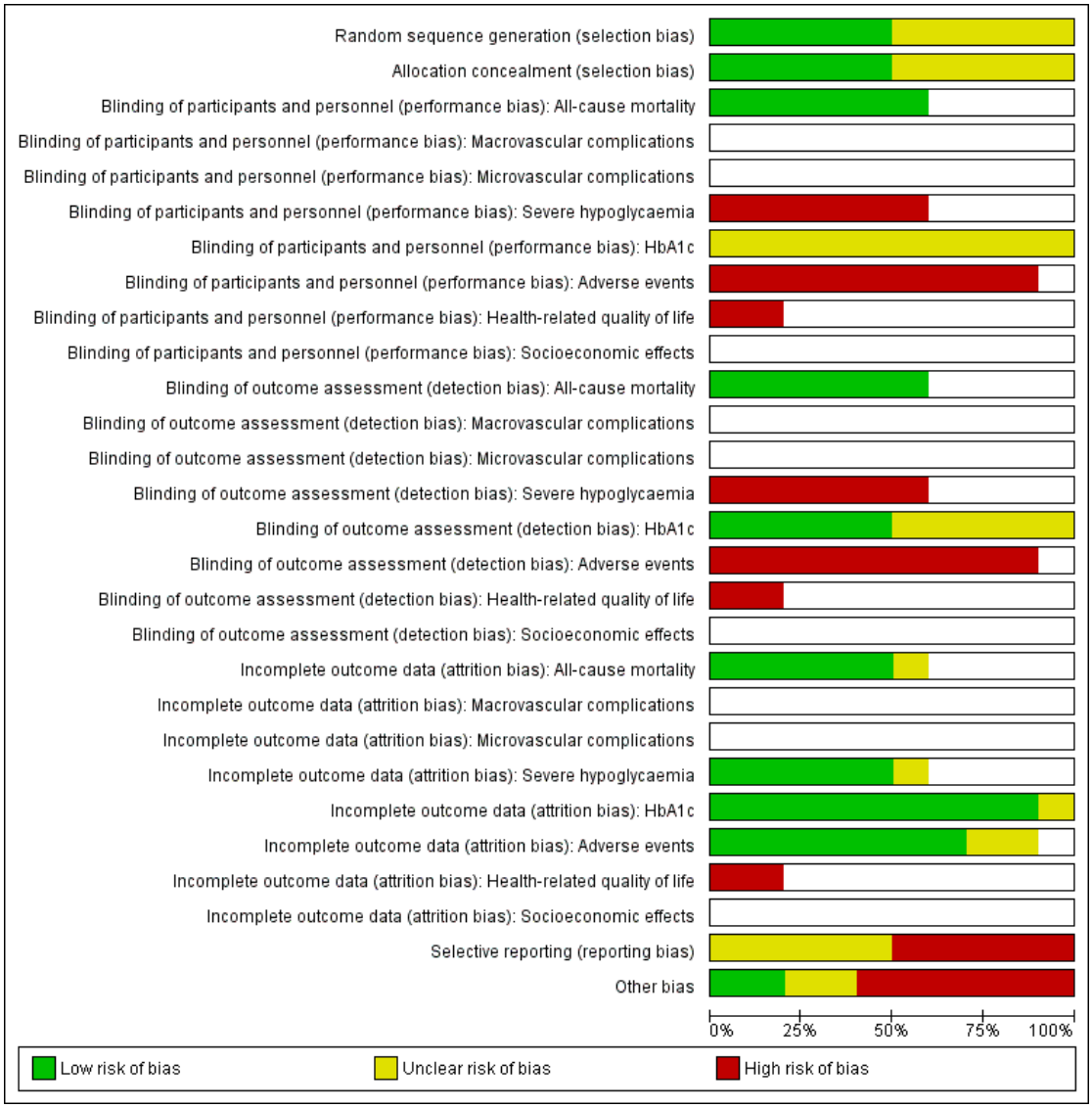
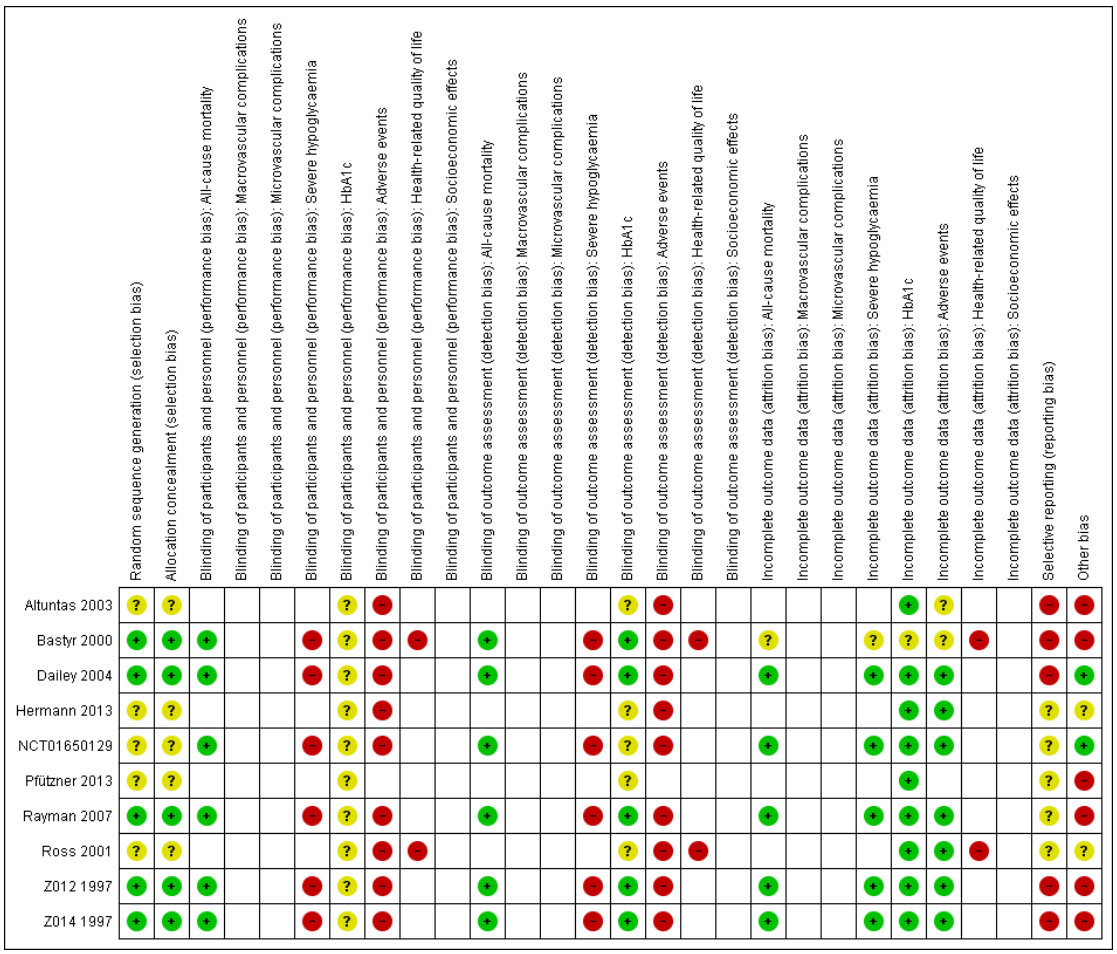


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study (note that not all trials measured all outcomes)



We investigated performance bias, detection bias, and attrition bias separately for each outcome measure.

Allocation

We considered the random sequence generation and allocation concealment as adequate in five trials (Bastyr 2000; Dailey 2004; Rayman 2007; Z012 1997; Z014 1997). The other trials did not provide sufficient information on their methods.

Blinding

All trials were open-label designs. The open-label design was commonly chosen because according to prescribing information, regular human insulin should be injected 30 to 45 minutes before meals, while short-acting insulin analogues can be injected immediately before a meal. An open-label study design, especially with no blinded outcome assessment and poor or unclear concealment of allocation, carries an increased risk of bias.

None of the trials provided explicit information on a blinded outcome assessment. Where measured, all except HbA1c, were patient-reported, investigator assessed, or both. For five trials, assessment of HbA1s was conducted in central laboratories (Bastyr 2000; Dailey 2004; Rayman 2007; Z012 1997; Z014 1997). Therefore, we assumed a blinded outcome assessment, and considered these trials to carry a low risk of detection bias for this outcome measure. None of the other trials provided information on HbA1c assessment, so we assumed an unclear risk of bias.

We assumed a low risk of bias for the outcome all-cause mortality (Bastyr 2000; Dailey 2004; NCT01650129; Rayman 2007; Z012 1997; Z014 1997).

Because of the open-label design, and because they were patient-

reported, investigator assessed, or both, we judged the outcomes severe hypoglycaemia and adverse events to carry a high risk of bias, when they were reported.

Because of the open-label design, we judged the outcome health-related quality of life as having a high risk of bias for Bastyr 2000 and Ross 2001.

None of the included trials reported on macrovascular or microvascular complications.

Incomplete outcome data

The proportion of participants lost to follow-up ranged from 0% (Altuntas 2003; Hermann 2013; Pfützner 2013), to 16% (Bastyr 2000). The trials either did not report the method used for imputing missing data, or reported a method that was not in keeping with current recommended practice, such as multiple imputation.

All-cause mortality

We judged attrition bias as low for five trials (Dailey 2004; NCT01650129; Rayman 2007; Z012 1997; Z014 1997). For the other five trials, the risk remained unclear, because either the outcome was not reported or insufficient information was available.

Microvascular and macrovascular complications

None of the included trials reported on these outcomes.

Severe hypoglycaemic episodes

We judged attrition bias as low for five trials (Dailey 2004; NCT01650129; Rayman 2007; Z012 1997; Z014 1997). For the other five trials, the risk remained unclear, because either the outcome was not reported or insufficient information was available.

HbA1c

We judged attrition bias as low for nine of the ten trials. For Bastyr 2000, the risk remained unclear because insufficient information on the number of analysed participants was available.

Adverse events other than severe hypoglycaemic episodes

We judged attrition bias as low for seven trials. For three trials, the risk remained unclear, because either the outcome was not reported or insufficient information on the number of analysed participants was available (Altuntas 2003; Bastyr 2000; Pfützner 2013).

Health-related quality of life

We judged attrition bias as high for Bastyr 2000 and Ross 2001. None of the other trials reported this outcome.

Socioeconomic effects

None of the included trials reported on these outcomes.

Selective reporting

Since some study protocols were not available, it was generally difficult to judge risk of bias due to selective reporting. However, for most of the trials, we found outcomes mentioned in the abstract, methods section, or other documents related to the trial not sufficiently reported in the results section. Therefore, we judged all trials as having an unclear or high risk of bias regarding selective reporting. Risk of reporting bias was high in five trials (Altuntas 2003; Bastyr 2000; Dailey 2004; Z012 1997; Z014 1997).

Other potential sources of bias

Regarding other sources of bias, we considered the lack of definition of a primary outcome and the inconsistent or clearly erroneous presentation of data as a potential risk. Six trials did not clearly define a primary outcome (Altuntas 2003; Bastyr 2000; Hermann 2013; Ross 2001; Z012 1997; Z014 1997). In three trials the presentation of data contained substantial errors or inconsistencies, so we judged these three trials to have a high risk of bias in this category (Altuntas 2003; Bastyr 2000; Rayman 2007). Pfützner 2013 was a pilot project with very few participants, which was only published as a poster and conference abstract. For Z012 1997 and Z014 1997, only results for pooled analyses were available from the original publication (Anderson 1997). The authors did not inform readers that these were results from pooled analyses. Therefore, we judged these three trials as also having a high risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Short-acting insulin analogues compared to regular human insulin for adults with type 2 diabetes mellitus

Baseline characteristics

For details on baseline characteristics, see Appendix 5 and Appendix 6.

Primary outcomes

All-cause mortality

None of the included trials defined all-cause mortality as a primary outcome, but information on the number of participants who died during the trial was available for all but two trials (Altuntas 2003; Ross 2001). In Hermann 2013 and Pfützner 2013, the number of deaths was not explicitly reported, but we assumed it

was zero, based on the presentation of the results (see Appendix 8). Overall, events were rare; across trials, there were five deaths out of 1272 participants in the insulin analogues groups (0.4%) and three deaths out of 1247 participants in the regular human insulin groups (0.2%), Peto odds ratio (POR) 1.66 (95% confidence interval (CI) 0.47 to 6.64); P = 0.48; 3 trials, 2519 participants; Analysis 1.1; moderate-certainty evidence.

There was no clear difference between the different types of insulin (Analysis 1.2).

Microvascular and macrovascular complications

None of the included trials reported on microvascular or macrovascular complications.

Severe hypoglycaemic episodes

Six trials reported severe hypoglycaemic episodes. Although three trials had explicitly defined severe hypoglycaemic episodes as either a primary or secondary outcome (Dailey 2004; Rayman 2007; Ross 2001), only two of these trials (Dailey 2004; Rayman 2007) reported results accordingly. Four other trials reported on severe hypoglycaemic events as part of their safety data (Bastyr 2000; NCT01650129; Z012 1997; Z014 1997). The reporting of severe hypoglycaemia across trials was diverse. Authors reported the overall number of participants with severe hypoglycaemic episodes in two trials (Dailey 2004; Rayman 2007). In three trials, information on severe hypoglycaemia was only available for participants who experienced coma, were treated with intravenous glucose, or were given glucagon separately (Bastyr 2000; Z012 1997; Z014 1997). In Dailey 2004, the number of participants with severe hypoglycaemic episodes was reported for the last two months of the trial only. The definition of severe hypoglycaemia differed somewhat between trials, but was mostly associated with the necessity of third party help, intravenous glucose infusions, glucagon administration, recovery after oral carbohydrate intake, or the occurrence of coma.

Overall, the incidence of severe hypoglycaemic events was low, and no trial showed a clear difference between the two treatment arms.

In the three insulin lispro trials, coma occurred in two of the 327 participants in the intervention groups (0.6%) and in five of the 333 participants in the control groups (1.5% (Bastyr 2000; Z012 1997; Z014 1997)). Four participants needed intravenous glucose, and one participant in each of the intervention and control groups needed glucagon. In Rayman 2007, six of 448 glulisine-treated participants and 14 of 442 participants taking regular human insulin experienced a severe hypoglycaemic episode. In Dailey 2004, six of 435 glulisine-treated participants and five of the 441 participants in the control group experienced severe hypoglycaemia during the last two months of follow-up. In NCT01650129, two out of 58 aspart-treated participants and one of 25 participants taking regular human insulin experienced severe hypoglycaemic episodes.

Because of the diverse reporting of severe hypoglycaemic episodes and the small number of events, we did not conduct a meta-analysis. Overall, there was no clear difference between the number of severe hypoglycaemic episodes experienced by those taking short-acting insulin analogues and those taking regular human insulin (low-certainty evidence).

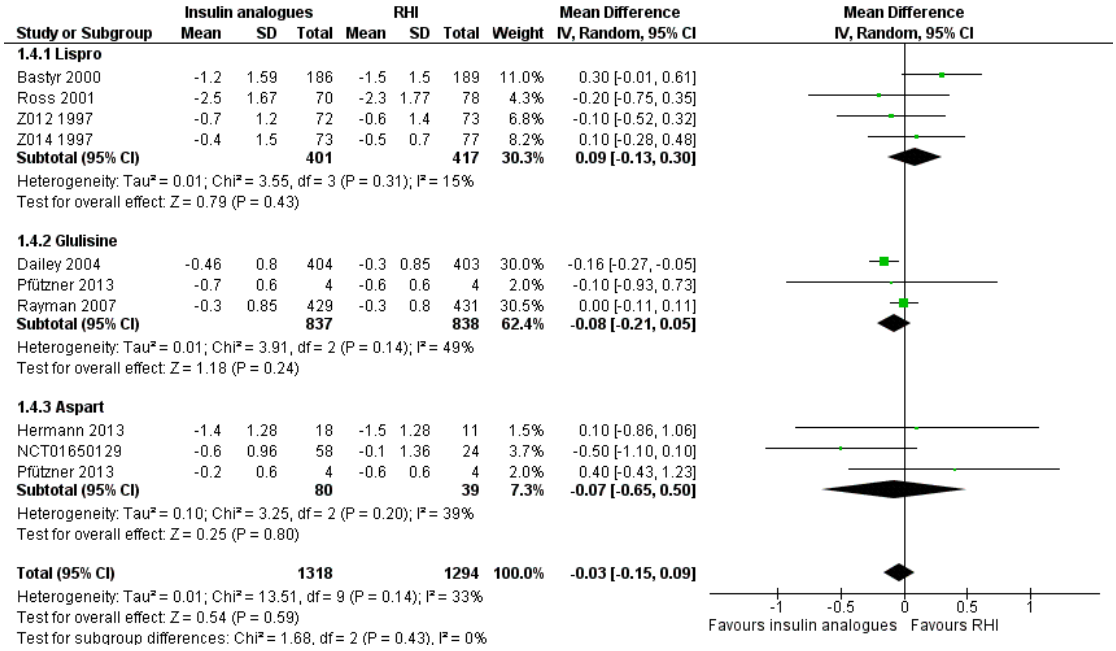
Secondary outcomes

Glycaemic control (HbA1c)

One trial had to be excluded from the analyses of HbA1c, since the treatment groups were inconsistently labelled in different tables, we were unable to attribute the reported HbA1c results to the appropriate treatment arm (Altuntas 2003). Dailey 2004 and Pfützner 2013 did not report a standard deviation (SD) for the mean HbA1 at endpoint, so we used the baseline SD in the treatment groups instead.

The mean difference (MD) in the change of HbA1c between short-acting insulin analogue and regular human insulin was -0.03% (95% CI -0.16 to 0.09); P = 0.60; 9 trials, 2608 participants; Analysis 1.3; low-certainty evidence. The 95% prediction interval ranged between -0.31% and 0.25%. There was no clear difference between the different types of insulin (Analysis 1.4; Figure 4).

Figure 4. Forest plot of comparison: Short-acting insulin analogues versus regular human insulin (RHI); outcome 1.4. HbA1c changes for different types of insulin (%)



Adverse events other than sever hypoglycaemic episodes

All non-severe hypoglycaemic episodes

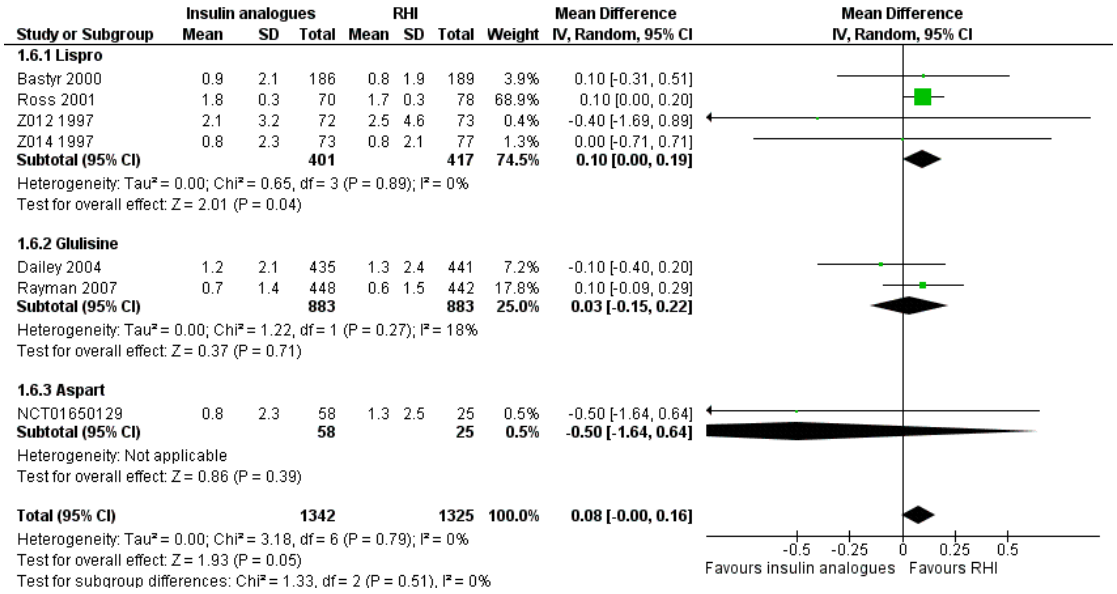
All but one trial reported on overall hypoglycaemic events (Pfützner 2013). Hypoglycaemic events were usually defined as the participant experiencing symptoms typically associated with hypoglycaemia. In four of the trials, hypoglycaemic events could also be counted if blood glucose measured below a certain value (Altuntas 2003; Bastyr 2000; Z012 1997; Z014 1997). This value varied between 36 mg/dL and 63 mg/dL (2.0 mmol/mL and 3.5 mmol/mL) across trials. The authors did not define hypoglycaemic episodes in Hermann 2013.

We excluded two trials from the meta-analysis because the unit of measurement was unclear, or was defined in a way that did not allow the results to be pooled (Altuntas 2003; Hermann 2013). Altuntas 2003 reported an increase in the overall hypoglycaemia rate in the lispro group compared to the regular human insulin group (0.57% versus 0.009%). However, the units to which the reported numbers referred were unclear. Hermann 2013 reported that five of 18 participants treated with insulin aspart experienced up to three hypoglycaemic episodes per year compared to three of 11 participants treated with regular human insulin.

For the remaining seven trials, we summarised results provided as mean episodes per participant per month. NCT01650129 reported the mean rate of hypoglycaemic episodes, but did not provide a measure of variance. Therefore, we imputed the SD from the mean SD of all other included trials (sensitivity analyses using the minimum and maximum SDs from other trials resulted in similar results; data not shown).

The MD of the overall mean hypoglycaemic episodes per participant per month was 0.08 episode (95% CI -0.00 to 0.16); P = 0.05; 7 trials, 2667 participants; Analysis 1.5; very low-certainty evidence. The 95% prediction interval ranged between -0.03 and 0.19. There was no clear difference between the different types of insulin (Analysis 1.6; Figure 5).

Figure 5. Forest plot of comparison: Short-acting insulin analogues versus regular human insulin (RHI); outcome 1.6. All non-severe hypoglycaemic episodes (mean episode/participant/month) for different types of insulin



Overall, none of the trials assessed hypoglycaemia in a blinded manner. The reporting of symptoms and the decision to carry out a blood glucose measurement are highly subjective, therefore, the results are at a high risk of bias and should be interpreted with caution.

Nocturnal hypoglycaemia

Four trials measured nocturnal hypoglycaemic episodes (Bastyr 2000; Dailey 2004; Rayman 2007; Ross 2001). Nocturnal hypoglycaemic episodes were either defined as those occurring between midnight and 6:00 am (Bastyr 2000; Ross 2001), or more generally, as events occurring at night or during sleep (Dailey 2004; Rayman 2007). Trial authors reported results using different units (such as number of participants with more than one episode per year, number of participants with at least one episode during the whole study period or just the last two months, number of episodes per participant per month, or number of episodes per participant per year), which made a meta-analysis not feasible. Apart from Rayman 2007, who distinguished between overall and severe nocturnal hypoglycaemic episodes, no information was provided regarding the severity of recorded events.

Bastyr 2000 reported on nocturnal hypoglycaemic events, even though the original study report did not mention this outcome; therefore, we assumed that it was a retrospective analysis of the data (IQWIG 2005). There was no clear difference between groups in the number of participants without any events; no statistics were reported for the comparison of participants with one event (lispro 10.4% and regular human insulin 13.7%), or more than one event (lispro 9.3% and regular human insulin 8.2%). Ross 2001 reported 0.08 nocturnal episodes per participant per 30 days for the lispro group versus 0.16 for the regular human insulin group (P = 0.057). The two trials on glulisine reported the number of participants with at least one nocturnal hypoglycaemic episode (Dailey 2004; Rayman 2007). While Dailey 2004 found no clear difference in overall nocturnal hypoglycaemic episodes between the two groups, Rayman 2007 found a higher number of participants who were taking regular human insulin who reported at least one episode of symptomatic nocturnal hypoglycaemia compared to those taking insulin analogues; there was no clear difference between groups for severe events. However, Rayman 2007 reported hypoglycaemia results based on the last two trial months only. In the original study report, results for nocturnal hypoglycaemic episodes were presented for the full study period; these results were very similar between groups (symptomatic hypoglycaemia: 95 participants (21.2%) in the intervention group versus 100 participants (22.6%) in the control group with at least one episode; severe hypoglycaemia: three participants (0.7%) in the intervention group versus five participants (1.1%) in the control group with at least one episode).

Weight gain

All but one trial provided some data on weight gain in the two

treatment groups (Pfützner 2013). However, in Altuntas 2003, there were discrepancies in the reporting of the results, so it was not clear which results belonged to which treatment arm. Hermann 2013 only presented results on the change of BMI, and reported no clear differences between treatment groups. NCT01650129 only stated that no treatment differences were observed, without reporting the results in detail. For the remaining trials, participants gained, on average, between 2 kg and 5 kg over the trial period. The amount of weight gain was similar for both groups in all trials. Since only three trials provided measures of variance of the weight gain, and trial durations differed, we decided not to pool results in a meta-analysis (Bastyr 2000; Z012 1997; Z014 1997).

Other adverse events

Most trials provided at least some information on adverse events. The majority of adverse events were mild, and the frequency and type of events was generally similar for the two treatment groups. The attrition rate because of adverse events varied between 0% and 4%, and was comparable between the two treatment arms in all trials. Ross 2001 reported the attrition rate because of adverse events for the overall trial sample only.

Four trials reported hyperglycaemic events (symptomatic or severe) as part of the safety data, which occurred only rarely (range across trials: 0% to 1.6% of participants with at least one event (Bastyr 2000; Rayman 2007; Z012 1997; Z014 1997)). Two trials measured events of ketoacidosis (Bastyr 2000; Rayman 2007). Bastyr 2000 reported that one participant in the lispro group (0.5%) experienced a ketoacidotic coma; in Rayman 2007, ketoacidosis occurred in 0.2% of the participants in the glulisine group, but there were no cases in the control group.

Finally, no clinically relevant differences were noted for vital signs, physical parameters, results of electrocardiography, or clinical laboratory findings. None of the trials provided information on carcinogenicity.

Health-related quality of life

Two trials assessed health-related quality of life, however, the results were generally unreliable (very low-certainty evidence (Bastyr 2000; Ross 2001)). In Bastyr 2000, it was reported that health-related quality of life was only assessed for a subgroup of participants from the USA and Canada. However, the original study report suggested that these data were also collected from participants in France. Trial authors presented results without any quantitative measures, they only reported that treatment groups showed no significant differences in any domain of the health-related quality of life questionnaire. Ross 2001 only reported subgroup data (69% of the overall population) on health-related quality of life too, assessed with the Diabetes Quality of Life (DQOL) questionnaire, which was originally developed for the Diabetes Control and Complications Trial (DCCT 1988). Trial authors provided no information on how this subgroup was chosen. The results showed a greater improvement on the diabetes-related worry subscale, but no clear differences for any of the other three subscales, or the overall score. The trial authors did not report any baseline or other outcome data for this subgroup, which made it difficult to relate these results to the results of the full trial population.

The two trials on glulisine collected data on treatment satisfaction (Dailey 2004; Rayman 2007). For Dailey 2004, the US Federal Drug Administration (FDA) and European Medicines Agency (EMA) drug approval documents stated that these data had been collected, but the results have not been published. Rayman 2007 neither reported results in the original study report (according to IQWIG 2005), nor in the journal publication. Treatment satisfaction was assessed using the Diabetes Treatment Satisfaction Questionnaire (DTSQ). Data were only presented for 69% (611 participants) of the trial population. Data were excluded for participants who participated in the trial for less than eight weeks, and for participants from countries that used questionnaires that had not been validated in their primary language. The DTSQ consists of eight questions, six of which were used to calculate the overall treatment satisfaction score. The glulisine group showed better improvement in the treatment satisfaction score than the control group. No clear difference was seen for the other two questions of the DTSQ. Results for the overall DTSQ score were based on data from 548 participants; the other two questions collected data from 528 and 531 participants. The exclusion of a large number of participants and the inconsistent number of participants for the different subgroup results, make it difficult to interpret the data.

For a description of the health-related quality of life instruments used in these trials see Appendix 14.

Socioeconomic effects

None of the included trials reported socioeconomic effects.

Subgroup analyses

We had planned to carry out subgroup analyses for additional anti-hyperglycaemic treatment, age, gender, different short-acting insulin analogues, different methods of insulin application, duration of disease, duration of follow-up, and hypoglycaemia unawareness.

In several trials, there was no or insufficient information on the use of additional anti-hyperglycaemic treatment with OADs. We requested further information from the trial authors, but most authors did not reply. None of the included trials provided data on subgroups according to age, gender, or hypoglycaemia unawareness either. In all included trials, participants administered their insulin in multiple daily injections. Therefore, we did not conduct subgroup analyses for any of these variables.

A separate analysis of trials according to insulin type showed similar effects, independent of the type of insulin analogues used, for all-

cause mortality, HbA1c, and all hypoglycaemic episodes. However, due to the low number of trials, these results should be interpreted with caution.

Sensitivity analyses

Given the very low number of trials, there was not much room for sensitivity analyses. Restricting the analysis to very long trials was not possible, because the longest trial was 24 months; all other trials had a treatment duration of 12 months or less, all trials were published in English, and the funding was usually commercial or not known. Using a fixed-effect model instead of a random-effects models resulted in similar effect estimates for HbA1c and all non-severe hypoglycaemic episodes (data not shown).

Assessment of reporting bias

We did not draw funnel plots due to limited number of trials per outcome.

DISCUSSION

Summary of main results

This Cochrane Review included data from 10 trials. Overall, there was a lack of data on long-term clinical outcomes. We had defined all-cause mortality, microvascular and macrovascular complications, and severe hypoglycaemic episodes as primary outcomes. Most trials reported all-cause-mortality, or provided data from which we were able to deduce numbers. There was no clear difference between the intervention and control groups. None of the included trials reported results on any microvascular or macrovascular complications. Six trials reported on severe hypoglycaemic episodes. However, since the incidence of severe hypoglycaemic episodes was low and reporting of data was diverse across trials, it was not feasible to carry out a meta-analysis. Overall, the incidence of severe hypoglycaemia was similar for participants using short-acting insulin analogues or regular human insulin in all trials.

Our analysis on the secondary outcomes of HbA1c and all non-severe hypoglycaemic episodes found no clinically relevant differences between the use of short-acting insulin analogues or regular human insulin. Health-related quality of life or treatment satisfaction was mentioned in four trials, but we considered the results as unreliable. None of the included trials reported on socioeconomic effects.

Overall completeness and applicability of evidence

In contrast to the previous review, this update was restricted to trials with a follow-up duration of at least 24 weeks. This restriction was introduced to better focus on the effects of insulin analogues on patient-relevant outcomes. In order to come to conclusions on long-term outcomes, such as mortality or microvascular or macrovascular complications of diabetes, trials with a follow-up duration of several years would be required. The longest trials we found in our systematic search had a follow-up duration of 24 months. None of the included trials investigated the effects of insulin analogues on microvascular or macrovascular complications. For a reliable assessment of metabolic control, trials should also be long enough to obtain a valid measure that can be interpreted in relation to the occurrence of hypoglycaemic events. However, by excluding trials with short follow-up durations, the number of trials that we included in this review was low, so for many outcomes, we could not draw any firm conclusions. The inclusion of observational trials would have potentially been more fruitful in this case, but at the cost of relying on data with high risk of bias.

Data were insufficient for costs of treatment, health-related quality of life, and many adverse events, such as potential carcinogenic effects. The results presented in these trials did not allow us to investigate whether effects were different for various subgroups.

The populations included in the clinical trials in this review were likely healthier and more motivated than what might be expected in clinical practice, since most trials had defined exclusion criteria, such as microvascular complications, lack of glycaemic control, or compliance with treatment. The trials were all conducted in Europe, Northern America, or Asia, and the majority of the trials provided no information on the ethnic groups included, so we could not judge whether they were representative of the populations of the countries included. The trial populations seemed within the range of normal clinical practice in terms of age, gender, and diabetes duration. The average age ranged from 55 to 60 years, disease duration from 8 to 14 years, the proportion of female participants from 35% to 60%, and the baseline HbA1c from 7.5% to 10.6%. The BMI ranged from 23 kg/m² to 35 kg/m², but in all trials but NCT01650129, the mean BMI was above 27 kg/m², indicating obesity.

Heterogeneity might have been introduced by combining trials that used different insulin analogues and variations in the number and times of insulin administration per day. One trial used a premixed insulin regime (NCT01650129). Trials also differed in allowing oral glucose-lowering medication. Seven RCTs did not allow additional oral antidiabetic medication during the trial, while in the remaining three trials patients were allowed to continue the oral glucose-lowering medication taken at the time of randomisation. This comprised all medications (Dailey 2004), all medications except glinides or glitazones (Rayman 2007), or was restricted to metformin (Pfützner 2013).

Overall, our results are based on trials identified through an extensive and systematic literature search, including articles in all lan-

guages. We also searched trials registers to find potentially relevant but not yet published trials.

Quality of the evidence

We considered the certainty of the evidence to be low or very low for most outcome measures analysed in this review (see Summary of findings for the main comparison). For all-cause mortality, we considered the certainty of the evidence to be moderate, but events were rare in both groups. Severe hypoglycaemic episodes were assessed in diverse ways across trials, which did not allow us to carry out a meta-analysis. In several of the included trials, the need for assistance of another person was sufficient to fulfil the definition of a serious hypoglycaemic episode. Such a definition is highly susceptible to bias, especially in open-label trials. More robust definitions, such as 'injection of glucose or glucagon by another person' may have resulted in more reliable data (Muehlhauser 1998). The risk of bias was likely higher for overall non-severe hypoglycaemic episodes, which in all of the trials were at least partially defined by symptoms potentially associated with hypoglycaemia, and therefore highly subjective.

For all included trials, there remained questions regarding information on the trial design, or incomplete or unclear data presentation. We asked all trial authors to clarify these questions, but received only one response. Due to this lack of information, we excluded some data from analysis, and we might not have judged the risk of bias appropriately.

Finally, we could not rule out sponsorship bias, since all but two trials (for which the funding source was unclear) were at least partially sponsored by industry.

Potential biases in the review process

Because the number of included trials was small, any pooled effect estimate should be interpreted with caution. Due to this lack of data, there was not much room for sensitivity analyses. However, the results across trials were similar, and in general, our results are in agreement with previous meta-analyses (Rys 2011; Singh 2009).

For glycaemic control, we only investigated HbA1c and hypoglycaemic episodes as outcomes. Several trials investigated multipoint daily blood glucose profiles, and found that short-acting insulin analogues were associated with superior postprandial blood glucose values compared to regular human insulin (Altuntas 2003; Dailey 2004; NCT01650129; Rayman 2007; Ross 2001). The extent to which postprandial blood glucose is an independent risk factor for macrovascular complications that can provide predictive information beyond what is already contained in HbA1c is still a matter of debate (Cavalot 2006; Parkin 2002; Shiraiwa 2005; Standl 2011). HbA1c is known to be the better surrogate measure for long-term complications (ADA 2018).

In this review, we only compared short-acting insulin analogues with regular human insulin, requiring that all other diabetic medication was the same in both treatment groups. Therefore, we excluded trials that for example, compared a short-acting insulin plus a long-acting insulin analogue with regular human insulin plus NPH, so we could single out the effects due to the use of short-acting insulin analogues alone. It is possible that there are interaction effects between short-acting and long-acting insulin types, so that for example, the benefits of short-acting insulin analogues could only be seen if used in combination with a long-acting insulin analogue. This question is not the topic of this review. However, for completeness, we do want to mention that there is evidence that short-acting insulin analogues combined with long-acting insulin analogues can provide advantages over regular insulin combined with NPH (Hermansen 2009; Home 2012). For type 1 diabetes, these trials have shown a reduction in HbA1c and hypoglycaemia in the combined analogue approach compared to the combined human insulin approach (Ashwell 2006; Hermansen 2004). For type 2 diabetes, the combined insulin analogue treatment resulted in a lower rate of nocturnal hypoglycaemia (Raslova 2004). For those trials, it remains a challenge to conclude to what extent the observed effects are due to the use of both analogue insulins together, rather than the use of the long-acting insulin analogue alone.

Finally, it should be noted that the majority of participants in this review used NPH as basal insulin. Therefore, little can be said about whether observed effects would be the same if a long-acting insulin analogue was used instead.

Agreements and disagreements with other studies or reviews

In our review, we found no clear differences in HbA1c changes between people being treated with short-acting insulin analogues or regular human insulin. This result is consistent with other meta-analyses (Banerjee 2007; IQWIG 2005; Rys 2011; Singh 2009). However, the meta-analysis by Mannucci 2009 found slightly lower HbA1c levels in participants treated with short-acting insulin analogues. Another review that compared biphasic insulin aspart to biphasic human insulin found no clear difference in HbA1c levels between the two treatments (Davidson 2009). This review reported a lower risk of nocturnal or major hypoglycaemia for the biphasic insulin aspart, but an increased risk for daytime hypoglycaemia compared to biphasic human insulin. The majority of reviews did not find a clear difference in the risk of experiencing hypoglycaemia between participants who took short-acting insulin analogues and those who took regular human insulin regarding (Banerjee 2007; Mannucci 2009; Rys 2011). Singh 2009 concluded that the evidence was inconsistent.

We agree with other reviews that health-related quality of life was rarely investigated, and frequently only reported on subsamples,

which made it difficult to draw any conclusions (Banerjee 2007; Rys 2011; Singh 2009).

As we found no RCTs comparing the costs of treatment with short-acting insulin analogues or regular human insulin, we have no conclusions on the issue of cost-effectiveness. In the political debate about the use of insulin analogues, their higher cost, while providing only a small improvement in glycaemic control, is one of the main arguments against the wide-spread use of insulin analogues (Davidson 2014). Grunberger 2014 points out the complexity of assessing cost-effectiveness of this issue, especially if one considers that insulin prices are highly dependent on the healthcare system, and vary immensely over time, and across different countries.

Overall, there is also a lack of observational studies reporting on the long-term benefits and harms of short-term insulin analogues. Rathmann 2014 investigated the risk of microvascular or macrovascular complications, based on the medical records of people with type 2 diabetes, treated in general practice. A comparison of participants who had been treated with short-acting insulin analogues for at least three years with those who had been treated with regular human insulin, showed no clear difference in the risk of microvascular and macrovascular complications. In trials of the effects of insulin analogues on cancer, the trial authors usually did not distinguish between long-acting and short-acting insulin analogues. While for some long-acting insulin analogues, the literature presents inconsistent results on the risk of cancer, to date, there are no trials suggesting an increased risk of cancer associated with the use of short-acting insulin analogues (Sciacca 2012; Smith 2009).

AUTHORS' CONCLUSIONS

Implications for practice

The current evidence from clinical trials suggests neither clear benefits nor clear harms from the use of short-acting insulin analogues over regular human insulin.

Based on the most recent position statement of the American Diabetes Association, a patient-centred approach that incorporates a patient's age, life style, preferences, hypoglycaemia risk, cardiovascular risk, and other factors is preferred over prescriptive recommendations. Patients and doctors should look at the advantages and disadvantages of different medication regimes, and choose a cost-effective treatment, given the individual requirements of the patient (ADA 2018).

Implications for research

In general, high-certainty evidence that compares the effects of the various regimens in different patient groups is needed to provide better evidence-based guidance for healthcare providers.

For safety purposes, we need trials with long-term follow-up on a large number of people who use short-acting insulin analogues. Due to fears of potentially carcinogenic and proliferative effects, most trials to date have excluded participants with advanced diabetic complications. The current trials with a maximum follow-up of 24 months do not allow us to draw conclusions on long-term clinical effects of short-acting insulin analogues. For an economic analysis, cost data should be collected in future RCTs.

Future research will have to take into account new, even faster-acting insulins, which are currently being developed and tested (Heise 2014; Kaye 2013; Krasner 2012). In addition, the methods of insulin application will likely become more variable in the future. More people are already using different types of insulin pumps, and new research shows that modulation of the injection site or other needle-free applications can have effects on the pharmacokinetic and pharmacodynamic profiles of short-acting insulins (Engwerda 2011; Landau 2014; Pfützner 2014).

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REFERENCES

References to studies included in this review

Altuntas 2003 *{published data only}*

* Altuntas Y, Ozen B, Ozturk B, Sengul A, Ucak S, Ersoy O, et al. Comparison of additional metformin or NPH insulin to mealtime insulin lispro therapy with mealtime human insulin therapy in secondary OAD failure. *Diabetes, Obesity and Metabolism* 2003;**5**(6):371–8. PUBMED: 14617222]

IQWiG (Institute for Quality and Efficiency in Health Care). Short-acting insulin analogues in the treatment of diabetes mellitus type 2. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG); 2005 December. Abschlusbericht A05-04.

Bastyr 2000 *{published data only}*

* Bastyr EJ III, Huang Y, Brunelle RL, Vignati L, Cox DJ, Kotsanos JG. Factors associated with nocturnal hypoglycaemia among patients with type 2 diabetes new to insulin therapy: experience with insulin Lispro. *Diabetes Obesity and Metabolism* 2000;**2**(1):39–46. PUBMED: 11220353]

IQWiG (Institute for Quality and Efficiency in Health Care). Short-acting insulin analogues in the treatment of diabetes mellitus type 2. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG); 2005 December. Abschlusbericht A05-04.

Dailey 2004 *{published data only}*

* Dailey G, Rosenstock J, Moses RG, Ways K. Insulin Glulisine provides improved glycemic control in patients with type 2 diabetes. *Diabetes Care* 2004;**27**(10):2363–8. PUBMED: 15451901]

IQWiG (Institute for Quality and Efficiency in Health Care). Short-acting insulin analogues in the treatment of diabetes mellitus type 2. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG); 2005 December. Abschlusbericht A05-04.

Hermann 2013 *{published data only}*

* Hermann BL, Kasser C, Keuthage W, Huptas M, Dette H, Klute A. Comparison of insulin Aspart vs. regular human insulin with or without insulin Detemir concerning adipozytokines and metabolic effects in patients with type 2 diabetes mellitus. *Experimental & Clinical Endocrinology & Diabetes* 2013;**121**(4):210–3. PUBMED: 23512415]

NCT01650129 *{unpublished data only}*

NCT01650129. Safety and efficacy of biphasic insulin Aspart 50 in subjects with type 2 diabetes. clinicaltrials.gov/ct2/show/NCT01650129 (first posted July 26, 2012).

* Novo Nordisk. An open-labelled randomised, parallel group, multicentre, safety and efficacy study of NN-X14Mix50 (BIAsp50) in a twice daily regimen in type 2 diabetic subjects. novonordisk-trials.com (accessed 4 December 2018).

Pfützner 2013 *{published data only}*

EudraCT2011-003733-34. Human insulin analogs: evaluation of inflammatory mRNA expression of macrophages and endothelial function of short-acting insulin - HERMES pilot study [Humaninsulin–Analoga: Evaluation der inflammatorischen mRNA–Expression von Makrophagen und der endothelialen Funktion von kurzwirkendem Insulin– HERMES Pilotstudie]. www.clinicaltrialsregister.eu/ctr-search/trial/2011-003733-34/DE (first posted 25 August 2011).

NCT01417897. Human insulin analogs: evaluation of inflammatory mRNA expression of macrophages and endothelial function of short-acting insulin - HERMES pilot study (HERMES). clinicaltrials.gov/ct2/show/NCT01417897 (first posted 16 August 2011).

* Pfützner A, Forst T, Mitri M, Löffler A, Heise J, Forkel C, et al. Impact of short-acting insulin analogs on biomarkers of oxidative stress and chronic systemic inflammation in patients with type 2 diabetes: results from a pilot study. *Diabetes* 2013;**62**(Suppl. 1):A235–6.

Rayman 2007 *{published data only}*

IQWiG (Institute for Quality and Efficiency in Health Care). Short-acting insulin analogues in the treatment of diabetes mellitus type 2. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG); 2005 December. Abschlusbericht A05-04.

* Rayman G, Profozic V, Middle M. Insulin Glulisine imparts effective glycaemic control in patients with type 2 diabetes. *Diabetes Research and Clinical Practice* 2007;**76**(2): 304–12. PUBMED: 17113676]

Ross 2001 *{published data only}*

IQWiG (Institute for Quality and Efficiency in Health Care). Short-acting insulin analogues in the treatment of diabetes mellitus type 2. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG); 2005 December. Abschlusbericht A05-04.

* Ross SA, Zinman B, Campos RV, Strack T. A comparative study of insulin lispro and human regular insulin in patients with type 2 diabetes mellitus and secondary failure of oral hypoglycemic agents. *Clinical and Investigative Medicine. Medecine Clinique et Experimentale* 2001;**24**(6):292–8. PUBMED: 11767232]

Z012 1997 *{published data only}*

* Anderson JH, Brunelle RL, Koivisto VA, Trautmann ME, Vignati L, DiMarchi R. Improved mealtime treatment of diabetes mellitus using an insulin analogue. *Clinical Therapeutics* 1997;**19**(1):62–72. PUBMED: 9083709]

IQWiG (Institute for Quality and Efficiency in Health Care). Short-acting insulin analogues in the treatment of diabetes mellitus type 2. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG); 2005 December. Abschlusbericht A05-04.

Z014 1997 *{published data only}*

* Anderson JH Jr, Brunelle RL, Koivisto VA, Trautmann ME, Vignati L, DiMarchi R. Improved mealtime treatment of diabetes mellitus using an insulin analogue. *Clinical Therapeutics* 1997;**19**(1):62–72. PUBMED: 9083709]

IQWiG (Institute for Quality and Efficiency in Health Care). Short-acting insulin analogues in the treatment

of diabetes mellitus type 2. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG); 2005 December. Abschlusbericht A05-04.

References to studies excluded from this review

Bi 2007 *{published data only}*

* Bi YF, Zhao LB, Li XY, Wang WQ, Sun SY, Chen YH, et al. A 2-way cross-over, open-labeled trial to compare efficacy and safety of insulin Aspart and Novolin R delivered with CSII in 21 Chinese diabetic patients. *Chinese Medical Journal* 2007;**120**(19):1700–3. PUBMED: 17935674]

Boehm 2004 *{published data only}*

* Boehm BO, Vaz JA, Bronsted L, Home PD. Long-term efficacy and safety of biphasic insulin Aspart in patients with type 2 diabetes. *European Journal of Internal Medicine* 2004;**15**(8):496–502. PUBMED: 15668084]

Boivin 1999 *{published data only}*

* Boivin S, Belicar P, Melki V. Assessment of in vivo stability of a new insulin preparation for implantable insulin pumps. A randomized multicenter prospective trial. *Diabetes Care* 1999;**22**(12):2089–90. PUBMED: 10587853]

Bott 2003 *{published data only}*

* Bott U, Ebrahim S, Hirschberger S, Skovlund SE. Effect of the rapid-acting insulin analogue insulin Aspart on quality of life and treatment satisfaction in patients with type 1 diabetes. *Diabetic Medicine* 2003;**20**:626-34. PUBMED: 12873289]

Caixas 1998 *{published data only}*

* Caixàs A, Pérez A, Payés A, Otal C, Carreras G, Ordóñez-Llanos J, et al. Effects of a short-acting insulin analog (insulin Lispro) versus regular insulin on lipid metabolism in insulin-dependent diabetes mellitus. *Metabolism: Clinical & Experimental* 1998;**47**(4):371–6. PUBMED: 9580247]

Chan 2004 *{published data only}*

* Chan WB, Chow CC, Yeung VT, Chan JC, So WY, Cockram CS. Effect of insulin Lispro on glycaemic control in Chinese diabetic patients receiving twice-daily regimens of insulin. *Chinese Medical Journal* 2004;**117**(9):1404–7. PUBMED: 15377436]

Chen 2011 *{published data only}*

* Chen SF, Li H. Comparison on the efficacy of biphasic insulin Aspart 30 and premixed human insulin 30/70 through continuous glucose monitoring system. *Chung-Hua Liu Hsing Ping Hsueh Tsa Chih (Chinese Journal of Epidemiology)* 2011;**32**(8):827–9. PUBMED: 22093477]

Chlup 2004 *{published data only}*

* Chlup R, Zapletalová J, Seckar P, Chlupová L, Táncosová S, Reznícková M. Benefits of insulin Aspart vs phosphate-buffered human regular insulin in persons with type 1 diabetes treated by means of an insulin pump. *Biomedical Papers of the Medical Faculty of Palacky University in Olomouc, Czech Republic* 2004;**148**(1):27–32. PUBMED: 15523542]

Cypryk 2004 *{published data only}*

* Cypryk K, Sobczak M, Petynska-Marczewska M, Zawodniak-Szalapska M, Szymczak W, Wilczynski J, et al. Pregnancy complications and perinatal outcome in diabetic women treated with Humalog (insulin lispro) or regular human insulin during pregnancy. *Medical Science Monitor* 2004;**10**(2):29–32. PUBMED: 14737056]

Ferguson 2001 *{published data only}*

* Ferguson SC, Strachan MWJ, Janes JM, Frier BM. Severe hypoglycaemia in patients with type 1 diabetes and impaired awareness of hypoglycaemia: a comparative study of insulin Lispro and regular human insulin. *Diabetes/metabolism Research and Reviews* 2001;**17**(4):285–91. PUBMED: 11544612]

Fineberg 1996 *{published data only}*

* Fineberg NS, Fineberg SE, Anderson JH, Birkett MA, Gibson RG, Hufferd S. Immunologic effects of insulin lispro (Lys (B28), Pro (B29) human insulin) in IDDM and NIDDM patients previously treated with insulin. *Diabetes* 1996;**45**(12):1750–4. PUBMED: 8922361]

Gao 2009 *{published data only}*

* Gao Y, Pan CY, Zou DJ, Xu ZR, Liu XM, Guo XH. Postprandial glycemic control using insulin Aspart with NPH in inadequately controlled diabetics. *Chung-Hua i Hsueh Tsa Chih (Chinese Medical Journal)* 2009;**89**(28): 1960–3. PUBMED: 19950569]

Garg 1996 *{published data only}*

* Garg SK, Carmain JA, Braddy KC, Anderson JH, Vignati L, Jennings MK, et al. Pre-meal insulin analogue insulin Lispro vs humulin insulin treatment in young subjects with type 1 diabetes. *Diabetic Medicine* 1996;**13**(1):47–52. PUBMED: 8741812]

Garg 2000 *{published data only}*

* Garg SK, Anderson JH, Gerard LA, Mackenzie TA, Gottlieb PA, Jennings MK, et al. Impact of insulin Lispro on HbA1c values in insulin pump users. *Diabetes Obesity and Metabolism* 2000;**2**(5):307–11. PUBMED: 11225746]

Gram 2011 *{published data only}*

* Gram J, Henriksen JE, Grodum E, Juhl H, Hansen TB, Christiansen C, et al. Pharmacological treatment of the pathogenetic defects in type 2 diabetes: the randomized multicenter South Danish diabetes study. *Diabetes Care* 2011;**34**(1):27–33. PUBMED: 20929990]

Holleman 1997 *{published data only}*

* Holleman F, Schmitt H, Symanowski S, Rees A, Rottiers R, Anderson J. Pre-meal therapy with Lispro insulin and regular insulin in IDDM patients. *The Netherlands Journal of Medicine* 1997;**50**(5):A20–1. CENTRAL: CN–00415872]

Home 2000 *{published data only}*

Home PD, Lindholm A, Riis A. Insulin Aspart vs. human insulin in the management of long-term blood glucose control in type 1 diabetes mellitus: a randomized controlled trial. *Diabetic Medicine* 2000;**17**(11):762–70. PUBMED: 11131100]

Home 2006 *{published data only}*

* Home PD, Hallgren P, Usadel KH, Sane T, Faber J, Grill V, et al. Pre-meal insulin Aspart compared with pre-meal soluble human insulin in type 1 diabetes. *Diabetes Research*

and Clinical Practice 2006;**71**(2):131–9. PUBMED: 16054266]

Kaplan 2004 ***{published data only}***

* Kaplan W, Rodriguez LM, Smith OE, Haymond MW, Heptulla RA. Effects of mixing Glargine and short-acting insulin analogs on glucose control. *Diabetes Care* 2004;**27** (11):2739–40. PUBMED: 15505016]

Lalli 1999 ***{published data only}***

* Lalli C, Ciofetta M, Del Sindaco P, Torlone E, Pampanelli S, Compagnucci P, et al. Long-term intensive treatment of type 1 diabetes with the short-acting insulin analog Lispro in variable combination with NPH insulin at mealtime. *Diabetes Care* 1999;**22**(3):468–77. PUBMED: 10097931]

Laube 1996 ***{published data only}***

* Laube H, Heller M, Liersch J, Mäser E, Linn T. Experience with Lispro-insulin in the intensified therapy of IDDM and NIDDM patients. *Diabetes und Stoffwechsel* 1996;**5**(6): 273–6. EMBASE: 1996358262]

Lindholm 1999 ***{published data only}***

* Lindholm A, McEwen J, Riis AP. Improved postprandial glycemic control with insulin Aspart. A randomized double-blind cross-over trial in type 1 diabetes. *Diabetes Care* 1999; **22**(5):801–5. PUBMED: 10332685]

Lindholm 2002 ***{published data only}***

* Lindholm A, Jensen LB, Home PD, Raskin P, Boehm BO, Rastam J. Immune responses to insulin Aspart and biphasic insulin Aspart in people with type 1 and type 2 diabetes. *Diabetes Care* 2002;**25**(5):876–82. PUBMED: 11978684]

Loukovaara 2003 ***{published data only}***

* Loukovaara S, Immonen I, Teramo KA, Kaaja R. Progression of retinopathy during pregnancy in type 1 diabetic women treated with insulin lispro. *Diabetes Care* 2003;**26**(4):1193–8. PUBMED: 12663596]

Miikkulainen 2016 ***{published data only}***

Miikkulainen K, Caruso A, Mast O, Zhang R, Borisenko O. Systematic literature review of use of blood glucose monitoring in phase III clinical studies of insulin analogs. *BMC Endocrine Disorders* 2016;**16**(1):21. PUBMED: 27145817]

Perez-Maraver 2013 ***{published data only}***

* Pérez-Maraver M, Caballero-Corchuelo J, Boltana A, Insa R, Soler J, Montanya E. Comparison of human insulin and insulin analogues on hypoglycaemia and metabolic variability in type 1 diabetes using standardized measurements (HYPO score and Lability Index). *Acta Diabetologica* 2013;**50**(4):529–35. PUBMED: 21874353]

Perriello 2005 ***{published data only}***

* Perriello G, Pampanelli S, Porcellati F, Avogaro A, Bosi E, Petrella G, et al. Insulin Aspart improves meal time glycaemic control in patients with Type 2 diabetes: a randomized, stratified, double-blind and cross-over trial. *Diabetic Medicine* 2005;**22**(5):606–11. PUBMED: 15842516]

Persson 2002 ***{published data only}***

* Persson B, Swahn ML, Hjertberg R, Hanson U, Nord E, Nordlander E, et al. Insulin Lispro therapy in pregnancies complicated by type 1 diabetes mellitus. *Diabetes Research & Clinical Practice* 2002;**58**(2):115–21. PUBMED: 12213353]

Provenzano 2001 ***{published data only}***

* Provenzano C, Vero R, Oliva A, Leto G, Puccio L, Vecci E, et al. Lispro insulin in type 1 diabetic patients on a Mediterranean or normal diet: A randomized, cross-over comparative study with regular insulin. *Diabetes, Nutrition & Metabolism* 2001;**14**(3):133–9. PUBMED: 11476360]

Rami 1997 ***{published data only}***

* Rami B, Schober E. Postprandial glycaemia after regular and Lispro insulin in children and adolescents with diabetes. *European Journal of Pediatrics* 1997;**156**(11):838–40. EMBASE: 1997333022]

Raskin 2000 ***{published data only}***

* Raskin P, Guthrie RA, Leiter L, Riis A, Jovanovic L. Use of insulin Aspart, a fast-acting insulin analog, as the mealtime insulin in the management of patients with type 1 diabetes. *Diabetes Care* 2000;**23**(5):583–8. PUBMED: 10834413]

Recasens 2003 ***{published data only}***

* Recasens M, Aguilera E, Morinigo R, Casamitjana R, Nicoletti F, Gomis R, et al. Insulin Lispro is as effective as regular insulin in optimising metabolic control and preserving ß-cell function at onset of type 1 diabetes mellitus. *Diabetes Research and Clinical Practice* 2003;**60**: 153–9. PUBMED: 12757987]

Roach 2001 ***{published data only}***

Roach P, Strack T, Arora V, Zhao Z. Improved glycemic control with the use of self-prepared mixtures of insulin Lispro and insulin Lispro protamine suspension in patients with types 1 and 2 diabetes. *International Journal of Clinical Practice* 2001;**55**(3):177–82. PUBMED: 11351771]

Schernthaner 2004 ***{published data only}***

* Schernthaner G, Kopp HP, Ristic S, Muzyka B, Peter L, Mitteregger G. Metabolic control in patients with type 2 diabetes using Humalog Mix50 injected three times daily: crossover comparison with human insulin 30/70. *Hormone and Metabolic Research* 2004;**36**(3):188–93. PUBMED: 15057674]

Skhra 2002 ***{published data only}***

* Skrha J, Smahelova A, Andě l M, Vrtovec M, Subi ć J, Kreze A, et al. Insulin Lispro improves postprandial glucose control in patients with diabetes mellitus. *Sbornik Lekarsky* 2002;**103**(1):15–21. PUBMED: 12448933]

Tubiana-Rufi 1997 ***{published data only}***

* Tubiana-Rufi N, Munz-Licha G. Lispro analog and quality of life. *Diabetes & Metabolism* 1997;**3**:58–62. PUBMED: 9410554]

Vignati 1997 ***{published data only}***

* Vignati L, Anderson JH Jr, Iversen PW. Efficacy of insulin Lispro in combination with NPH human insulin twice per day in patients with insulin-dependent or non-insulin dependent diabetes mellitus. Multicenter Iinsulin Lispro Study Group. *Clinical Therapeutics* 1997;**19**(6):1408–21. PUBMED: 9444449]

Yanagisawa 2013 *{published data only}*

* Yanagisawa K, Yamagishi S, Ashihara J, Obara S, Wada N. Evaluation of efficacy, safety and QOL of glulisine on Japanese type 1 diabetes. Diabetes. 2013; Vol. 62 Suppl1: A654 (2574-PO). EMBASE: 71288930]

References to studies awaiting assessment

Farshchi 2016 *{published data only}*

* Farshchi A, Aghili R, Oskuee M, Rashed M, Noshad S, Kebriaeezadeh A, et al. Biphasic insulin Aspart 30 vs. NPH plus regular human insulin in type 2 diabetes patients; a cost-effectiveness study. *BMC Endocrine Disorders* 2016;**16** (1):35. PUBMED: 27278922]

NCT01889095. Biphasic insulin Aspart versus NPH plus regular human insulin in type 2 diabetic patients. clinicaltrials.gov/ct2/show/NCT01889095 (first posted 23 June 2013).

NCT01500850 *{published data only}*

NCT01500850. Establishing cardiovascular biomarkers to define preferred Lantus® use. clinicaltrials.gov/ct2/show/NCT01500850 (first posted 29 December 2011).

Additional references

ACCORD 2008

The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *New England Journal of Medicine* 2008;**358**: 2545–59.

ADA 1997

American Diabetes Association (ADA). Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 1997;**20**:1183–97.

ADA 2003

Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 2003;**26**(Suppl 1):S5–20.

ADA 2017

American Diabetes Association (ADA). Standards of medical care in diabetes - 2017. *Diabetes Care* 2017;**40** (Supplement 1):S 11-33.

ADA 2018

American Diabetes Association (ADA). Standards of medical care in diabetes - 2018. *Diabetes Care* 2018;**41** (Suppl 1):S1–S159.

ADVANCE 2008

The ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *New England Journal of Medicine* 2008;**358**(24): 2560–72.

Alexander 2008

Alexander GC, Sehgal NL, Moloney RM, Stafford RS. National trends in treatment of type 2 diabetes mellitus. *Archives of Internal Medicine* 2008;**168**(19):2088–94.

Altman 2003

Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *BMJ* 2003;**326**(7382):219. [PUBMED: 12543843]

Anderson 1997

Anderson JH, Brunelle RL, Koivisto VA, Trautmann ME, Vignati L, DiMarchi R. Improved mealtime treatment of diabetes mellitus using an insulin analogue. *Clinical Therapeutics* 1997;**19**(1):62–72. [PUBMED: 9083709]

Ashwell 2006

Ashwell SG, Amiel SA, Bilous RW, Dashora U, Heller SR, Hepburn DA, et al. Improved glycaemic control with insulin Glargine plus insulin Lispro: a multicentre, randomized, cross-over trial in people with type 1 diabetes. *Diabetic Medicine* 2006;**23**:285-92.

Banerjee 2007

Banerjee S, Tran K, Li H, Cimon K, Daneman D, Simpson S, et al. Short-acting insulin analogues for diabetes mellitus: meta-analysis of clinical outcomes and assessment of cost-effectiveness. Ottawa (ON); Canadian Agency for Drugs and Technologies in Health; 2007. Technology Report no 87.

Bell 2013

Bell ML, McKenzie JE. Designing psycho-oncology randomised trials and cluster randomised trials: variance components and intra-cluster correlation of commonly used psychosocial measures. *Psycho-oncology* 2013;**22**:1738–47.

Bennett 1991

Bennett PH. Classification and diagnosis of diabetes mellitus. In: Pickup JC, Williams G editor(s). *Textbook of Diabetes*. London: Blackwell Scientific Publications, 1991: 37–46.

Berger 2001

Berger M, Jörgens V. *Insulintherapie in der Praxis*. Berlin, Heidelberg: Springer Verlag, 2001.

Borenstein 2017a

Borenstein M, Higgins JP, Hedges LV, Rothstein HR. Basics of meta-analysis: I^2 is not an absolute measure of heterogeneity. *Research Synthesis Methods* 2017;**8**(1):5–18.

Borenstein 2017b

Borenstein M. Prediction intervals. www.meta-analysis.com/prediction (accessed 3 July 2017).

Boutron 2014

Boutron I, Altman DG, Hopewell S, Vera-Badillo F, Tannock I, Ravaud P. Impact of spin in the abstracts of articles reporting results of randomized controlled trials in the field of cancer: the SPIIN randomized controlled trial. *Journal of Clinical Oncology* 2014;**32**(36):4120–6.

Brunner 2000

Brunner GA, Hirschberger S, Sendlhofer G, Wutte A, Ellmerer M, Balent B, et al. Post-prandial administration of the insulin analogue insulin Aspart in patients with type 1 diabetes mellitus. *Diabetic Medicine* 2000;**17**(5):371–5.

Cameron 2009
Cameron CG, Bennett HA. Cost-effectiveness of insulin analogues for diabetes mellitus. *Canadian Medical Association Journal* 2009;**180**(4):400–7.

Cavalot 2006
Cavalot F, Petrelli A, Traversa M, Bonomo K, Fiora E, Conti M, et al. Postprandial blood glucose is a stronger predictor of cardiovascular events than fasting blood glucose in type 2 diabetes mellitus, particularly in women: lessons from the San Luigi Gonzaga Diabetes Study. *The Journal of Clinical Endocrinology and Metabolism* 2006;**91**(3):813-9.

CENTRAL creation details
CENTRAL creation details. www.cochranelibrary.com/central/central-creation (accessed 21 August 2018).

Cohen 2011
Cohen D. The prickly problem of access to insulin. *BMJ* 2011;**343**:d5782.

Corbett 2014
Corbett MS, Higgins JP, Woolacott NF. Assessing baseline imbalance in randomised trials: implications for the Cochrane risk of bias tool. *Research Synthesis Methods* 2014; **5**(1):79–85.

Davidson 2009
Davidson JA, Liebl A, Christiansen JS, Fulcher G, Ligthelm RJ, Brown P, et al. Risk for nocturnal hypoglycemia with biphasic insulin Aspart 30 compared with biphasic human insulin 30 in adults with type 2 diabetes mellitus: a meta-analysis. *Clinical Therapeutics* 2009;**31**(8):1641–51.

Davidson 2014
Davdison MB. Insulin analogs-Is there a compelling case to use them? No!. *Diabetes Care* 2014;**37**(6):1771–4.

DCCT 1988
The DCCT Research Group. Reliability and validity of a diabetes quality-of-life measure for the diabetes control and complications trial (DCCT). *Diabetes Care* 1988;**11**: 725–32.

DCCT 1993
The Diabetes Control and Complications Trial Research Group (DCCT). The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *The New England Journal of Medicine* 1993;**329**:977–86.

Deeks 2017
Deeks JJ, Higgins JPT, Altman DG, editor(s), on behalf of the Cochrane Statistical Methods Group. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Churchill R, Chandler J, Cumpston MS, editor(s). Cochrane Handbook for Systematic Reviews of Interventions version 5.2.0 (updated June 2017). Cochrane, 2017. Available from www.training.cochrane.org/handbook.

Duckworth 2009
Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *New England Journal of Medicine* 2009;**360**(2):129–39.

Egbewale 2014
Egbewale BE, Lewis M, Sim J. Bias, precision and statistical power of analysis of covariance in the analysis of randomized trials with baseline imbalance: a simulation study. *BMC Medical Research Methodology* 2014;**14**:49. [PUBMED: 24712304]

EMA 2002
European Medicines Agency. Note for guidance on clinical investigation of medicinal products in the treatment of diabetes mellitus. www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003262.pdf 2002.

Engwerda 2011
Engwerda EE, Abbink EJ, Tack C J, de Galan BE. Improved pharmacokinetic and pharmacodynamic profile of rapid-acting insulin using needle-free jet injection technology. *Diabetes Care* 2011;**34**(8):1804–8.

Frick 2008
Frick M, Knollmeyer J, Riederer H, Heinemann C. Modern insulins - comment on facts and assumptions in a recent editorial. *Diabetologia* 2008;**51**(4):689–91.

Gale 2011
Gale EAM. Commentary: politics of affordable insulin. *BMJ (Clinical research ed.)* 2011;**343**:d5675.

Gale 2012
Gale EAM. Newer insulins in type 2 diabetes. *BMJ (Clinical research ed.)* 2012;**345**:e4611. DOI: 10.1136/bmj.e461

Gerstein 2001
Gerstein HC, Haynes RB. *Evidence-based Diabetes Care*. Hamilton (ON): BC Decker Inc, 2001.

Giugliano 2008
Giugliano D, Ceriello A, Razzoli E, Esposito K. Defining the role of insulin Lispro in the management of postprandial hyperglycaemia in patients with type 2 diabetes mellitus. *Clinical Drug Investigation* 2008;**28**(4):199–210.

Gough 2007
Gough SC. A review of human and analogue insulin trials. *Diabetes Research and Clinical Practice* 2007;**77**(11):1–15.

GRADEpro GDT 2015 [Computer program]
McMaster University (developed by Evidence Prime). GRADEpro GDT. Version (accessed 9 April 2018). Hamilton (ON): McMaster University (developed by Evidence Prime), 2015.

Grant 1993
Grant MB, Mames RN, Fitzgerald C, Ellis EA, Aboufrikha M, Guy J. Insulin-like growth factor I acts as an angiogenic agent in rabbit cornea and retina: comparative studies with basic fibroblast growth factor. *Diabetologia* 1993;**36**: 282–91.

Grunberger 2014
Grunberger G. Insulin analogs-are they worth it? Yes!. *Diabetes Care* 2014;**37**(6):1767–70.

Haffner 1998
Haffner SM. The importance of hyperglycemia in the non-fasting state to the development of cardiovascular disease. *Endocrine Reviews* 1998;**19**(5):583–92.

Hart 2012
Hart B, Lundh A, Bero L. Effect of reporting bias on meta-analyses of drug trials: reanalysis of meta-analyses. *BMJ (Clinical research ed.)* 2012;**344**:d7202. DOI: 10.1136/bmj.d7202

Heinemann 1996
Heinemann L, Kapitza C, Starke AAR, Heise T. Time-action profile of the insulin analogue B28Asp. *Diabetic Medicine* 1996;**13**:683–4.

Heise 2014
Heise T, Haahr H, Jensen L, Erichsen L, Hompesch M. Faster-acting insulin Aspart improves postprandial glycaemia versus insulin Aspart in patients with type 1 diabetes mellitus. *Diabetes* 2014;**63**(Suppl 1):A34.

Hermansen 2004
Hermansen K, Fontaine P, Kukolja KK, Peterkova V, Leth G, Gall MA. Insulin analogues (insulin Detemir and insulin Aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. *Diabetologia* 2004;**47**(4):622–9.

Hermansen 2009
Hermansen K, Dornhorst A, Sreenan S. Observational, open-label study of type 1 and type 2 diabetes patients switching from human insulin to insulin analogue basal-bolus regimens: insights from the PREDICTIVE study. *Current Medical Research and Opinion* 2009;**25**(11):2601–8.

Higgins 2002
Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* 2002;**21**:1539–58.

Higgins 2003
Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analysis. *BMJ (Clinical research ed.)* 2003;**327**:557–60.

Higgins 2009
Higgins JPT, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. *Journal of the Royal Statistical Society: Series A (Statistics in Society)* 2009;**172**(1):137–59.

Higgins 2011
Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ (Clinical Research Ed.)* 2011;**343**:d5928.

Higgins 2017
Higgins JPT, Altman DG, Sterne JAC, editor(s). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Churchill R, Chandler J, Cumpston MS, editor(s), Cochrane Handbook for Systematic Reviews of Interventions Version 5.2.0 (updated June 2017). Cochrane, 2017. Available from www.training.cochrane.org/handbook.

Holden 2011
Holden SE, Poole CD, Morgan CL, Currie CJ. Evaluation of the incremental cost to the National Health Service of prescribing analogue insulin. *BMJ Open* 2011;**1**(2):e000258.

Holleman 2007
Holleman F, Gale EAM. Nice insulins, pity about the evidence. *Diabetologia* 2007;**50**:1783-90.

Home 2012
Home PD. The pharmacokinetics and pharmacodynamics of rapid-acting insulin analogues and their clinical consequences. *Diabetes, Obesity and Metabolism* 2012;**14**(9):780–8.

Howey 1994
Howey DC, Bowsher RR, Brunelle RL, Woodworth JR. (Lys(B28), Pro(B29))-human insulin. A rapidly absorbed analogue of human insulin. *Diabetes* 1994;**43**:396–402.

Hozo 2005
Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Medical Research Methodology* 2005;**5**:13. DOI: 10.1186/1471-2288-5-13

Hróbjartsson 2013
Hróbjartsson A, Thomsen AS, Emanuelsson F, Tendal B, Hilden J, Boutron I, et al. Observer bias in randomized clinical trials with measurement scale outcomes: a systematic review of trials with both blinded and nonblinded assessors. *Canadian Medical Association Journal* 2013;**185**(4):E201–11.

IQWIG 2005
Institute for Quality and Efficiency in Health Care. Short acting insulin analogues for the treatment of type 2 diabetes mellitus [Kurzwirksame Insulinanaloga zurBehandlung des Diabetes mellitusTyp 2]. www.iqwig.de/download/A05-04_Abschlussbericht_Kurzwirksame_Insulinanaloga_bei_Typ_2_Diabetes_mellitus.pdf. Köln, 15 December 2005.

Jones 2015
Jones CW, Keil LG, Holland WC, Caughey MC, Platts-Mills TF. Comparison of registered and published outcomes in randomized controlled trials: a systematic review. *BMC Medicine* 2015;**13**:282. DOI: 10.1186/s12916-015-0520-3

Jørgensen 1992
Jørgensen LN, Didriksen LH, Drejer K. Carciogen effect of the human insulin analogue B10 Asp in female rats. *Diabetologia* 1992;**35 Suppl 1**:A3.

Kaye 2013
Kaye J, Krasner A, Canney L, Pichotta P, Simms P, Krishnarajah J, et al. Novel formulations BIOD-238 and BIOD-250 result in more rapid absorption and declines from peak than Humalog. 49th Annual Meeting of the European Association for the Study of Diabetes. Barcelona, Spain: EASD, 2013:56 S413.

King 1985
King GL, Goodman AD, Buzney S, Moses A, Kahn CR. Receptors and growth-promoting effects of insulin and insulin-like growth factors on cells from bovine retinal

capillaries and aorta. *Journal of Clinical Investigation* 1985; **75**:1028–36.

Kirkham 2010
Kirkham JJ, Dwan KM, Altman DG, Gamble C, Dodd S, Smyth R, et al. The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews. *BMJ (Clinical research ed.)* 2010;**340**:c365. DOI: 10.1136/bmj.c365

Krasner 2012
Krasner A, Pohl R, Simms P, Pichotta P, Hauser R, De Souza E. A review of a family of ultra-rapid-acting insulins: formulation development. *Journal of Diabetes Science and Technology* 2012;**6**(4):786–96.

Kurtzhals 2000
Kurtzhals P, Schäffer L, Sorensen A, Kristensen C, Jonassen I, Schmid C, et al. Correlation of receptor binding and metabolic and metogenic potencies of insulin analogues designed for clinical use. *Diabetes* 2000;**49**:999–1005.

Landau 2014
Landau Z, Klonoff D, Nayberg I, Feldman D, Levit SB, Lender D, et al. Improved pharmacokinetic and pharmacodynamic profiles of insulin analogues using InsuPatch, a local heating device. *Diabetes/metabolism Research and Reviews* 2014;**30**(8):686–92.

Liberati 2009
Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic and meta-analyses of studies that evaluate interventions: explanation and elaboration. *PLoS Medicine* 2009;**6**(7):1–28. DOI: 10.1371/journal.pmed.1000100

Mannucci 2009
Mannucci E, Monami M, Marchionni N. Short-acting insulin analogues vs. regular human insulin in type 2 diabetes: a meta-analysis. *Diabetes, Obesity and Metabolism* 2009;**11**:53–9.

Marshall 1999
Marshall SM, Home PD, Rizza RA. *The Diabetes Annual 12*. Amsterdam: Elsevier Science Ltd, 1999.

Mathieu 2009
Mathieu S, Boutron I, Moher D, Altman DG, Ravaud P. Comparison of registered and published primary outcomes in randomized controlled trials. *JAMA* 2009;**302**:977–84.

Meader 2014
Meader N, King K, Llewellyn A, Norman G, Brown J, Rodgers M, et al. A checklist designed to aid consistency and reproducibility of GRADE assessments: development and pilot validation. *Systematic Reviews* 2014;**3**:82.

Meneghini 2013
Meneghini L. Insulin therapy for type 2 diabetes. *Endocrine* 2013;**43**(3):529–34.

Mosekilde 1989
Mosekilde E, Skovbo JK, Binder C, Pramming S, Thorsteinsson B. Modeling absorption kinetics of subcutaneous injected soluble insulin. *Journal of Pharmacokinetics and Biopharmaceutics* 1989;**17**(1):67–87.

Muehlhauser 1998
Muehlhauser I, Overmann H, Bender R, Bott U, Berger M. Risk factors of severe hypoglycaemia in adult patients with type 1 diabetes - a prospective population based study. *Diabetologia* 1998;**41**:1274–82.

NICE 2008
National Collaborating Centre for Chronic Conditions (UK). Type 2 diabetes: National Clinical Guideline for management in primary and secondary care (update). London: Royal College of Physicians (UK); 2008. NICE Clinical Guidelines, No. 66.

Nissen 2007
Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *New England Journal of Medicine* 2007;**256**(4):2457–71.

Nordwall 2009
Nordwall M, Arnqvist HJ, Bojestig M, Ludvigsson J. Good glycaemic control remains crucial in prevention of late diabetic complication - the Linköping Diabetes Complication Study. *Pediatric Diabetes* 2009;**10**(3): 168–76.

NVL 2013
Bundesärztekammer, Kassenärztliche Bundesvereinigung, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften. [Nationale Versorgungsleitlinie Therapie des Typ–2–Diabetes. Kurzfassung, 1. Aufl., Version 4]. Berlin: Ärztliches Zentrum für Qualität in der Medizin; 2013.

Overman 1999
Overmann, H, Heinemann, L. Injection-meal interval: recommendations of diabetologists and how patients handle it. *Diabetes Research and Clinical Practice* 1999;**43**:137–42.

Parkin 2002
Parkin CG, Brooks N. Is postprandial glucose control important? Is it practical in primary care settings?. *Clinical Diabetes* 2002;**20**(2):71–6.

Pfützner 2014
Pfützner A, Dissel S, Forkel C, Grenningloh M, Bitton G, Nagar R, et al. Standardized modulation of the injection site allows for insulin dose reduction without deterioration of metabolic control. *Current Medical Research and Opinion* 2014;**30**(10):2001–8.

Raslova 2004
Raslová K, Bogoev M, Raz I, Leth G, Gall MA, Hâncu N. Insulin Detemir and insulin Aspart: a promising basal-bolus regimen for type 2 diabetes. *Diabetes Research and Clinical Practice* 2004;**66**(2):193–201.

Rathmann 2014
Rathmann W, Schloot NC, Kostev K, Reaney M, Zagar AJ, Haupt A. Macro- and microvascular outcomes in patients with type 2 diabetes treated with rapid-acting insulin analogues or human regular insulin: a retrospective database analysis. *Experimental and Clinical Endocrinology & Diabetes* 2014;**122**(2):92–9.

RevMan 2014 [Computer program]
Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Riley 2011
Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ* 2011;**342**:d549.

Riley 2013
Riley RD, Kauser I, Bland M, Thijs L, Staessen JA, Wang J, et al. Meta-analysis of randomised trials with a continuous outcome according to baseline imbalance and availability of individual participant data. *Statistics in Medicine* 2013;**32**(16):2747–66. [PUBMED: 23303608]

Rys 2011
Rys P, Pankiewicz O, Ł ach K, Kwaskowski A, Skrzekowska-Baran I, Malecki MT. Efficacy and safety comparison of rapid-acting insulin Aspart and regular human insulin in the treatment of type 1 and type 2 diabetes mellitus: a systematic review. *Diabetes & Metabolism* 2011;**37**(3):190–200.

Sawicki 2011
Sawicki PT. Commentary: does additional benefit justify additional costs of insulin analogues?. *BMJ* 2011;**343**:d5858.

Schernthaner 1998
Schernthaner G, Wein W, Sandholzer K, Equiluz-Bruck S, Bates PC, Birkett MA. Postprandial insulin lispro: a new therapeutic option for type 1 diabetic patients. *Diabetes Care* 1998;**21**(4):570–3.

Schroll 2015
Schroll JB, Bero L. Regulatory agencies hold the key to improving Cochrane Reviews of drugs. Cochrane Database of Systematic Reviews 2015; Vol. 4. DOI: 10.1002/14651858.ED000098

Schünemann 2011
Schünemann HJ, Oxman AD, Higgins JPT, Vist GE, Glasziou P, Guyatt GH, et al. on behalf of the Cochrane Applicability and Recommendations Methods Group and the Cochrane Statistical Methods Group. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JPT, Green S, editor(s), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Sciacca 2012
Sciacca L, Le Moli R, Vigneri R. Insulin analogs and cancer. *Frontiers in Endocrinology* 2012;**3**(21):1–9.

Shiraiwa 2005
Shiraiwa T, Kaneto H, Miyatsuka T, Kato K, Yamamoto K, Kawashima A, et al. Postprandial hyperglycemia is a better predictor of the progression of diabetic retinopathy than HbA1c in Japanese type 2 diabetic patients. *Diabetes Care* 2005;**28**(11):2806–7.

Singh 2007
Singh S, Loke YK, Furberg CD. Longterm risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA* 2007;**298**(10):1189–95.

Singh 2009
Singh SR, Ahmad F, Lal A, Yu C, Bai Z, Bennett H. Efficacy and safety of insulin analogues for the management of diabetes mellitus: a meta-analysis. *Canadian Medical Association Journal* 2009;**180**(4):385–97.

Smith 2009
Smith U, Gale EAM. Does diabetes therapy influence the risk of cancer?. *Diabetologia* 2009;**52**(9):1699–708.

Standl 2011
Standl E, Schnell O, Ceriello A. Postprandial hyperglycemia and glycemic variability: should we care?. *Diabetes Care* 2011;**34**(Suppl 2):S120–7.

Sterne 2011
Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;**343**:d4002.

Stratton 2000
Stratton IM, Adler AI, Neil HAW, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2010;**321**:405–12.

Torlone 1994
Torlone E, Fanelli C, Rambotti AM, Kassi G, Modarelli F, Di Vicenzo A, et al. Pharmacokinetics, pharmacodynamics and glucose counter-regulation following subcutaneous injection of the monomeric insulin analogue (Lys(B28), Pro (B29)) in IDDM. *Diabetologia* 1994;**37**(7):713–20.

UKPDS 1998
UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;**352**(9131):837–53.

WHO 1999
World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications. *Report of a WHO Consultation. Part 1: Diagnosis and Classification of Diabetes Mellitus*. Geneva: World Health Organization, 1999:1–59.

WHO 2011
World Health Organization. Review of the evidence comparing insulin (human or animal) with analogue insulins. 18th Expert Committee on the Selection and Use of Essential Medicines; 2011 March 21-25; Accra, Ghana. World Health Organization, 2011.

Wild 2004
Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004;**27**(5):1047–53.

Wong 2006a

Wong SS, Wilczynski NL, Haynes RB. Comparison of top-performing search strategies for detecting clinically sound treatment studies and systematic reviews in MEDLINE and EMBASE. *Journal of the Medical Library Association* 2006; **94**(4):451–5.

Wong 2006b

Wong SSL, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. *Journal of the Medical Library Association* 2006;**94**(1):41–7.

Wood 2008

Wood L, Egger M, Gluud LL, Schulz KF, Juni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ* 2008;**336** (7644):601–5.

Zinman 1989

Zinman B. The physiological replacement of insulin: an elusive goal. *New England Journal of Medicine* 1989;**321**(6): 363–70.

References to other published versions of this review

Siebenhofer 2006

Siebenhofer A, Plank J, Berghold A, Jeitler K, Horvath K, Narath M, et al. Short acting insulin analogues versus regular human insulin inpatients with diabetes mellitus. *Cochrane Database of Systematic Reviews* 2006, Issue 2. DOI: 10.1002/14651858.CD003287.pub4

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Altuntas 2003

Methods	**Parallel randomised controlled clinical trial, randomisation ratio 1:1:1**
Participants	**Inclusion criteria**: type 2 diabetes, secondary OAD failure (defined as initial stabilization of BG control for at least 6 months followed by lack of control with max. sulphonylurea dose and full compliance regarding diet) **Exclusion criteria**: not reported **Diagnostic criteria**: ADA 1997
Interventions	**Number of study centres**: not reported **Treatment before study**: OADs **Titration period**: 6-month treatment period
Outcomes	**Outcomes reported in abstract of publication**: HbA1c levels, plasma glucose levels (10-day profile), triglyceride levels, hypoglycaemic episodes
Study details	**Run-in period**: not reported **Study terminated early**: no **Trial register ID**: not reported
Publication details	**Language of publication**: English **Funding:** not reported **Publication status:** full article in a peer review journal
Study aim for study	**Quote from publication:** "The aim was to assess the effects of three different insulin regimes (group 1: lispro insulin + NPH insulin, group 2: lispro insulin + metformin, and group 3: regular insulin + NPH insulin) on overall glycaemic control and metabolic parameters in type 2 diabetic patients with secondary oral anti-diabetic drug failure"
Notes	HbA1c was not shown because of inconsistent baseline HbA1c data Group 2 was not included in our systematic review because a different therapy regiment (insulin lispro + metformin) was used in this group, which did not fulfil our inclusion criteria

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote from publication**: "Patients were randomly assigned to three different groups" **Comment**: not enough details
Allocation concealment (selection bias)	Unclear risk	**Comment**: not reported

Altuntas 2003 (*Continued*)

Blinding of participants and personnel (performance bias) HbA1c	Unclear risk	**Quote from publication**: "open-label" **Comment:** investigator-reported outcome measurement
Blinding of participants and personnel (performance bias) Adverse events	High risk	**Quote from publication**: "open-label" **Comment:** self-reported and investigator-reported outcome measurement
Blinding of outcome assessment (detection bias) HbA1c	Unclear risk	**Quote from publication**: "open-label" **Comment**: investigator-reported outcome measurement
Blinding of outcome assessment (detection bias) Adverse events	High risk	**Quote from publication**: "open-label" **Comment:** self-reported and investigator-reported outcome measurement
Incomplete outcome data (attrition bias) HbA1c	Low risk	**Comment**: all participants completed the 6-month trial period
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	**Comment**: number of analysed participants unclear
Selective reporting (reporting bias)	High risk	**Comment**: outcome reporting bias for all hypoglycaemic episodes according to ORBIT (see Appendix 8)
Other bias	High risk	**Comment**: inconsistencies regarding reported outcomes in publication, no definition of primary outcome, no sample size calculation

Bastyr 2000

Methods	**Parallel randomised controlled clinical trial, randomisation ratio 1:1**
Participants	**Inclusion criteria**: type 2 diabetes, insulin treatment < 2 months before study entry; age 35 to 85 years **Exclusion criteria**: insulin pump therapy[1] **Diagnostic criteria**: WHO 1980[1]
Interventions	**Number of study centres**: 48 **Treatment before study**: insulin treatment < 2 months before study entry **Titration period**: 12 months
Outcomes	**Outcomes reported in abstract of publication**: HRQoL, hypoglycaemia rate, nocturnal hypoglycaemia, short- and long-term glucose control

Bastyr 2000 (*Continued*)

Study details	**Run-in period**: not reported **Study terminated early**: no **Trial register ID:** not reported
Publication details	**Language of publication**: English **Funding:** commercial (Eli Lilly) **Publication status:** Full article in a peer review journal
Study aim for study	**Quote from publication:** "To identify factors associated with nocturnal hypoglycaemia in patients with type 2 diabetes who were new (< 2 months therapy) to insulin therapy"
Notes	[1]From IQWIG 2005

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote from IQWiG report:** "computer generated sequence generation" **Comment**: adequate, based on description in original study report (from IQWIG 2005)
Allocation concealment (selection bias)	Low risk	**Quote from IQWiG report**: "allocation by central study centre" **Comment**: adequate, based on information in IQWIG 2005
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Quote from publication**: "open-label" **Comment:** outcome measure unlikely influenced by lack of blinding
Blinding of participants and personnel (performance bias) Severe hypoglycaemia	High risk	**Quote from publication**: "open-label" **Comment:** outcome measure likely influenced by lack of blinding
Blinding of participants and personnel (performance bias) HbA1c	Unclear risk	**Quote from publication**: "open-label"
Blinding of participants and personnel (performance bias) Adverse events	High risk	**Quote from publication**: "open-label" **Comment:** outcome measure likely influenced by lack of blinding
Blinding of participants and personnel (performance bias) Health-related quality of life	High risk	**Quote from publication**: "open-label" **Comment:** outcome measure likely influenced by lack of blinding

Bastyr 2000 (*Continued*)

Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Quote from publication**: "open-label" **Comment:** outcome measure unlikely influenced by lack of blinding
Blinding of outcome assessment (detection bias) Severe hypoglycaemia	High risk	**Quote from publication**: "open-label" **Comment:** outcome measure likely influenced by lack of blinding
Blinding of outcome assessment (detection bias) HbA1c	Low risk	**Quote from** IQWIG 2005: "adequate because HbA1c was analysed centrally"
Blinding of outcome assessment (detection bias) Adverse events	High risk	**Quote from publication**: "open-label" **Comment:** outcome measure likely influenced by lack of blinding
Blinding of outcome assessment (detection bias) Health-related quality of life	High risk	**Quote from publication**: "open-label" **Comment:** outcome measure likely influenced by lack of blinding
Incomplete outcome data (attrition bias) All-cause mortality	Unclear risk	**Comment:** reason for missing data related to outcome unclear. Similar reasons for missing data across interventions groups unclear. Appropriateness of method used for imputation of missing data unclear
Incomplete outcome data (attrition bias) Severe hypoglycaemia	Unclear risk	**Comment:** 2% and 3% of participants not included in analysis. Reason for missing data related to outcome unclear. Similar reasons for missing data across interventions groups unclear. Appropriateness of method used for imputation of missing data unclear
Incomplete outcome data (attrition bias) HbA1c	Unclear risk	**Comment:** reason for missing data related to outcome unclear. Similar reasons for missing data across interventions groups unclear. Appropriateness of method used for imputation of missing data unclear
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	**Comment:** reason for missing data related to outcome unclear. Similar reasons for missing data across interventions groups unclear. Appropriateness of method used for imputation of missing data unclear
Incomplete outcome data (attrition bias) Health-related quality of life	High risk	**Comment:** inconsistent information on participants included in analyses (either

Bastyr 2000 (*Continued*)

		53% or 79%). Reason for missing data related to outcome unclear. Similar reasons for missing data across interventions groups unclear. Appropriateness of method used for imputation of missing data unclear
Selective reporting (reporting bias)	High risk	**Comment**: nocturnal hypoglycaemia was not mentioned in original study report in IQWIG 2005 -> post-hoc analysis in Bastyr 2000. Inconsitent information on outcomes in Bastyr 2000 and study report (IQWIG 2005)
Other bias	High risk	**Comment**: primary outcome not clear, inconsistent information regarding number of trial participants and dropouts

Dailey 2004

Methods	**Parallel randomised controlled trial, randomisation ratio 1:1 (stratified according to OAD use), non-inferiority design (2-sided CI, upper 95% CI limit ≤ 0.4% (HbA1c))**
Participants	**Inclusion criteria**: participants with T2DM, age ≥ 18 years, insulin therapy for ≥ 6 months at beginning of study, HbA1c between 6.0 and 11.0% **Exclusion criteria**: not reported **Diagnostic criteria**: not reported
Interventions	**Number of study centres**: multicentre **Treatment before study**: at least 6 months of insulin therapy, with or without OADs **Titration period**: 26 weeks
Outcomes	**Outcomes reported in abstract of publication**: HbA1c change; post-breakfast and post-dinner glucose levels; overall, severe, and nocturnal hypoglycaemia; weight gain; change in insulin dose
Study details	**Run-in period**: 4 weeks **Study terminated early**: no **Trial register ID**: not reported
Publication details	**Language of publication**: English **Funding:** commercial (Aventis Pharma) **Publication status:** full article in a peer reviewed journal
Study aim for study	**Quote from publication:** "This study compared the effects of glulisine (Aventis Pharma) and RHI (Eli Lilly) on HbA1c, self-monitored blood glucose profiles, hypoglycaemia, and safety in patients with type 2 diabetes."

Dailey 2004 (*Continued*)

Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote from publication**: "Randomization was stratified according to whether subjects were treated with OADs at randomisation" **Quote from IQWiG report**: "computer-generated sequence" **Comment**: not clearly stated, but adequate based on IQWIG 2005
Allocation concealment (selection bias)	Low risk	**Quote from IQWiG report**: "allocation was done centrally" **Comment**: not reported, but adequate based on IQWIG 2005
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Quote from publication**: "open-label" **Comment:** outcome measure unlikely influenced by lack of blinding
Blinding of participants and personnel (performance bias) Severe hypoglycaemia	High risk	**Quote from publication**: "open-label" **Comment:** outcome measure likely influenced by lack of blinding
Blinding of participants and personnel (performance bias) HbA1c	Unclear risk	**Quote from publication**: "open-label"
Blinding of participants and personnel (performance bias) Adverse events	High risk	**Quote from publication**: "open-label" **Comment:** outcome measure likely influenced by lack of blinding
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Quote from publication**: "open-label" **Comment:** outcome measure unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) Severe hypoglycaemia	High risk	**Quote from publication**: "open-label" **Comment:** outcome measure likely influenced by lack of blinding
Blinding of outcome assessment (detection bias) HbA1c	Low risk	**Quote from publication**: "open-label; centrally measured" **Comment:** outcome measure unlikely to be influenced by lack of blinding

Dailey 2004 (*Continued*)

Blinding of outcome assessment (detection bias) Adverse events	High risk	**Quote from publication**: "open-label" **Comment:** outcome measure likely influenced by lack of blinding
Incomplete outcome data (attrition bias) All-cause mortality	Low risk	**Comment:** proportion included in analyses adequate. Missing data balanced across intervention groups
Incomplete outcome data (attrition bias) Severe hypoglycaemia	Low risk	**Comment:** proportion included in analyses adequate. Missing data balanced across intervention groups
Incomplete outcome data (attrition bias) HbA1c	Low risk	**Comment:** proportion included in analyses adequate. Missing data balanced across intervention groups
Incomplete outcome data (attrition bias) Adverse events	Low risk	**Comment:** proportion included in analyses adequate. Missing data balanced across intervention groups
Selective reporting (reporting bias)	High risk	**Comment**: no study protocol available, some reported variables not mentioned in the methods section; according to FDA and EMEA documents, quality of life was assessed, but results have not been published
Other bias	Low risk	**Comment**: none detected

Hermann 2013

Methods	**Parallel randomised clinical trial, randomisation ratio 2:1**
Participants	**Inclusion criteria**: participants with T2DM, age: 18 to 75 years, OADs for at least 6 months (biguanides, sulphonylureas, glinides, α-glucosidase inhibitors), HbA1c > 7.0% **Exclusion criteria**: not reported **Diagnostic criteria**: not reported
Interventions	**Number of study centres**: multicentre **Treatment before study**: at least 6 months of treatment with OADs **Titration period**: 6 months
Outcomes	**Outcomes reported in abstract of publication**: adiponectin, HbA1c, fasting plasma glucose, BMI, triglycerides, cholesterol levels
Study details	**Run-in period**: not reported **Study terminated early**: no **Trial register ID:** not reported

Hermann 2013 (*Continued*)

Publication details	**Language of publication**: English **Funding:** commercial (Novo Nordisk, Roche) **Publication status**: full article in a peer reviewed journal
Study aim for study	**Quote from publication:** "The aim of the prospective multicenter study is to compare the efficacy of insulin aspart analogue concerning metabolic and cardiovascular effects in patients with type 2 diabetes mellitus in comparison with human regular insulin"
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Quote from publication**: "Patients were randomised into two groups"; "11 patients were randomised into the regular human insulin-group (RHI-group) and 18 patients into the insulin aspart group (IA-group)" **Comment**: not described sufficiently; group sizes are quite different
Allocation concealment (selection bias)	Unclear risk	**Comment**: not reported
Blinding of participants and personnel (performance bias) HbA1c	Unclear risk	**Quote from publication**: "open-label" **Comment:** investigator-reported outcome measurement
Blinding of participants and personnel (performance bias) Adverse events	High risk	**Quote from publication**: "open-label" **Comment:** self-reported and investigator-reported outcome measurement, outcome measure likely influenced by lack of blinding
Blinding of outcome assessment (detection bias) HbA1c	Unclear risk	**Quote from publication**: "open-label" **Comment:** investigator-reported outcome measurement
Blinding of outcome assessment (detection bias) Adverse events	High risk	**Quote from publication**: "open-label" **Comment:** self-reported and investigator-reported outcome measurement, outcome measure likely influenced by lack of blinding
Incomplete outcome data (attrition bias) HbA1c	Low risk	**Comment:** data from all participants included

Hermann 2013 (*Continued*)

Incomplete outcome data (attrition bias) Adverse events	Low risk	**Comment:** data from all participants included
Selective reporting (reporting bias)	Unclear risk	**Comment**: no protocol available; not enough information in publication to judge; hypoglycaemic episodes were not defined in the publication, but then were reported in the results section as number of participants who had up to 3 episodes per year
Other bias	Unclear risk	**Comment**: no definition of primary outcome

NCT01650129

Methods	**Parallel randomised controlled trial, randomisation ratio 2:1**
Participants	**Inclusion criteria**: age ≥ 20 years; diagnosed with T2DM; treated with insulin ≥ 24 weeks and on current treatment with premixed biphasic human insulin preparation (rapid acting/intermediate acting (NPH) = 5:5) in a twice daily regimen (before breakfast and dinner) ≥ 12 weeks; HbA1c ≤ 11.0 %; BMI < 30.0 kg/m² **Exclusion criteria**: not reported **Diagnostic criteria**: T2DM according to Japanese Diabetes Society classification
Interventions	**Number of study centres**: 14 **Treatment before study**: treatment with insulin ≥ 24 weeks, treatment with premixed biphasic human insulin preparation in twice daily regimen ≥ 12 weeks **Titration period**: 24 weeks
Outcomes	**Outcomes reported in abstract of publication**: adverse events; incidence of hypoglycaemic episodes; insulin antibodies; HbA1c; blood glucose control parameters; safety profile through laboratory tests (haematology and biochemistry)
Study details	**Run-in period**: not reported **Study terminated early**: no **Trial register ID:** NCT01650129
Publication details	**Language of publication**: English **Funding**: commercial (Novo Nordisk) **Publication status**: other (NovoNordisk Clinical Trial report BIAsp-1352)
Study aim for study	**Quote from publication:** "Primary objective was to: Investigate the safety profile of NN-X14Mix50 as measured by the occurrence of adverse events during 24 weeks of treatment compared to BHI50"
Notes	-

NCT01650129 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Quote from publication**: "A total of 75 subjects were planned to be randomised" **Comment**: not enough details
Allocation concealment (selection bias)	Unclear risk	**Comment**: not reported
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Quote from study report:** "open-labelled" **Comment:** outcome measure unlikely to be influenced by lack of blinding
Blinding of participants and personnel (performance bias) Severe hypoglycaemia	High risk	**Quote from study report:** "open-labelled" **Comment:** outcome measure likely influenced by lack of blinding
Blinding of participants and personnel (performance bias) HbA1c	Unclear risk	**Quote from study report:** "open-labelled" **Comment:** laboratory measure, not clear if measured centrally
Blinding of participants and personnel (performance bias) Adverse events	High risk	**Quote from study report:** "open-labelled" **Comment:** outcome measure likely influenced by lack of blinding
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Quote from study report:** "open-labelled" **Comment:** outcome measure unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) Severe hypoglycaemia	High risk	**Quote from study report:** "open-labelled" **Comment:** outcome measure likely influenced by lack of blinding
Blinding of outcome assessment (detection bias) HbA1c	Unclear risk	**Quote from study report:** "open-labelled" **Comment:** laboratory measure, not clear if measured centrally
Blinding of outcome assessment (detection bias) Adverse events	High risk	**Quote from study report:** "open-labelled" **Comment:** outcome measure likely influenced by lack of blinding
Incomplete outcome data (attrition bias) All-cause mortality	Low risk	**Comment**: proportion of participants included in analyses adequate. Missing data balanced across intervention groups

NCT01650129 (*Continued*)

Incomplete outcome data (attrition bias) Severe hypoglycaemia	Low risk	**Comment**: proportion of participants included in analyses adequate. Missing data balanced across intervention groups
Incomplete outcome data (attrition bias) HbA1c	Low risk	**Comment**: proportion of participants included in analyses adequate. Missing data balanced across intervention groups
Incomplete outcome data (attrition bias) Adverse events	Low risk	**Comment**: proportion of participants included in analyses adequate. Missing data balanced across intervention groups
Selective reporting (reporting bias)	Unclear risk	**Comment**: for several outcomes, the results were not reported in detail, trial authors only reported that no significant difference was found
Other bias	Low risk	**Comment**: none detected

Pfützner 2013

Methods	**Parallel randomised controlled trial, randomisation ratio 1:1:1**
Participants	**Inclusion criteria**: not reported **Exclusion criteria**: not reported **Diagnostic criteria**: type 2 diabetes
Interventions	**Number of study centres**: 1 (although not explicitly stated) **Treatment before study**: not reported **Titration period**: not reported
Outcomes	**Outcomes reported in abstract of publication**: OGTT: blood glucose, nitrotyrosine, hsCRP and mRNA macrophage activation markers (IL6, TNFalpha, eNOS, MAPK1) after 0, 1, and 2 hr, Hba1c
Study details	**Run-in period**: not reported **Study terminated early**: no **Trial register ID:** NCT01417897; EUCTR2011-003733-34-DE
Publication details	**Language of publication**: English **Funding:** commercial (partial funding from Sanofi Germany) **Publication status:** conference poster
Study aim for study	**Quote from publication:** "Primary objective of this pilot study was to collect data for hypothesis generation regarding the impact of short-acting insulin analogues (insulin aspart, IA and insulin glulisine, IG) in comparison to regular human insulin (RHI) on biomarkers of inflammation and oxidative stress during an oral glucose challenge experiment (OGTT) in patients with type 2 diabetes"

Pfützner 2013 (*Continued*)

Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment**: not reported
Allocation concealment (selection bias)	Unclear risk	**Comment**: not reported
Blinding of participants and personnel (performance bias) HbA1c	Unclear risk	**Quote from study report:** "open-labelled"
Blinding of outcome assessment (detection bias) HbA1c	Unclear risk	**Quote from study report:** "open-labelled"
Incomplete outcome data (attrition bias) HbA1c	Low risk	**Comment:** all randomised participants included in analysis
Selective reporting (reporting bias)	Unclear risk	**Comment**: not enough information to judge
Other bias	High risk	**Comment**: pilot project, very few participants, exploratory design, only published as poster and conference abstract

Rayman 2007

Methods	**Parallel randomised controlled trial, randomisation ratio 1:1 (stratified according to OADs use), non-inferiority design (1-sided CI, upper bound of CI ≤ 0.4% for HbA1c)**
Participants	**Inclusion criteria**: T2DM and insulin treatment > 6 months; HbA1c 6.0 to 11.0 %; age ≥ 18 years **Exclusion criteria**: active proliferative or unstable diabetic retinopathy; treatment with repaglinide, nateglinide, glitazones, or any investigational drug in the 4 weeks prior to study; history of seizure disorders; impaired renal or hepatic function; major systemic disease **Diagnostic criteria**: according to medical record[1]
Interventions	**Number of study centres**: 90 **Treatment before study**: > 6 months continuous insulin treatment (short-acting, rapid-acting, basal, or a combination) with or without OAD **Titration period**: 26 weeks

Rayman 2007 (*Continued*)

Outcomes	**Outcomes reported in abstract of publication**: difference in HbA1c change; postprandial PG at 2 hr; postprandial PG excursions at 1 hr and 2 hr; symptomatic hypoglycaemia; nocturnal hypoglycaemia from month 4 to treatment end
Study details	**Run-in period**: 4 weeks **Study terminated early**: no **Trial register ID:** not reported
Publication details	**Language of publication**: English **Funding:** commercial (Sanofi-Aventis) **Publication status**: full article in a peer reviewed journal
Study aim for study	**Quote from publication:** "This study aimed to demonstrate the non-inferiority of insulin glulisine with RHI in terms of changes in HbA1c levels from baseline to endpoint (week 26 or patients' last available value during treatment), and the safety of insulin glulisine (in terms of AEs, clinical chemistry, lipids and haematology)"
Notes	[1]from IQWIG 2005

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote from publication**:"Randomization was stratified according to whether or not patients were treated with OHAs at the time of randomisation" **Comment**: not clearly stated, but likely adequate; according to IQWIG 2005, adequate
Allocation concealment (selection bias)	Low risk	**Comment**: not reported, but according to IQWIG 2005, adequate
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Quote from publication**: "open-label" **Comment**: outcome measure unlikely influenced by lack of blinding
Blinding of participants and personnel (performance bias) Severe hypoglycaemia	High risk	**Quote from publication**: "open-label" **Comment**: self-reported and investigator-reported outcome measurement, outcome measure likely to be influenced by lack of blinding
Blinding of participants and personnel (performance bias) HbA1c	Unclear risk	**Quote from publication**: "open-label" **Comment**: investigator-reported outcome measurement

Rayman 2007 (*Continued*)

Blinding of participants and personnel (performance bias) Adverse events	High risk	**Quote from publication**: "open-label" **Comment**: self-reported and investigator-reported outcome measurement, outcome measure likely influenced by lack of blinding
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Quote from publication**: "open-label" **Comment:** outcome measure unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) Severe hypoglycaemia	High risk	**Quote from publication**: "open-label" **Comment**: self-reported and investigator-reported outcome measurement, outcome measure likely influenced by lack of blinding
Blinding of outcome assessment (detection bias) HbA1c	Low risk	**Quote from publication**: "HbA1c levels in whole blood were analysed in a single central laboratory" **Comment**: according to IQWIG 2005, blinded outcome assessment
Blinding of outcome assessment (detection bias) Adverse events	High risk	**Quote from publication**: "open-label" **Comment**: self-reported and investigator-reported outcome measurement, outcome measure likely influenced by lack of blinding
Incomplete outcome data (attrition bias) All-cause mortality	Low risk	**Comment**: all participants included in analysis
Incomplete outcome data (attrition bias) Severe hypoglycaemia	Low risk	**Comment**: all participants included in analysis
Incomplete outcome data (attrition bias) HbA1c	Low risk	**Comment**: 96% and 98% of participants included in analysis
Incomplete outcome data (attrition bias) Adverse events	Low risk	**Comment**: all participants included in analysis
Selective reporting (reporting bias)	Unclear risk	**Comment**: no study protocol was available, but some results were reported for endpoints not mentioned in the methods section of the paper
Other bias	High risk	**Comment**: inconsistent information on hypoglycaemia data in Rayman 2007, data appear not to be correct

Ross 2001

Methods	**Parallel randomised clinical trial, randomisation ratio 1:1, non-inferiority design (2-sided CI)**
Participants	**Inclusion criteria**: type 2 diabetes; maximum tolerated dose of oral hypoglycaemic agents (metformin and sulphonylurea) without achieving acceptable glycaemic control (defined as an HbA1c level less than 130% above upper normal range despite full compliance with diet and medication), no long-term insulin therapy **Exclusion criteria**: severe retinopathy or neuropathy, more than 2 severe hypoglycaemic episodes in the past year **Diagnostic criteria**: not reported
Interventions	**Number of study centres**: not reported **Treatment before study**: OADs (metformin and sulphonylurea) **Titration period**: 5.5 months[1]
Outcomes	**Outcomes reported in abstract of publication**: 2-hr post-breakfast and 2-hr post-supper blood glucose levels; HbA1c improvement; overall hypoglycaemia; nocturnal hypoglycaemia; quality-of life
Study details	**Run-in period**: not reported **Study terminated early**: no **Trial register ID:** not reported
Publication details	**Language of publication**: English **Funding:** not reported **Publication status:** full article in peer reviewed journal
Study aim for study	**Quote from publication:** "To compare the effects of insulin lispro (LP) and human regular insulin (HRI) when given twice daily with NPH insulin on glycaemic control (HbA1c), daily blood glucose profiles and rates of hypoglycaemia in patients with type 2 diabetes mellitus after failure to respond to sulphonylurea drugs"
Notes	[1]According to IQWIG 2005, no information on the duration in weeks; 5.5 months correspond to min. 23.6 weeks, max. 24.1 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote from publication**: "Subjects were randomised to LP or HR together with NPH insulin for the entire treatment period´ " **Comment**: not enough details
Allocation concealment (selection bias)	Unclear risk	**Comment**: not reported

Ross 2001 (*Continued*)

Blinding of participants and personnel (performance bias) HbA1c	Unclear risk	**Quote from publication**: "open-label" **Comment**: investigator-reported outcome measurement
Blinding of participants and personnel (performance bias) Adverse events	High risk	**Quote from publication**: "open-label" **Comment**: self-reported and investigator-reported outcome measurement, outcome measure likely influenced by lack of blinding
Blinding of participants and personnel (performance bias) Health-related quality of life	High risk	**Quote from publication**: "open-label" **Comment**: self-reported outcome measurement, outcome measure likely influenced by lack of blinding
Blinding of outcome assessment (detection bias) HbA1c	Unclear risk	**Quote from publication**: "open-label" **Comment**: investigator-reported outcome measurement
Blinding of outcome assessment (detection bias) Adverse events	High risk	**Quote from publication**: "open-label" **Comment**: self-reported and investigator-reported outcome measurement, outcome measure likely influenced by lack of blinding
Blinding of outcome assessment (detection bias) Health-related quality of life	High risk	**Quote from publication**: "open-label" **Comment**: self-reported outcome measurement, outcome measure likely influenced by lack of blinding
Incomplete outcome data (attrition bias) HbA1c	Low risk	**Quote from publication**: "All efficacy results are presented as an intention-to-treat analysis"
Incomplete outcome data (attrition bias) Adverse events	Low risk	**Quote from publication**: "All efficacy results are presented as an intention-to-treat analysis"
Incomplete outcome data (attrition bias) Health-related quality of life	High risk	**Quote from publication**: "Forty-nine LP and 53 HR subjects completed the questionnaire at the beginning and end of the study" **Comment**: only 49/70 (70%) randomised participants in the lispro group and 53/78 (68%) participants in the regular human insulin group completed the questionnaire

Ross 2001 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	**Comment**: severe hypoglycaemia defined in the methods but not reported in results, instead, the results for nocturnal hypoglycaemia are reported, which was not mentioned in the methods; some baseline variables reported for groups separately, others were only given for the whole trial population (e.g. retinopathy, neuropathy)
Other bias	Unclear risk	**Comment**: no definition of primary outcome

Z012 1997

Methods	**Parallel randomised controlled trial, randomisation ratio 1:1, non-inferiority design**
Participants	**Inclusion criteria**: NIDDM, age = 35 to 70 years, insulin therapy for at least two months before study entry[1] **Exclusion criteria**: any other severe disease, current use of oral antidiabetic drugs or insulin infusion devices **Diagnostic criteria**: WHO 1980
Interventions	**Number of study centres**: multicenter (47 investigators) **Treatment before study**: human insulin therapy for at least 2 months before study **Titration period**: 12 months
Outcomes	**Outcomes reported in abstract of publication**: 1-hr and 2-hr postprandial rise in serum glucose, HbA1c
Study details	**Run-in period**: 1 month[2] **Study terminated early**: no **Trial register ID:** not reported
Publication details	**Language of publication**: English **Funding:** commercial (Eli Lilly) **Publication status:** full article in peer review journal[3]
Study aim for study	**Quote from publication:** "We examined the safety and efficacy of insulin lispro in the pre-meal treatment of patients with diabetes mellitus"
Notes	[1]Anderson 1997 combined two trials including type 1 and type 2 diabetic participants. The inclusion criteria listed here only refer to participants with type 2 diabetes [2]According to IQWIG 2005 2 to 4 weeks [3]Anderson 1997 reports on the pooled results of trials Z012 1997 and Z014 1997; details on the individual trials were taken from IQWIG 2005

Z012 1997 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**Quote from publication:** "Patients were then randomly assigned to receive either insulin lispro or regular human insulin as a pre-meal injection" **Comment**: considered adequate in IQWIG 2005
Allocation concealment (selection bias)	Low risk	**Quote from IQWiG report:** "Allocation was done centrally" **Comment**: considered adequate in IQWIG 2005
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Quote from publication**: "open-label" **Comment:** outcome measure unlikely to be influenced by lack of blinding
Blinding of participants and personnel (performance bias) Severe hypoglycaemia	High risk	**Quote from publication**: "open-label" **Comment:** outcome measure likely influenced by lack of blinding
Blinding of participants and personnel (performance bias) HbA1c	Unclear risk	**Quote from publication**: "open-label"
Blinding of participants and personnel (performance bias) Adverse events	High risk	**Quote from publication**: "open-label" **Comment:** outcome measure likely influenced by lack of blinding
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Quote from publication**: "open-label" **Comment:** outcome measure unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) Severe hypoglycaemia	High risk	**Quote from publication**: "open-label" **Comment:** outcome measure likely influenced by lack of blinding
Blinding of outcome assessment (detection bias) HbA1c	Low risk	**Quote from publication**: "Blood samples were taken at 3-month intervals for the determination of glycated haemoglobin (HbA1c) levels and analysed by a central laboratory" **Comment:** outcome measure was unlikely influenced by lack of blinding

Z012 1997 (*Continued*)

Blinding of outcome assessment (detection bias) Adverse events	High risk	**Quote from publication**: "open-label" **Comment:** outcome measure likely influenced by lack of blinding
Incomplete outcome data (attrition bias) All-cause mortality	Low risk	**Quote from IQWiG report**: "Patients lost to follow-up lispro 3%; patients lost to follow-up regular human insulin 3%"
Incomplete outcome data (attrition bias) Severe hypoglycaemia	Low risk	**Quote from IQWiG report**: "Patients lost to follow-up lispro 3%; patients lost to follow-up regular human insulin 3%"
Incomplete outcome data (attrition bias) HbA1c	Low risk	**Quote from IQWiG report**: "Patients lost to follow-up lispro 3%; patients lost to follow-up regular human insulin 3%"
Incomplete outcome data (attrition bias) Adverse events	Low risk	**Quote from IQWiG report**: "Patients lost to follow-up lispro 3%; patients lost to follow-up regular human insulin 3%"
Selective reporting (reporting bias)	High risk	**Comment**: inconsistent information on primary outcomes in different study reports and publication
Other bias	High risk	**Comment**: primary outcome not clear; the publication only provided results for pooled analyses of trials Z012 and Z014. The trial authors did not make clear that these were results from pooled analyses

Z014 1997

Methods	**Parallel randomised controlled trial, randomisation ratio 1:1, non-inferiority design**
Participants	**Inclusion criteria**: NIDDM, age = 35 to 70 years, insulin therapy for at least two months before study entry[1] **Exclusion criteria**: any other severe disease, current use of oral antidiabetic drugs or insulin infusion devices **Diagnostic criteria**: WHO 1980
Interventions	**Number of study centres**: multicentre (47 investigators) **Treatment before study**: human insulin therapy for at least 2 months before study **Titration period**: 12 months
Outcomes	**Outcomes reported in abstract of publication**: 1-hr and 2-hr postprandial rise in serum glucose, HbA1c

Z014 1997 (*Continued*)

Study details	**Run-in period**: 1 month[2] **Study terminated early**: no **Trial register ID:** not reported
Publication details	**Language of publication**: English **Funding:** commercial (Eli Lilly) **Publication status:** full article in peer reviewed journal[3]
Study aim for study	**Quote from publication:** "We examined the safety and efficacy of insulin lispro in the pre-meal treatment of patients with diabetes mellitus"
Notes	[1]Anderson 1997 combined two trials including type 1 and type 2 diabetic participants. The inclusion criteria listed here only refer to participants with type 2 diabetes [2]According to IQWIG 2005, 2 to 4 weeks [3]Anderson 1997 reports on the pooled results of trials Z012 1997 and Z014 1997; details on the individual trials were taken from IQWIG 2005

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote from publication:** "Patients were then randomly assigned to receive either insulin lispro or regular human insulin as a pre-meal injection" **Comment**: considered adequate in IQWIG 2005
Allocation concealment (selection bias)	Low risk	**Quote from IQWiG report:** "Allocation was done centrally" **Comment**: considered adequate in IQWIG 2005
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Quote from publication**: "open-label" **Comment:** outcome measure unlikely to be influenced by lack of blinding
Blinding of participants and personnel (performance bias) Severe hypoglycaemia	High risk	**Quote from publication**: "open-label" **Comment:** outcome measure likely influenced by lack of blinding
Blinding of participants and personnel (performance bias) HbA1c	Unclear risk	**Quote from publication**: "open-label"
Blinding of participants and personnel (performance bias) Adverse events	High risk	**Quote from publication**: "open-label" **Comment:** outcome measure likely influenced by lack of blinding

Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Quote from publication**: "open-label" **Comment:** outcome measure unlikely influenced by lack of blinding
Blinding of outcome assessment (detection bias) Severe hypoglycaemia	High risk	**Quote from publication**: "open-label" **Comment:** outcome measure likely influenced by lack of blinding
Blinding of outcome assessment (detection bias) HbA1c	Low risk	**Quote from publication**: "Blood samples were taken at 3-month intervals for the determination of glycated haemoglobin (HbA1c) levels and analysed by a central laboratory" **Comment**: outcome measure unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) Adverse events	High risk	**Quote from publication**: "open-label" **Comment:** outcome measure likely influenced by lack of blinding
Incomplete outcome data (attrition bias) All-cause mortality	Low risk	**Quote from IQWiG report**: "Patients lost to follow-up lispro N = 5 (6%); patients lost to follow-up regular human insulin N = 6 (7%)"
Incomplete outcome data (attrition bias) Severe hypoglycaemia	Low risk	**Quote from IQWiG report**: "Patients lost to follow-up lispro N = 5 (6%); patients lost to follow-up regular human insulin N = 6 (7%)"
Incomplete outcome data (attrition bias) HbA1c	Low risk	**Quote from IQWiG report**: "Patients lost to follow-up lispro n = 5 (6%); patients lost to follow up regular human insulin n = 6 (7%)"
Incomplete outcome data (attrition bias) Adverse events	Low risk	**Quote from IQWiG report**: "Patients lost to follow-up lispro N = 5 (6%); patients lost to follow-up regular human insulin N = 6 (7%)"
Selective reporting (reporting bias)	High risk	**Comment**: inconsistent information on primary outcomes in different study reports and publication
Other bias	High risk	**Comment**: primary outcome not clear; publication only provided results for pooled analyses of trials Z012 and Z014. The trial authors did not inform readers

		that these were results from pooled analyses

Note: where the judgement is 'Unclear' and the description is blank, the trial did not report that particular outcome.
ADA: American Diabetes Association
AE: adverse events
BG: blood glucose
BMI: body mass index
CI: confidence interval
DM: diabetes mellitus
hr: hour(s)
HbA1c: glycosylated haemoglobin A1c
HR: human regular insulin
HRQoL: health-related quality of life
IDDM: insulin-dependent diabetes mellitus
LP: insulin lispro
NIDDM: non-insulin-dependent diabetes mellitus
OAD: oral antidiabetic drug
OGTT: oral glucose tolerance test
ORBIT: Outcome Reporting Bias In Trials
PG: plasma glucose
RHI: regular human insulin
T2DM: type 2 diabetes
WHO: World Health Organization

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bi 2007	Treatment duration too short (3 weeks)
Boehm 2004	Not a randomised trial
Boivin 1999	No comparison of short-acting insulin analogue versus regular human insulin
Bott 2003	Not type 2 diabetes
Caixas 1998	Not type 2 diabetes
Chan 2004	Treatment duration too short (12 weeks)
Chen 2011	Treatment duration too short (about 2 weeks)
Chlup 2004	Not a randomised trial

(*Continued*)

Cypryk 2004	Not type 2 diabetes
Ferguson 2001	Not type 2 diabetes
Fineberg 1996	Pooled data of 4 randomised controlled trials
Gao 2009	Treatment duration too short (3 months)
Garg 1996	Not type 2 diabetes
Garg 2000	Not type 2 diabetes
Gram 2011	No comparison of short-acting insulin analogue versus regular human insulin
Holleman 1997	Not type 2 diabetes
Home 2000	Not type 2 diabetes
Home 2006	Not type 2 diabetes
Kaplan 2004	Not type 2 diabetes
Lalli 1999	Not type 2 diabetes
Laube 1996	Treatment duration too short (3 months)
Lindholm 1999	Not type 2 diabetes
Lindholm 2002	No adequate separate data for type 2 diabetic participants
Loukovaara 2003	Not type 2 diabetes
Miikkulainen 2016	Not a randomised trial
Perez-Maraver 2013	No comparable insulin regimen in intervention and control groups
Perriello 2005	Treatment duration too short (1 trial day)
Persson 2002	Not type 2 diabetes
Provenzano 2001	Not type 2 diabetes
Rami 1997	Treatment duration too short (2 days)
Raskin 2000	Not type 2 diabetes
Recasens 2003	Not type 2 diabetes

(*Continued*)

Roach 2001	No comparable insulin regimen in intervention and control groups
Schernthaner 2004	No comparable insulin regimen in intervention and control groups
Skhra 2002	Treatment duration too short (2 months)
Tubiana-Rufi 1997	Not type 2 diabetes
Vignati 1997	Treatment duration too short (2 months)
Yanagisawa 2013	Not a randomised trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Farshchi 2016

Methods	Parallel randomised controlled trial, randomisation ratio 1:1
Participants	**Inclusion criteria**: participants with T2DM; age 25 to 65 years; HbA1c ≥ 8 % despite adequate therapy with lifestyle modification and one or two classes of OADs **Exclusion criteria**: alteration in insulin sensitivity such as major surgery, infection, renal failure (glomerular filtration rate < 50); glucocorticoid treatment; recent (within 2 weeks) serious hypoglycaemic episode (requires assistance of another); using any type of insulin; sight or hearing impaired; active proliferative retinopathy or maculopathy requiring treatment within 6 months prior to screening; breast feeding, pregnancy or nursing, intention of becoming pregnant or not using adequate contraceptive measures; participating in another clinical study **Diagnostic criteria**: not reported
Interventions	**Number of study centres**: 1 **Treatment before study**: OADs **Titration period**: not reported
Outcomes	**Outcomes reported in abstract of publication**: HbA1c; FPG; PPG; hypoglycaemia (minor, major, nocturnal); weight gain; utility; cost-effectiveness; costs (medical, non-medical)
Reason for awaiting classification	**Run-in period**: none **Study terminated early**: no **Trial register ID:** NCT01889095
Stated aim of study	**Language of publication**: English **Funding:** commercial (Novo Nordisk Pars, Iran) **Publication status:** full article in a peer reviewed journal
Trial identifier	**Quote from publication:** "The aim of the present piggyback study was to investigate the cost-effectiveness of BIAsp 30, using the data from a clinical trial of Iranian patients with T2DM"

Farshchi 2016 (*Continued*)

Notes	According to information available from ClinicalTrials.gov and Farshchi 2016, treatment goals were fasting BG between 80 and 120 mg/dL, postprandial BG less than 160 mg/dL, and HbA1c less than 7.0% in both comparison groups. However, the authors also mentioned an additional target for the pre-dinner BG of less than 100 mg/dL for the NPH/Reg group. In addition, the authors report that BG targets for dose titration were based on pre-meal targets alone and according to this information, dose titration started only at BG above 126 mg/dL. It thus remains unclear whether there was an additional BG target in the NPG/Reg group. We contacted the author for clarification and additional information but did not get an answer

NCT01500850

Methods	**Type of trial:** interventional trial **Allocation:** randomised **Intervention model**: parallel assignment **Masking:** none(open label) **Primary purpose:** treatment
Participants	**Condition**: insulin-requiring type 2 diabetes mellitus **Enrollment**: estimated 60 **Inclusion criteria**: type 2 diabetes ≥ 1 year of diagnosis; experienced in self blood glucose measurement for ≥ 3 months; HbA1c ≤ 9% and > 6.5%; BMI > 30 kg/m²; age ≥ 18 years; waist circumference > 88 cm (female) and > 102 cm (male); NPH insulin treatment plus 1 or 2 OAD (except TZD) **Exclusion criteria**: anamnestic history of hypersensitivity to the study drugs (or any component of the study drug) or to drugs with similar chemical structures; history of severe or multiple allergies; treatment with any other investigational drug within 3 months prior to screening; progressive fatal disease; history of significant cardiovascular, respiratory, gastrointestinal, hepatic, renal, neurological, psychiatric, or hematological disease (or a combination), as judged by the investigator; treatment with GLP1-analogue or TZD; hsCRP > 10 mg/L; already treated with intensified conventional insulin therapy
Interventions	**Intervention(s)**: insulin glargine + insulin glulisine for 24 weeks; insulin glargine + human insulin for 24 weeks **Comparator(s)**: NPH insulin + insulin glulisine for 24 weeks; NPH insulin + human insulin for 24 weeks
Outcomes	**Primary outcome(s)**: fasting intact proinsulin after 24 weeks **Secondary outcome(s)**: weight; hsCRP; adiponectin; MMP-9; OGTT parameters; HOMA-IR score; HbA1c; responder rate; hypoglycaemic events **Other outcome(s)**: not reported
Reason for awaiting classification	**Quote from trials register record**: "The recruitment status of this study is unknown. The completion date has passed and the status has not been verified in more than two years"
Stated aim of study	**Quote from trials register record**: "...to observe changes in cardiovascular biomarkers during treatment with Lantus in patients with type 2 diabetes mellitus"
Trial identifier	NCT01500850

NCT01500850 (*Continued*)

Notes	Completed study identified through trial registry search. No publication or trial results available. No information provided by trial investigators

BMI: body mass index; **FPG**: fasting plasma glucose; **GLP-1**: glucagon-like peptid 1; **HbA1c**: glycosylated haemoglobin A1c; **HOMA-IR**: homeostatic model assessment insulin resistance; **hsCRP**: highly-reactive C-reactive protein; **MMP-9**: matrix metallopeptidase 9; **NPH**: neutral protamine Hagedorn insulin; **OAD**: oral antidiabetic drugs; **OGTT**: oral glucose tolerance test; **PPG**: postprandial glucose; **RHI**: regular human insulin; **T2DM**: type 2 diabetes mellitus; **TZD**: thiazolidinediones

DATA AND ANALYSES

Comparison 1. Short-acting insulin analogues versus regular human insulin (RHI)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	6	2519	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.66 [0.41, 6.64]
2 All-cause mortality for different types of insulin	6	2519	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.66 [0.41, 6.64]
2.1 Lispro	3	670	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.55 [0.47, 121.16]
2.2 Glulisine	2	1766	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.20, 4.96]
2.3 Aspart	1	83	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 HbA1c changes	9	2608	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.16, 0.09]
4 HbA1c changes for different types of insulin	9	2612	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.15, 0.09]
4.1 Lispro	4	818	Mean Difference (IV, Random, 95% CI)	0.09 [-0.13, 0.30]
4.2 Glulisine	3	1675	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.21, 0.05]
4.3 Aspart	3	119	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.65, 0.50]
5 All non-severe hypoglycaemic episodes (mean episode/participant/month)	7	2667	Mean Difference (IV, Random, 95% CI)	0.08 [-0.00, 0.16]
6 All non-severe hypoglycaemic episodes (mean episode/participant/month) for different types of insulin	7	2667	Mean Difference (IV, Random, 95% CI)	0.08 [-0.00, 0.16]
6.1 Lispro	4	818	Mean Difference (IV, Random, 95% CI)	0.10 [0.00, 0.19]
6.2 Glulisine	2	1766	Mean Difference (IV, Random, 95% CI)	0.03 [-0.15, 0.22]
6.3 Aspart	1	83	Mean Difference (IV, Random, 95% CI)	-0.5 [-1.64, 0.64]

Analysis 1.1. Comparison 1 Short-acting insulin analogues versus regular human insulin (RHI), Outcome 1 All-cause mortality.

Review: Short-acting insulin analogues versus regular human insulin for adult, non-pregnant persons with type 2 diabetes mellitus

Comparison: 1 Short-acting insulin analogues versus regular human insulin (RHI)

Outcome: 1 All-cause mortality

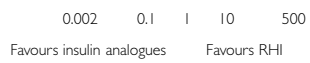
Study or subgroup	Insulin analogues n/N	RHI n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Bastyr 2000	2/186	0/189		25.0 %	7.55 [0.47, 121.16]
Dailey 2004	1/435	2/441		37.5 %	0.52 [0.05, 5.01]
NCT01650129	0/58	0/25			Not estimable
Rayman 2007	2/448	1/442		37.5 %	1.92 [0.20, 18.55]
Z012 1997	0/72	0/73			Not estimable
Z014 1997	0/73	0/77			Not estimable
Total (95% CI)	**1272**	**1247**		**100.0 %**	**1.66 [0.41, 6.64]**

Total events: 5 (Insulin analogues), 3 (RHI)

Heterogeneity: $Chi^2 = 2.17$, df = 2 (P = 0.34); $I^2 = 8\%$

Test for overall effect: Z = 0.71 (P = 0.48)

Test for subgroup differences: Not applicable

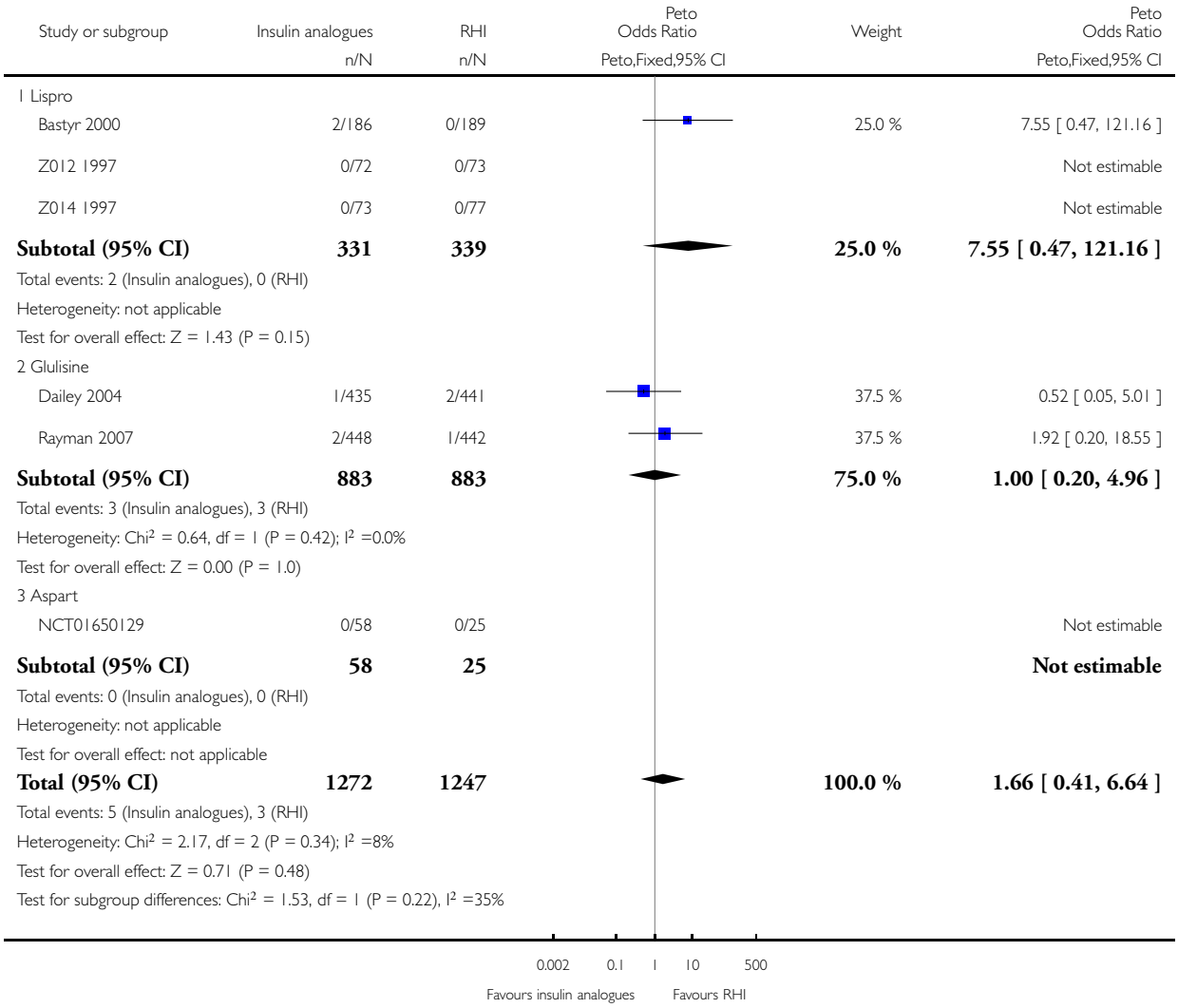


Analysis 1.2. Comparison 1 Short-acting insulin analogues versus regular human insulin (RHI), Outcome 2 All-cause mortality for different types of insulin.

Review: Short-acting insulin analogues versus regular human insulin for adult, non-pregnant persons with type 2 diabetes mellitus

Comparison: 1 Short-acting insulin analogues versus regular human insulin (RHI)

Outcome: 2 All-cause mortality for different types of insulin



Analysis 1.3. Comparison 1 Short-acting insulin analogues versus regular human insulin (RHI), Outcome 3 HbA1c changes.

Review: Short-acting insulin analogues versus regular human insulin for adult, non-pregnant persons with type 2 diabetes mellitus

Comparison: 1 Short-acting insulin analogues versus regular human insulin (RHI)

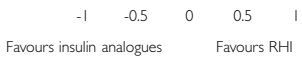
Outcome: 3 HbA1c changes

Study or subgroup	Insulin analogues		RHI		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
NCT01650129	58	-0.6 (0.96)	24	-0.1 (1.36)		3.9 %	-0.50 [-1.10, 0.10]
Ross 2001	70	-2.5 (1.67)	78	-2.3 (1.77)		4.5 %	-0.20 [-0.75, 0.35]
Dailey 2004	404	-0.46 (0.8)	403	-0.3 (0.85)		29.9 %	-0.16 [-0.27, -0.05]
Z012 1997	72	-0.7 (1.2)	73	-0.6 (1.4)		7.1 %	-0.10 [-0.52, 0.32]
Rayman 2007	429	-0.3 (0.85)	431	-0.3 (0.8)		30.3 %	0.0 [-0.11, 0.11]
Z014 1997	73	-0.4 (1.5)	77	-0.5 (0.7)		8.5 %	0.10 [-0.28, 0.48]
Hermann 2013	18	-1.4 (1.28)	11	-1.5 (1.28)		1.6 %	0.10 [-0.86, 1.06]
Pfützner 2013	8	-0.4 (0.6)	4	-0.6 (0.6)		2.8 %	0.20 [-0.52, 0.92]
Bastyr 2000	186	-1.2 (1.59)	189	-1.5 (1.5)		11.3 %	0.30 [-0.01, 0.61]
Total (95% CI)	**1318**		**1290**			**100.0 %**	**-0.03 [-0.16, 0.09]**

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 12.83$, df = 8 (P = 0.12); $I^2 = 38\%$

Test for overall effect: Z = 0.53 (P = 0.60)

Test for subgroup differences: Not applicable

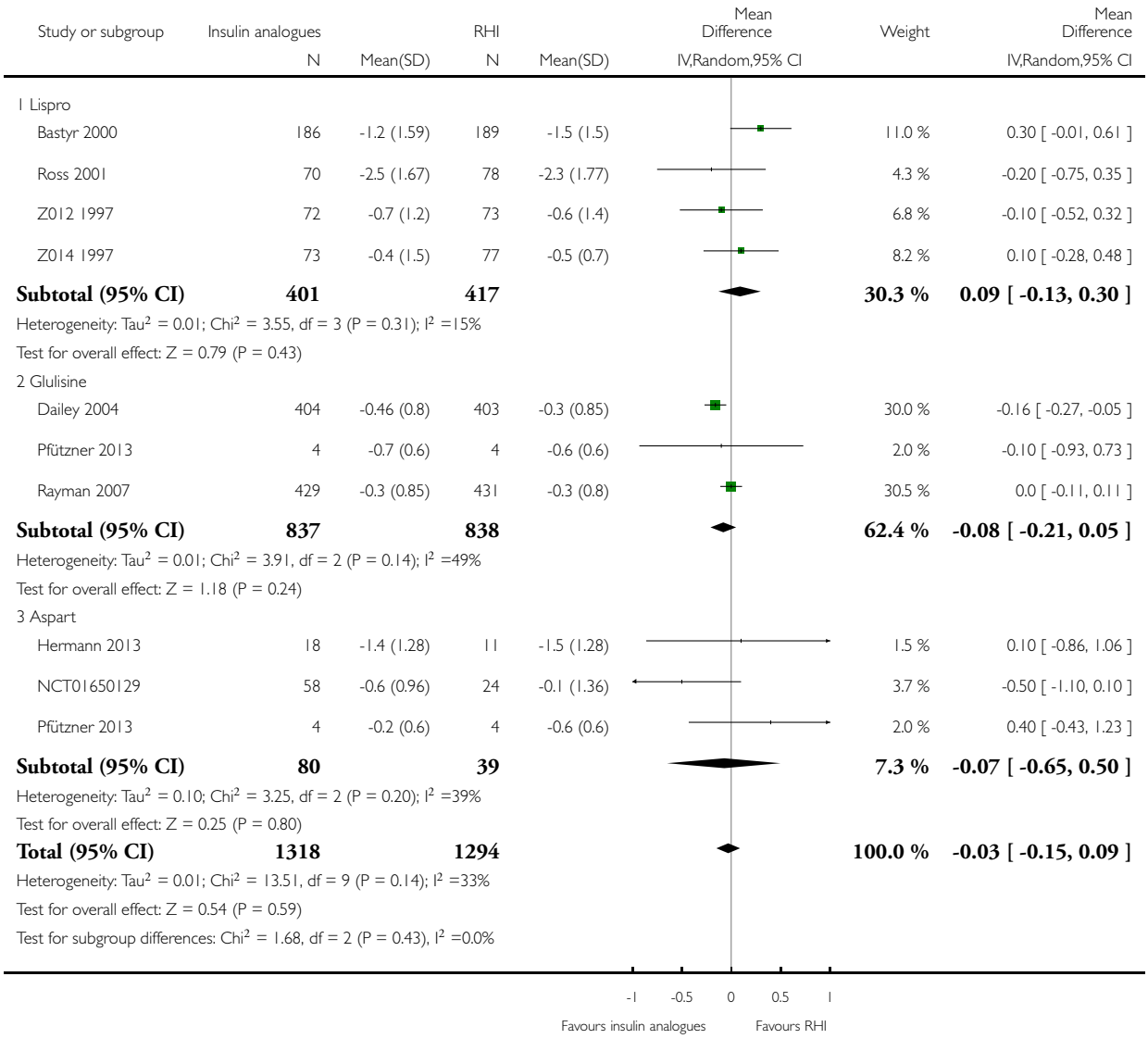


Analysis 1.4. Comparison 1 Short-acting insulin analogues versus regular human insulin (RHI), Outcome 4 HbA1c changes for different types of insulin.

Review: Short-acting insulin analogues versus regular human insulin for adult, non-pregnant persons with type 2 diabetes mellitus

Comparison: 1 Short-acting insulin analogues versus regular human insulin (RHI)

Outcome: 4 HbA1c changes for different types of insulin



Analysis 1.5. Comparison 1 Short-acting insulin analogues versus regular human insulin (RHI), Outcome 5 All non-severe hypoglycaemic episodes (mean episode/participant/month).

Review: Short-acting insulin analogues versus regular human insulin for adult, non-pregnant persons with type 2 diabetes mellitus

Comparison: 1 Short-acting insulin analogues versus regular human insulin (RHI)

Outcome: 5 All non-severe hypoglycaemic episodes (mean episode/participant/month)

Study or subgroup	Insulin analogues N	Mean(SD)	RHI N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Bastyr 2000	186	0.9 (2.1)	189	0.8 (1.9)		3.9 %	0.10 [-0.31, 0.51]
Dailey 2004	435	1.2 (2.1)	441	1.3 (2.4)		7.2 %	-0.10 [-0.40, 0.20]
NCT01650129	58	0.8 (2.3)	25	1.3 (2.5)		0.5 %	-0.50 [-1.64, 0.64]
Rayman 2007	448	0.7 (1.4)	442	0.6 (1.5)		17.8 %	0.10 [-0.09, 0.29]
Ross 2001	70	1.8 (0.3)	78	1.7 (0.3)		68.9 %	0.10 [0.00, 0.20]
Z012 1997	72	2.1 (3.2)	73	2.5 (4.6)		0.4 %	-0.40 [-1.69, 0.89]
Z014 1997	73	0.8 (2.3)	77	0.8 (2.1)		1.3 %	0.0 [-0.71, 0.71]
Total (95% CI)	**1342**		**1325**			**100.0 %**	**0.08 [0.00, 0.16]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.18$, df = 6 (P = 0.79); $I^2 = 0.0\%$

Test for overall effect: Z = 1.93 (P = 0.053)

Test for subgroup differences: Not applicable

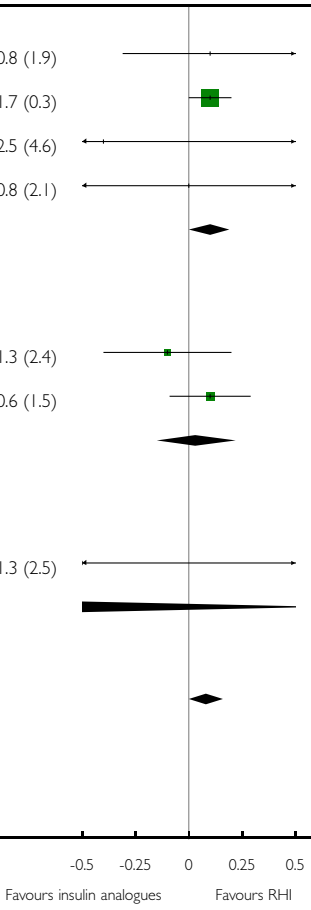
Analysis 1.6. Comparison 1 Short-acting insulin analogues versus regular human insulin (RHI), Outcome 6 All non-severe hypoglycaemic episodes (mean episode/participant/month) for different types of insulin.

Review: Short-acting insulin analogues versus regular human insulin for adult, non-pregnant persons with type 2 diabetes mellitus

Comparison: 1 Short-acting insulin analogues versus regular human insulin (RHI)

Outcome: 6 All non-severe hypoglycaemic episodes (mean episode/participant/month) for different types of insulin

Study or subgroup	Insulin analogues N	Mean(SD)	RHI N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Lispro							
Bastyr 2000	186	0.9 (2.1)	189	0.8 (1.9)		3.9 %	0.10 [-0.31, 0.51]
Ross 2001	70	1.8 (0.3)	78	1.7 (0.3)		68.9 %	0.10 [0.00, 0.20]
Z012 1997	72	2.1 (3.2)	73	2.5 (4.6)		0.4 %	-0.40 [-1.69, 0.89]
Z014 1997	73	0.8 (2.3)	77	0.8 (2.1)		1.3 %	0.0 [-0.71, 0.71]
Subtotal (95% CI)	**401**		**417**			**74.5 %**	**0.10 [0.00, 0.19]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.65$, df = 3 (P = 0.89); $I^2 = 0.0\%$							
Test for overall effect: Z = 2.01 (P = 0.044)							
2 Glulisine							
Dailey 2004	435	1.2 (2.1)	441	1.3 (2.4)		7.2 %	-0.10 [-0.40, 0.20]
Rayman 2007	448	0.7 (1.4)	442	0.6 (1.5)		17.8 %	0.10 [-0.09, 0.29]
Subtotal (95% CI)	**883**		**883**			**25.0 %**	**0.03 [-0.15, 0.22]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.22$, df = 1 (P = 0.27); $I^2 = 18\%$							
Test for overall effect: Z = 0.37 (P = 0.71)							
3 Aspart							
NCT01650129	58	0.8 (2.3)	25	1.3 (2.5)		0.5 %	-0.50 [-1.64, 0.64]
Subtotal (95% CI)	**58**		**25**			**0.5 %**	**-0.50 [-1.64, 0.64]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.86 (P = 0.39)							
Total (95% CI)	**1342**		**1325**			**100.0 %**	**0.08 [0.00, 0.16]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.18$, df = 6 (P = 0.79); $I^2 = 0.0\%$							
Test for overall effect: Z = 1.93 (P = 0.053)							
Test for subgroup differences: $Chi^2 = 1.33$, df = 2 (P = 0.51), $I^2 = 0.0\%$							



ADDITIONAL TABLES

Table 1. Overview of trial populations

Trial ID (trial design)	Intervention(s) and comparator(s)	Sample size	Screened/ eligible (N)	Randomised (N)	Safety (N)	ITT (N)	Finished trial (N)	Randomised finished trial (%)	Treatment duration (follow-up)
Altuntas 2003 (parallel RCT)	I: lispro	-	-/40	20	20	20	20	100	6 months
	C: RHI			20	20	20	20	100	
	total:			**40**	**40**	**40**	**40**	**100**	
Bastyr 2000 (parallel RCT)	I: lispro	-	-	186	-	-	156[a]	83.9	12 months
	C: RHI			189	-	-	161[a]	85.2	
	total:			**375**	**-**	**-**	**317**	**84.5**	
Dailey 2004 (parallel non-inferiority RCT)	I: glulisine	-	-/1186	-	435	435	407	-	26 weeks
	C: RHI			-	441	441	405	-	
	total:			**878**	**876**	**876**	**812**	**92.5**	
Hermann 2013 (parallel RCT)	I: aspart	-	-	18	-	-	18[b]	100	24 months
	C: RHI			11	-	-	11[b]	100	
	total:			**29**	**-**	**-**	**29**	**100**	
NCT01650 (parallel RCT)	I: biphasic insulin aspart	-	-/88	58	58	58	54	93	24 weeks
	C: biphasic human insulin			26	25	25	24	96	
	total:			**84**	**83**	**83**	**78**	**95**	
Pfützner 2013 (parallel RCT)	I1: lispro	-	-/12	4	4	4	4[b]	100	6 months
	I2: glulisine			4	4	4	4[b]	100	
	C: RHI			4	4	4	4[b]	100	
	total:			**12**	**12**	**12**	**12**	**100**	

Table 1. Overview of trial populations (*Continued*)

Rayman 2007 (parallel non-inferiority RCT)	I: glulisine	-	-/1088	448	448	448	420	94	26 weeks
	C: RHI			444	442	442	428	96	
	total:			**892**	**890**	**890**	**848**	**95**	
Ross 2001 (parallel non-inferiority RCT)	I: lispro	-	-	70	-	-	-	-	5.5 months [c]
	C: RHI			78	-	-	-	-	
	total:			**148**	**-**	**-**	**143**	**97**	
Z012 1997 (parallel non-inferiority RCT)	I: lispro	-	-	72	-	-	70	97	12 months
	C: RHI			73	-	-	71	97	
	total:			**145**	**-**	**-**	**141**	**97**	
Z014 1997 (parallel non-inferiority RCT)	I: lispro	-	-	73	-	-	68	93	12 months
	C: RHI			77	-	-	71	92	
	total:			**150**	**-**	**-**	**139**	**93**	
Totals	**All interventions**			***1388***					
	All comparators			***1363***					
	All interventions plus comparators			***2751***					

[a] These numbers are based on what was reported in the original study report. According to the publication, only 25 participants dropped out from the lispro study arm and 19 from the RHI

[b] Not explicitly reported, but assumed based on the number of participants presented in the figures and results section

[c] According to IQWIG 2005, no information provided on the duration in weeks; 5.5 months corresponds to a minimum of 23.6 weeks and a maximum of 24.1 weeks

-: denotes not reported

C: comparator; **I**: intervention; **ITT**: intention-to-treat; **RCT**: randomised controlled trial; **RHI**: regular human insulin

APPENDICES

Appendix 1. Search strategies

The Cochrane Library, MEDLINE Ovid, and Embase Ovid - run to April 2015

1 (Lyspro$ or Lispro$).ti,ab,ot.
2 (Lys$B28 or B28Lys$ or (lys$ adj1 B28)).ti,ab,ot.
3 (Pro$B29 or B29Pro$ or (pro$ adj1 B29)).ti,ab,ot.
4 humalog$.ti,ab,ot,tn.
5 133107-64-9.rn.
6 or/1-5
7 (insulin$ adj1 aspart$).ti,ab,ot.
8 (Asp$B28 or B28Asp$ or (asp$ adj1 B28)).ti,ab,ot.
9 (Novorapid$ or Novolog$).ti,ab,ot,tn.
10 116094-23-6.rn.
11 or/7-10
12 (Glulisin$ or Glulysin$).ti,ab,ot.
13 (Glu$B29 or B29Glu$ or (glu$ adj1 B29)).ti,ab,ot.
14 (Lys$B3 or B3Lys$ or (lys$ adj1 B3)).ti,ab,ot.
15 Apidra$.ti,ab,ot,tn.
16 207748-29-6.rn.
17 or/12-16
18 6 or 11 or 17
19 (insulin$ adj6 (analog$ or derivat$)).ti,ab,ot.
20 ((shortacting or fastacting or rapidacting) adj6 insulin$).ti,ab,ot.
21 ((short$ or fast$ or rapid$) adj1 acting adj6 insulin$).ti,ab,ot.
22 ((novel or new) adj6 insulin$).ti,ab,ot.
23 or/19-22
24 exp insulin/aa
25 Insulin Derivative/ or insulin aspart/ or insulin glulisine/ or insulin lispro/ or recombinant human insulin/ or short acting insulin/ or synthetic insulin/
26 or/24-25
27 23 or 26
28 exp Diabetes Mellitus/
29 diabet$.ti,ab,ot.
30 mellitu$.ti,ab,ot.
31 IDDM.ti,ab,ot.
32 MODY.ti,ab,ot.
33 NIDDM.ti,ab,ot.
34 (T1DM or T2DM or ((T1 or T2) adj1 DM)).ti,ab,ot.
35 (insulin$ depend$ or insulin?depend$ or noninsulin$ or noninsulin?depend$).ti,ab,ot.
36 ((matury or late) adj onset$ adj6 diabet$).ti,ab,ot.
37 (typ$ adj6 diabet$).ti,ab,ot.
38 or/30-37
39 exp Diabetes Insipidus/
40 insipid$.ti,ab,ot.
41 or/39-40
42 28 or 38

(*Continued*)

43 42 or (29 not (41 not 42))
44 (18 or 27) and 43
45 44 use pmoz
46 44 use emed
47 44 use cctr
48 randomized controlled trial.pt.
49 controlled clinical trial.pt.
50 randomized.ab.
51 placebo.ab.
52 clinical trials as topic.sh.
53 randomly.ab.
54 trial.ti.
55 or/48-54
56 exp animals/ not humans.sh.
57 55 not 56
58 crossover procedure/
59 Double Blind Procedure/
60 Randomized Controlled Trial/
61 Single Blind Procedure/
62 random$.ti,ab.
63 factorial$.ti,ab.
64 (crossover$ or cross-over$).ti,ab.
65 placebo$.ti,ab.
66 (doubl$ adj blind$).ti,ab.
67 (singl$ adj blind$).ti,ab.
68 assign$.ti,ab.
69 allocat$.ti,ab.
70 volunteer$.ti,ab.
71 or/58-70
72 45 and 57
73 46 and 71
74 47 or 72 or 73

MEDLINE Ovid - run from January 2015

1. (lyspro* or lispro*).tw.
2. (lys?B28 or B28lys* or (lys* adj1 B28)).tw.
3. (pro?B29 or B29pro* or (pro* adj1 B29)).tw.
4. (humalog* or admelog or liprolog).tw.
5. ("LY 275585" or LY275585).tw.
6. or/1-5
7. (insulin* adj1 aspart*).tw.
8. (asp*B28 or B28asp* or (asp* adj1 B28)).tw.
9. (novorapid* or novolog*).tw.
10. or/7-9
11. (glulisin* or glulysin*).tw.
12. (glu?B29 or B29Glu* or (glu* adj1 B29)).tw.
13. (lys*B3 or B3lys* or (lys* adj1 B3)).tw.
14. apidra*.tw.

(*Continued*)

15. "HMR 1964".tw.
16. or/11-15
17. insulin aspart/ or insulin glulisine/ or insulin lispro/ or insulin, short-acting/
18. ((shortacting or fastacting or rapidacting) adj3 insulin*).tw
19. ((short* or fast* or rapid*) adj1 acting adj3 insulin*).tw
20. or/17-19
21. 6 or 10 or 16 or 20
22. exp Diabetes Mellitus, Type 2/
23. diabet*.tw.
24. (MODY or NIDDM or T2D* or (T2 adj1 DM)).tw.
25. or/22-24
26. 21 and 25

[Cochrane Handbook 2008 RCT filter - sensitivity maximizing version]

27. randomized controlled trial.pt.
28. controlled clinical trial.pt.
29. randomi?ed.ab.
30. placebo.ab.
31. drug therapy.fs.
32. randomly.ab.
33. trial.ab.
34. groups.ab.
35. or/27-31
36. exp animals/ not humans/
37. 35 not 36
38. 26 and 37

*[*Wong 2006a*- systematic reviews filter - SensSpec version]*

39. meta analysis.mp,pt. or review.pt. or search*.tw.
40. 26 and 39
41. 38 or 40
42. limit 41 to yr="2015-Current"
43. remove duplicates from 42

Embase Ovid - run from January 2015

1. (lyspro* or lispro*).tw.
2. (lys?B28 or B28lys* or (lys* adj1 B28)).tw.
3. (pro?B29 or B29pro* or (pro* adj1 B29)).tw.
4. (humalog* or admelog or liprolog).tw.
5. ("LY 275585" or LY275585).tw.
6. or/1-5
7. (insulin* adj1 aspart*).tw.
8. (asp*B28 or B28asp* or (asp* adj1 B28)).tw.
9. (novorapid* or novolog*).tw.
10. or/7-9
11. (glulisin* or glulysin*).tw.
12. (glu?B29 or B29Glu* or (glu* adj1 B29)).tw.
13. (lys*B3 or B3lys* or (lys* adj1 B3)).tw.
14. apidra*.tw.
15. "HMR 1964".tw.

(*Continued*)

16. or/11-15
17. ((shortacting or fastacting or rapidacting) adj3 insulin*).tw
18. ((short* or fast* or rapid*) adj1 acting adj3 insulin*).tw
19. or/17-18
20. 6 or 10 or 16 or 19
21. non insulin dependent diabetes mellitus/
22. diabet*.tw.
23. (MODY or NIDDM or T2D* or (T2 adj1 DM)).tw.
24. or/21-23
25. 20 and 24
[Wong 2006b "sound treatment studies" filter - best optimization of sens. and spec. version]
26. random*.tw. or placebo*.mp. or double-blind*.tw.
27. 25 and 26
28. (2015* or 2016* or 2017*).dc.
29. 27 and 28
30. remove duplicates from 29

Cochrane Register of Studies Online (CRSO) - run 31 October 2018

1. (lyspro* or lispro*):TI,AB,KY
2. (lys?B28 or B28lys* or (lys* adj1 B28)):TI,AB,KY
3. (pro?B29 or B29pro* or (pro* adj1 B29)):TI,AB,KY
4. (humalog* or admelog or liprolog):TI,AB,KY
5. ("LY 275585" or LY275585):TI,AB,KY
6. #1 or #2 or #3 or #4 or #5
7. (insulin* adj1 aspart*):TI,AB,KY
8. (asp*B28 or B28asp* or (asp* adj1 B28)):TI,AB,KY
9. (novorapid* or novolog*):TI,AB,KY
10. #7 or #8 or #9
11. (glulisin* or glulysin*):TI,AB,KY
12. (glu?B29 or B29Glu* or (glu* adj1 B29)):TI,AB,KY
13. (lys*B3 or B3lys* or (lys* adj1 B3)):TI,AB,KY
14. apidra*:TI,AB,KY
15. "HMR 1964":TI,AB,KY
16. #11 or #12 or #13 or #14 or #15
17. MESH DESCRIPTOR Insulin Aspart
18. MESH DESCRIPTOR Insulin Glulisine
19. MESH DESCRIPTOR Insulin Lispro
20. MESH DESCRIPTOR Insulin, Short-Acting
21. ((shortacting or fastacting or rapidacting) adj3 insulin*):TI,AB,KY
22. ((short* or fast* or rapid*) adj1 acting adj3 insulin*):TI,AB,KY
23. #17 or #18 or #19 or #20 or #21 or #22
24. #6 or #10 or #16 or #23
25. MESH DESCRIPTOR Diabetes Mellitus, Type 2 EXPLODE ALL TREES
26. diabet*:TI,AB,KY
27. (MODY or NIDDM or T2D* or (T2 adj1 DM)):TI,AB,KY
28. #25 or #26 OR #27
29. #24 and #28
30. 2015 TO 2017:YR

(*Continued*)

31. #29 AND #30
ICTRP (advanced search) - run on 31 October 2018
diabet* AND lispro* OR diabet* AND lyspro* OR diabet* AND humalog* OR diabet* AND admelog* OR diabet* AND liprolog* OR diabet* AND aspart OR diabet* AND novorapid* OR diabet* AND novolog* OR diabet* AND glulisin* OR diabet* AND glulysin* OR diabet* AND apidra* OR T2D* AND lispro* OR T2D* AND lyspro* OR T2D* AND humalog* OR T2D* AND admelog* OR T2D* AND liprolog* OR T2D* AND aspart OR T2D* AND novorapid* OR T2D* AND novolog* OR T2D* AND glulisin* OR T2D* AND glulysin* OR T2D* AND apidra*
ClinicalTrials.gov (expert search) - run on 31 October 2018
(lyspro OR lispro OR humalog OR admelog OR liprolog OR "LY 275585" OR "LY275585" OR aspart OR novorapid OR novolog OR glulisine OR glulisin OR glulysine OR apidra OR "HMR 1964" OR "short acting insulin" OR "fast acting insulin" OR "rapid acting insulin") [TREATMENT] AND(diabetes OR diabetics OR MODY OR NIDDM OR T2D OR T2DM OR "T2 DM") [DISEASE] AND EXACT "Interventional" [STUDY-TYPES]

Appendix 2. Assessment of risk of bias

Risk of bias domains
1. Random sequence generation (selection bias due to inadequate generation of a randomised sequence) For each included trial, we described the method used to generate the allocation sequence in sufficient detail to enable assessment of whether it should produce comparable groups • Low risk of bias: used computer-generated random numbers or a random number table. Drawing of lots, tossing a coin, shuffling cards or envelopes, and throwing dice were adequate if an independent person, who was not otherwise involved in the trial, performed this. We considered the use of the minimisation technique as equivalent to being random. • Unclear risk of bias: insufficient information about the sequence generation process • High risk of bias: the sequence generation method was non-random or quasi-random (e.g. sequence generated by odd or even

date of birth; sequence generated by some rule based on date (or day) of admission; sequence generated by some rule based on hospital or clinic record number; allocation by judgement of the clinician; allocation by preference of the participant; allocation based on the results of a laboratory test or a series of tests; or allocation by availability of the intervention).

2. Allocation concealment (selection bias due to inadequate concealment of allocation prior to assignment) - assessment at trial level

For each included trial, we described the method used to conceal allocation to interventions prior to assignment, and we assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment

- Low risk of bias: central allocation (including telephone, interactive voice-recorder, internet-based, and pharmacy-controlled randomisation); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes
- Unclear risk of bias: insufficient information about the allocation concealment
- High risk of bias: using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards; alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure

We also evaluated trial baseline data to incorporate assessment of baseline imbalance into the 'Risk of bias' judgement for selection bias (Corbett 2014; Egbewale 2014; Riley 2013). Chance imbalances may also affect judgements on the risk of attrition bias. In the case of unadjusted analyses, we distinguished between trials we rated as at low risk of bias on the basis of both randomisation methods and baseline similarity, and trials we judged as at low risk of bias on the basis of baseline similarity alone (Corbett 2014). We re-classified judgements of unclear, low, or high risk of selection bias as specified in Appendix 4.

3. Blinding of participants and study personnel (performance bias due to knowledge of the allocated interventions by participants and personnel during the trial)

We evaluated the risk of detection bias separately for each outcome (Hróbjartsson 2013). We noted whether endpoints were self-reported, investigator-assessed, or adjudicated outcome measures

- Low risk of bias: blinding of participants and key study personnel was ensured, and it was unlikely that the blinding could have been broken; no blinding or incomplete blinding, but we judged that the outcome was unlikely to have been influenced by lack of blinding.
- Unclear risk of bias: insufficient information about the blinding of participants and study personnel; the trial did not address this outcome
- High risk of bias: no blinding or incomplete blinding, and the outcome was likely to have been influenced by lack of blinding; blinding of trial participants and key personnel attempted, but likely that the blinding could have been broken, and the outcome was likely to be influenced by lack of blinding

4. Blinding of outcome assessment (detection bias due to knowledge of the allocated interventions by outcome assessment)

We evaluated the risk of detection bias separately for each outcome (Hróbjartsson 2013). We noted whether endpoints were self-reported, investigator-assessed, or adjudicated outcome measures

- Low risk of bias: blinding of outcome assessment was ensured, and it was unlikely that the blinding could have been broken; no blinding of outcome assessment, but we judged that the outcome measurement was unlikely to have been influenced by lack of blinding.
- Unclear risk of bias: insufficient information about the blinding of outcome assessors; the trial did not address this outcome.
- High risk of bias: no blinding of outcome assessment, and the outcome measurement was likely to have been influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding.

5. Incomplete outcome data (attrition bias due to amount, nature, or handling of incomplete outcome data)

For each included trial, each outcome, or both, we described the completeness of data, including attrition and exclusions from the analyses. We stated whether the trial reported attrition and exclusions, and the number of participants included in the analysis at each stage (compared with the number of randomised participants per intervention or comparator groups). We also noted if the trial reported the reasons for attrition or exclusion, and whether missing data were balanced across groups, or were related to outcomes. We considered the implications of missing outcome data per outcome, such as high dropout rates (e.g. above 15%), or disparate attrition rates (e.g. difference of 10% or more between trial arms)

- Low risk of bias: no missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to introduce bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed

(*Continued*)

event risk was not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (mean difference or standardised mean difference) among missing outcomes was not enough to have a clinically relevant impact on observed effect size; appropriate methods, such as multiple imputation, were used to handle missing data.

- Unclear risk of bias: insufficient information to assess whether missing data, in combination with the method used to handle missing data, were likely to induce bias; the trial did not address this outcome.
- High risk of bias: reason for missing outcome data was likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk was enough to induce clinically relevant bias in the intervention effect estimate; for continuous outcome data, plausible effect size (mean difference or standardised mean difference) among missing outcomes was enough to induce clinically-relevant bias in observed effect size; 'as-treated' or similar analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.

6. Selective reporting (reporting bias due to selective outcome reporting)

We assessed outcome reporting bias by integrating the results of the Appendix 7 'Matrix of trial endpoints (publications and trial documents)' (Boutron 2014; Jones 2015; Mathieu 2009)), with those of the Appendix 8 'High risk of outcome reporting bias according to ORBIT classification' (Kirkham 2010). This analysis formed the basis for the judgement of selective reporting

- Low risk of bias: the trial protocol was available and all of the trial's pre-specified (primary and secondary) outcomes that were of interest in the review had been reported in the pre-specified way; the study protocol was unavailable, but it was clear that the published reports included all expected outcomes (ORBIT classification).
- Unclear risk of bias: insufficient information about selective reporting
- High risk of bias: not all of the trial's pre-specified primary outcomes were reported; one or more primary outcomes were reported using measurements, analysis methods, or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting was provided, such as an unexpected adverse effect); one or more outcomes of interest in the Cochrane Review were reported incompletely, so that we could not include them in a meta-analysis; the trial report failed to include results for a key outcome that we would expect to have been reported for such a trial (ORBIT classification).

7. Other bias

- Low risk of bias: the trial appeared to be free of other sources of bias.
- Unclear risk of bias: there was insufficient information to assess whether an important risk of bias existed; insufficient rationale or evidence that an identified problem introduced bias.
- High risk of bias: the trial had a potential source of bias related to the specific trial design used; the trial had been claimed to have been fraudulent; or the trial had some other serious problem.

Appendix 3. Selection bias decisions

Selection bias decisions for trials that reported unadjusted analyses: comparison of results obtained using method details alone with results using method details and trial baseline information[a]

Reported randomisation and allocation concealment methods	Risk of bias judgement using methods reporting	Information gained from study characteristics data	Ris of bias using baseline information and methods reporting
Unclear methods	Unclear risk	Baseline imbalances present for important prognostic variable (s)	**High risk**

(*Continued*)

		Groups appear similar at baseline for all important prognostic variables	**Low risk**
		Limited or no baseline details	Unclear risk
Would generate a truly random sample, with robust allocation concealment	Low risk	Baseline imbalances present for important prognostic variable (s)	**Unclear risk**[b]
		Groups appear similar at baseline for all important prognostic variables	Low risk
		Limited baseline details, showing balance in some important prognostic variables[c]	Low risk
		No baseline details	**Unclear risk**
Sequence is not truly randomised, or allocation concealment is inadequate	High risk	Baseline imbalances present for important prognostic variable (s)	High risk
		Groups appear similar at baseline for all important prognostic variables	**Low risk**
		Limited baseline details, showing balance in some important prognostic variables[c]	**Unclear risk**
		No baseline details	High risk

[a] Taken from Corbett 2014; judgements highlighted in bold indicate situations in which the addition of baseline assessments would change the judgement about risk of selection bias, compared with using methods reporting alone.
[b] Imbalance identified that appears likely to be due to chance.
[c] Details for the remaining important prognostic variables are not reported

Appendix 4. Description of interventions

Trial ID	Intervention(s)	Comparator(s)
Altuntas 2003	Insulin lispro immediately before meal. NPH insulin before bedtime; target value for the 2-hr postprandial glucose levels: 160 mg/dL (8.9 mmol/L)	RHI 30 to 45 min before meal. NPH insulin before bedtime; target value for the 2-hr postprandial glucose levels: 160 mg/dL (8.9 mmol/L)
Bastyr 2000	Insulin lispro: within 15 min of the meal. NPH human insulin and ultralente human insulin once or twice daily as basal insulin Glycaemic targets: fasting blood glucose values < 7.8 mmol/L (< 140 mg/dL) without hypoglycaemia and maintenance of 2-hr postprandial glucose values < 10 mmol/L (< 180 mg/dL)	Regular human insulin: 30 to 45 min before the meal. NPH human insulin and ultralente human insulin once or twice daily as basal insulin Glycaemic targets: fasting blood glucose values < 7.8 mmol/L (< 140 mg/dL) without hypoglycaemia and maintenance of 2-hr postprandial glucose values < 10 mmol/L (< 180 mg/dL)
Dailey 2004	Subcutaneous injections of insulin glulisine 0 to 15 minutes before breakfast and dinner + twice-daily injections of NPH insulin. Continuation of OADs permitted at stable dose Glycaemic targets: 2-hr postprandial: 6.7 to 8.9 mmol/L; preprandial: 5.0 to 6.7 mmol/L	Subcutaneous injections of RHI 30 to 45 minutes before breakfast and dinner + twice-daily injections of NPH insulin. Continuation of OADs permitted at stable dose Glycaemic targets: 2-hr postprandial: 6.7 to 8.9 mmol/L; preprandial: 5.0 to 6.7 mmol/L
Hermann 2013	Insulin aspart: before each meal by pre-filled syringe; initial dose 8 IU, then titrated to < 140 mg/dL blood glucose postprandial Insulin Detemir (only some participants): initial dose of 8 IU was treated to < 110 mg/dL, fasting blood glucose in the morning after dose titration of insulin aspart	RHI: before each meal by pre-filled syringe; initial dose 8 IU, then titrated to < 140 mg/dL blood glucose postprandial Insulin Detemir (only some participants): initial dose of 8 IU was titrated to < 110 mg/dL, fasting blood glucose in the morning after dose titration of RHI
NCT01650129	Biphasic insulin aspart 50: 100 U/mL injected sc in a twice-daily regimen (immediately before breakfast and dinner). The dosage was adjusted throughout the trial by the investigator, based on the participant's blood glucose. Blood glucose targets not reported	Biphasic human insulin 50/50: 100 U/ml injected sc in a twice-daily regimen (30 minutes before breakfast and dinner). The dosage was adjusted throughout the trial by the investigator, based on the participant's blood glucose. Blood glucose targets not reported
Pfützner 2013	I1: insulin aspart: bolus injections before each main meal; blood glucose level of 2-hr PPG ≤ 135 mg/dL I2: insulin glulisine: bolus injections before each main meal; blood glucose level of 2-hr PPG ≤ 135 mg/dL Both groups: insulin Glargine ± metformin as basal therapy	RHI: bolus injections before each main meal; blood glucose level of 2-hr PPG ≤ 135 mg/dL Insulin Glargine ± metformin as basal therapy
Rayman 2007	Insulin glulisine (pen) at least twice daily before breakfast and dinner, in addition to NPH insulin twice daily with or without OADs Treatment target insulin glulisine: blood glucose 2-hr postprandial 120 to 160 mg/dL (6.7 to 8.9 mmol/L) Treatment target NPH insulin: average preprandial blood glucose 90 to 120 mg/dL (5.0 to 6.7 mmol/L)	RHI (pen) at least twice daily before breakfast and dinner, in addition to NPH insulin twice daily with or without OADs Treatment target RHI: blood glucose 2-hr postprandial 120 to 160 mg/dL (6.7 to 8.9 mmol/L) Treatment target NPH insulin: average preprandial

(*Continued*)

	OAD continued at a stable dose	blood glucose 90 to 120 mg/dL (5.0 to 6.7 mmol/L) OAD continued at a stable dose
Ross 2001	Insulin lispro and NPH insulin at least twice daily, immediately before breakfast and supper (recommended injection site: abdomen, by syringe or pen). Blood glucose target: 2-hr postprandial 8.9 mmol/L	RHI and NPH insulin at least twice daily 30 to 45 minutes before breakfast and supper (recommended injection site: abdomen, by syringe or pen). Blood glucose target: 2-hr postprandial 8.9 mmol/L
Z012 1997	Insulin lispro before every meal; Ultralente 1 to 2 times a day Blood glucose targets: preprandial: < 140 mg/dL; postprandial (2 hr): < 180 mg/dL	RHI before every meal; Ultralente 1 to 2 times a day. Blood glucose targets: preprandial: < 140 mg/dL; postprandial (2 hr): < 180 mg/dL
Z014 1997	Insulin lispro before every meal; NPH 1 to 2 times a day Blood glucose targets: preprandial: < 140 mg/dL; postprandial (2 hr): < 180 mg/dL	RHI before every meal Blood glucose targets: preprandial: < 140 mg/dL; postprandial (2 hr): < 180 mg/dL

C: comparator; **FBG**: fasting blood glucose; **I**: intervention; **IU**: international units; **NPH**: neutral protamine Hagedorn insulin; **OAD**: oral antidiabetic drugs; **PPG**: postprandial glucose; **RHI**: regular human insulin; **sc**: subcutaneous injections

Appendix 5. Baseline characteristics (I)

Trial ID	Intervention(s) and comparator (s)	Duration of intervention	Description of participants	Trial period (year to year)	Country	Setting	Ethnic groups (%)	Duration of diabetes (mean years (SD))
Altuntas 2003	I: insulin lispro	6 months	Insulin naive participants with type 2 diabetes with OAD failure	-	Turkey	-	-	6
	C: RHI							10
Bastyr 2000	I: insulin lispro	12 months	Adults participants with type 2 diabetes who had started insulin therapy within the last two months	1993-1994	USA, Europe, Canada, South Africa	Multicentre	**Clinical trial participants:** White: 76 North Americans: 73 Subset of clinical trial participants who	8

(*Continued*)

							completed **HRQoL:** White: 79 North Americans: 100	
	C: RHI							8
Dailey 2004	I: insulin glulisine	26 weeks	Participants with type 2 diabetes who had been on insulin treatment for at least 6 months	-	Australia, Canada, USA	Multicentre	White: 86 Black: 11 Asian: 2 Multiethnic: 2 Hispanic: 8	15 (8)
	C: RHI						White: 85 Black: 12 Asian: 2 Multiethnic: 1 Hispanic: 6	13 (8)
Hermann 2013	I: insulin aspart	24 months	Insulin naive type 2 diabetic participants who have been treated with oral antidiabetic medication	-	Germany	Multicentre	-	-
	C: RHI						-	-
NCT016501	I: biphasic insulin aspart 50	24 weeks	Participants with type 2 diabetes who had been on insulin treatment for at least 24 weeks	2001	Japan	Multicentre	-	-
	C: biphasic human insulin 50/50						-	-
Pfützner 2013	I1: insulin aspart	6 months	Participants with type 2 diabetes	-	Germany	-	-	-
	I2: insulin glulisine						-	-
	C: RHI						-	-

(*Continued*)

Rayman 2007	I: insulin glulisine	26 weeks	Participants with type 2 diabetes who had been on insulin treatment for at least 6 months	2001-2003	Multinational study in 22 countries (Europe, Oceania, Argentinia, South Africa, Israel)	Multicentre	-[a]	14 (8)
	C: RHI						-[a]	13 (7)
Ross 2001	I: insulin lispro	5.5 months	Insulin naive participants with type 2 diabetes after failure to respond to sulphonylurea	-	Canda	-	-	11 (8)
	C: RHI						-	11 (7)
Z012 1997	I: insulin lispro	12 months	Participants with type 2 diabetes who have been on insulin therapy for at least 2 months	1992-1993	USA, South Africa, Belgium, Canada	Multicentre, outpatient	-	11
	C: RHI						-	12
Z014 1997	I: insulin lispro	12 months	Participants with type 2 diabetes who have been on insulin therapy for at least 2 months	1992-1993	USA, South Africa, Belgium, Canada	Multicentre, outpatient	-	14
	C: RHI						-	12

[a] More Hispanic participants in the RHI group
-: denotes not reported
C: comparator; **HRQoL**: health-related quality of life questionnaire; **I**: intervention; **OAD**: oral antidiabetic drug; **SD**: standard deviation

Appendix 6. Baseline characteristics (II)

Trial ID	Intervention (s) and comparator (s)	Sex (female %)	Age (mean years (SD))	HbA1c (mean % (SD))	BMI (mean kg/m² (SD))	Co-medications, Co-interventions (% of participants)	Comorbidities (% of participants)
Altuntas 2003	I: insulin lispro	-	55 (34)	9.4 (1.5)	31 (-)	-	-
	C: RHI	-	55 (34)	9.6 (1.4)[a]	31 (-)	-	-
Bastyr 2000	I: insulin lispro	43	55 (-)	9.5 (1.9)[b]	28 (-)	-	-
	C: RHI	44	57 (-)	9.6 (1.8)[b]	28 (-)	-	-
Dailey 2004	I: insulin glulisine	44	59 (10)	7.6 (0.9)	35 (7)	-	-
	C: RHI	50	58 (10)	7.5 (1.0)	35 (7)	-	-
Hermann 2013	I: insulin aspart	27	58 (12)	8.7 (1.6)	31.5 (5.8)	-	-
	C: RHI	44	60 (9)	8.7 (1.6)	32.8 (4.8)	-	-
NCT01650129	I: biphasic insulin aspart 50	41	60 (11)	7.8 (1.2)	23 (3)	-	-
	C: biphasic human insulin 50/50	20	60 (10)	7.5 (1.6)	23 (3)	-	-
Pfützner 2013	I1: insulin aspart	9	64 (9)	7.1 (0.6)	32 (5)	-	-
	I2: insulin glulisine					-	-
	C: RHI					-	-
Rayman 2007	I: insulin glulisine	52	60 (9)	7.6 (0.9)	32 (5)[c]	Short-acting insulin: 72 Basal insulin: 60 Mixture insulin: 11 OAD: 34	-

(*Continued*)

	C: RHI	49	60 (10)	7.5 (0.9)	31 (5)	Short-acting insulin: 70 Basal insulin: 63 Mixture insulin: 13 OAD: 34	-
Ross 2001	I: insulin lispro	63	59 (8)	10.7 (1.7)	28 (8)	-	Retinopathy: 11 Neuropathy: 32 Hypertension and peripheral vascular disease: 11
	C: RHI	62	58 (9)	10.6 (1.6)	27 (9)	-	
Z012 1997	I: insulin lispro	56	50 (-)	8.7 (1.5)	29 (-)	-	-
	C: RHI	57	44 (-)	8.8 (1.8)	28 (-)	-	-
Z014 1997	I: insulin lispro	56	48 (-)	8.8 (1.4)	28 (-)	-	-
	C: RHI	55	51 (-)	9.0 (1.6)	29 (-)	-	-

[a] Inconsistency in reporting of HbA1c value between table and text in publication
[b] Measurement 2 weeks after randomisation
[c] According to IQWIG 2005: 31(5), difference possibly due to rounding
-: denotes not reported
BMI: body mass index; **C**: comparator; **HbA1c**: glycosylated haemoglobin A1c; **I**: intervention; **OAD**: oral antidiabetic drugs; **SD**: standard deviation; **SU**: sulphonylurea drugs

Appendix 7. Matrix of study endpoints (trial documents)

Trial ID	Endpoints quoted in trial document(s) (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a]	Trial results available in trial register Yes/No	Endpoints quoted in publication(s)[b,c]	Endpoints quoted in abstract of publication(s)[b,c]

(*Continued*)

Altuntas 2003	**Source:** IQWiG report A05-04[d] **Primary outcome measure(s)**: -	N/A	**Primary outcome measure(s)**: -	**Primary outcome measure(s)**: -
	Secondary outcome measure(s): -		**Secondary outcome measure**(s): -	**Secondary outcome measure**(s): -
	Other outcome measure (s): hypoglycaemia; AEs; HbA1c		**Other outcome measure (s)**: HbA1c; HDL; LDL; triglycerides; total cholesterol; 1 hr- and 2 hr-PPG; FPG; BMI; overall hypoglycaemia	**Other outcome measure (s)**: HbA1c; FPG; PPG; triglycerides; serious hypoglycaemia; overall hypoglycaemia
Bastyr 2000	**Source:** IQWiG report A05-04[d] **Primary outcome measure(s)**: unclear[e]	N/A	**Primary outcome measure(s)**: overall metabolic control; hypoglycaemia	**Primary outcome measure(s)**: -
	Secondary outcome measure(s): -		**Secondary outcome measure**(s): HRQoL	**Secondary outcome measure**(s): -
	Other outcome measure (s): hypoglycaemia; HRQoL; AEs; HbA1c		**Other outcome measure (s)**:	**Other outcome measure (s)**: nocturnal hypoglycaemia;
Dailey 2004	**Source:** IQWiG report A05-04[d] **Primary outcome measure(s)**: HbA1c	N/A	**Primary outcome measure(s)**: HbA1c	**Primary outcome measure(s)**: -
	Secondary outcome measure(s): -		**Secondary outcome measure**(s): -	**Secondary outcome measure**(s): -
	Other outcome measure(s): hypoglycaemia (overall, nocturnal, severe); AEs; treatment satisfaction		**Other outcome measure (s)**: hypoglycaemia (symptomatic, nocturnal, severe); SMBG; insulin dose, OAD use; AEs; insulin antibodies	**Other outcome measure (s)**: HbA1c; PPG; symptomatic hypoglycaemia; weight gain; insulin dose
Hermann 2013	**Source:** N/T		**Primary outcome measure(s)**: -	**Primary outcome measure(s)**: -
			Secondary outcome measure(s): -	**Secondary outcome measure**(s): -

(*Continued*)

			Other outcome measure(s): HbA1c; BMI; waist circumference; FPG; lipids; Adiponectin serum levels; insulin dose; hypoglycaemia	**Other outcome measure (s)**: BMI; FPG; lipids; Adiponectin serum levels; insulin dose;
NCT01650129	**Source:** NCT01650129; BIAsp-1352 study synopsis **Primary outcome measure(s)**: HbA1c	No	**Primary outcome measure(s):** no publication available	**Primary outcome measure(s):** no publication available
	Secondary outcome measure(s): AEs; blood glucose; hypoglycaemia; insulin antibodies; insulin doses; haematology; biochemistry		**Secondary outcome measure(s):** no publication available	**Secondary outcome measure(s):** no publication available
	Other outcome measure (s): -		**Other outcome measure (s):** no publication available	**Other outcome measure (s):** no publication available
	History of changes: 1 documented change; last change 22 February 2017			
Pfützner 2013	**Source:** NCT01417897; EUCTR2011-003733-34-DE **Primary outcome measure(s)**: nitrotyrosine	No	**Primary outcome measure(s)**: no full-text publication available	**Primary outcome measure(s)**:
	Secondary outcome measure(s): skin blood flow; mRNA expression of pro-inflammatory cytokines; insulin; HbA1c; FBG; hypoglycaemia; intact proinsulin		**Secondary outcome measure**(s): no full-text publication available	**Secondary outcome measure**(s):
	Other outcome measure (s): -		**Other outcome measure (s)**: no full-text publication available	**Other outcome measure (s)**: Inflammation and oxidative stress biomarkers; HbA1c
	History of changes: 2 documented change; last change 2 March 2012			

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Rayman 2007	**Source:** IQWiG report A05-04[d] www.iqwig.de/download/A05-04_Abschlussbericht_Kurzwirksame_Insulinanaloga_bei_Typ_2_Diabetes_mellitus.pdf **Primary outcome measure(s)**: HbA1c	N/A	**Primary outcome measure(s)**: HbA1c at study end; safety parameters (AEs, clinical chemistry; lipids; haematology)	**Primary outcome measure(s)**: -
	Secondary outcome measure(s): -		**Secondary outcome measure**(s): HbA1c at week 12 and week 26; SMBG; symptomatic hypoglycaemia; insulin dose	**Secondary outcome measure**(s): -
	Other outcome measure(s): hypoglycaemia (overall, nocturnal, severe); AEs; treatment satisfaction		**Other outcome measure (s)**: -	**Other outcome measure (s)**: HbA1c; PPG; hypoglycaemia (symptomatic; nocturnal)
Ross 2001	**Source:** IQWiG report A05-04[d] **Primary outcome measure(s)**: -	N/A	**Primary outcome measure(s)**: -	**Primary outcome measure(s)**: -
	Secondary outcome measure(s): -		**Secondary outcome measure**(s): -	**Secondary outcome measure**(s): -
	Other outcome measure (s): hypoglycaemia (overall, nocturnal); HRQoL; HbA1c		**Other outcome measure (s)**: PPG; insulin dose; HbA1c; hypoglycaemia (overall, nocturnal); body weight; blood pressure; HRQoL	**Other outcome measure (s)**: PPG; HbA1c; hypoglycaemia (overall, nocturnal); HRQoL
Z012 1997	**Source:** IQWiG report A05-04[d] **Primary outcome measure(s)**: unclear[e]	N/A	**Primary outcome measure(s)**: -	**Primary outcome measure(s)**: -
	Secondary outcome measure(s): -		**Secondary outcome measure**(s): -	**Secondary outcome measure**(s): -
	Other outcome measure (s): hypoglycaemia; AEs; HbA1c		**Other outcome measure (s)**: PPG; hypoglycaemia; HbA1c; FPG; insulin dose; AEs	**Other outcome measure (s)**: PPG; HbA1c

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Z014 1997	**Source:** IQWiG report A05-04[d] **Primary outcome measure(s)**: unclear[e]	N/A	**Primary outcome measure(s)**: -	**Primary outcome measure(s)**: -
	Secondary outcome measure(s): -		**Secondary outcome measure**(s): -	**Secondary outcome measure**(s): -
	Other outcome measure (s): hypoglycaemia; AEs; HbA1c		**Other outcome measure (s)**: PPG; hypoglycaemia; HbA1c; FPG; insulin dose; AEs	**Other outcome measure (s)**: PPG; HbA1c

[a] Trial document(s) refers to all available information from published design papers and sources other than regular publications (e.g. FDA/EMA documents, manufacturer's websites, trial registers)
[b] Publication(s) refers to trial information published in scientific journals (primary reference, duplicate publications, companion documents or multiple reports of a primary trial)
[c] Primary and secondary outcomes refer to verbatim specifications in publication/records. Other outcome measures refer to all outcomes not specified as primary or secondary outcome measures
[d] Information from IQWiG report based on unpublished manufacturer´ s clinical study reports
[e] According to IQWiG report 2005 conflicting informations from the study report: PPG was mentioned as primary endpoint, but power calculation was based on HbA1c, FBG and hypoglycaemia
-: denotes not reported
AE: adverse events; **BMI**: body mass index; **FPG**: fasting plasma glucose; **HbA1c**: glycosylated haemoglobin A1c; **HDL**: high density lipoprotein; **HRQoL**: health related quality of life; **LDL**: low density lipoprotein; **N/A**: not applicable; **N/T**: no trial document available; **OAD**: oral antidiabetic drug; **PPG**: postprandial glucose; **SAE**: serious adverse events; **SMBG**: self-measured blood glucose

Appendix 8. High risk of outcome reporting bias according to ORBIT classification

Trial ID	Outcome	High risk of bias (category A)[a]	High risk of bias (category D)[b]	High risk of bias (category E)[c]	High risk of bias (category G)[d]
Altuntas 2003	All-cause mortality	No	**Yes**	No	No
	Severe hypoglycaemic episodes	No	**Yes**	No	No
	All hypoglycaemic episodes	**Yes**	No	No	No
	Other adverse events	No	**Yes**	No	No
Bastyr 2000	All-cause mortality	No	No	**Yes**	No

(*Continued*)

	Severe hypoglycaemic episodes	No	No	No	**Yes**
	All hypoglycaemic episodes	No	No	**Yes**	No
	HbA1c	No	No	**Yes**	No
	Health-related quality of life	No	**Yes**	No	No
Dailey 2004	N/A				
Hermann 2013	All-cause mortality	No	No	**Yes**	No
	Severe hypoglycaemic episodes	No	No	No	**Yes**
NCT01650129	N/A[e]				
Pfützner 2013	All-cause mortality	No	No	**Yes**	No
	Severe hypoglycaemic episodes	No	**Yes**	No	No
	All hypoglycaemic episodes	No	**Yes**	No	No
Rayman 2007	N/A				
Ross 2001	Severe hypoglycaemic episodes	No	**Yes**	No	No
	Other adverse events	No	No	No	**Yes**
Z012 1997	All-cause mortality	No	**Yes**	No	No
	Severe hypoglycaemic episodes	No	**Yes**	No	No
	Other adverse events	**Yes**	No	No	No
Z014 1997	All-cause mortality	No	**Yes**	No	No
	Severe hypoglycaemic episodes	No	**Yes**	No	No
	Other adverse events	**Yes**	No	No	No

(*Continued*)

[a] Clear that outcome was measured and analysed; trial report states that outcome was analysed but reports only that result was not significant
(Classification A, table 2, Kirkham 2010)
[b] Clear that outcome was measured and analysed; trial report states that outcome was analysed but report no results
(Classification D, table 2, Kirkham 2010)
[c] Clear that outcome was measured but was not necessarily analysed; judgement says likely to have been analysed but not reported because of non-significant results
(Classification E, table 2, Kirkham 2010)
[d] Unclear whether outcome was measured; not mentioned, but clinical judgement says likely to have been measured and analysed but not reported on the basis of non-significant results
(Classification G, table 2, Kirkham 2010)
[e] None of the data have been published, therefore assessment of risk of outcome reporting bias is not applicable
N/A: not applicable; **HbA1c**: glycosylated haemoglobin A1c; **ORBIT**: Outcome Reporting Bias In Trials

Appendix 9. Definition of endpoint measurement (I)

Trial ID	All-cause mortality	Macrovascular complications	Microvascular complications	Severe hypoglycaemia	HbA1c
Altuntas 2003	N/I	N/I	N/I	N/I	ND
Bastyr 2000	N/D	N/I	N/I	ND	ND
Dailey 2004	N/D	N/I	N/I	Severe: symptomatic hypoglycaemia requiring assistance from another person and confirmed by blood glucose < 2.0 mmol/L or associated with prompt recovery following oral carbohydrate, intravenous glucose, or glucagon administration	ND
Hermann 2013	N/I	N/I	N/I	N/I	ND
NCT01650129	N/D	N/I	N/I	Major A: requiring third party assistance Major B: requiring treatment intervention with glucagon or IV glucose	ND

(*Continued*)

Pfützner 2013	N/I	N/I	N/I	N/I	ND
Rayman 2007	N/D	N/I	N/I	Severe: symptoms and requiring assistance by another person and BG < 36 mg/dL (2.0 mmol/L) or prompt recovery with oral carbohydrate or glucose IV or glucagon Severe nocturnal: symptoms and requiring assistance by another person and BG < 36 mg/dL (2.0 mmol/L) or prompt recovery with oral carbohydrate or glucose IV, or glucagon occurring between bedtime and rising in the morning SAE: hypoglycaemia also fulfilling at least one criteria of a SAE	ND
Ross 2001	N/I	N/I	N/I	N/I	ND
Z012 1997	N/D	N/I	N/I	N/D	
Z014 1997	N/D	N/I	N/I	N/D	ND

BG: blood glucose; **HbA1c**: glycosylated haemoglobin A1c; **N/D**: not defined; **N/I**: not investigated; **SAE**: serious adverse events;**IV**: intravenous; **BG**: blood glucose

Appendix 10. Definition of endpoint measurement (II)

Trial ID	Adverse events: hypoglycaemia	Other adverse events	Health-related quality of life	Socioeconomic effects
Altuntas 2003	All: any time a participant had symptoms associated with hypoglycaemia or a BG level < 3.3 mmol/L	N/I	N/I	N/I

(*Continued*)

	Nocturnal: N/D			
Bastyr 2000	All: (1) any time a participant felt he or she was experiencing signs or symptoms that he or she associated with hypoglycaemia; or (2) had a blood glucose measurement < 3.5 mmol/L (63 mg/dL), even if it was not associated with signs, symptoms, or treatment Nocturnal: occurred between midnight and 6:00 a.m.	N/I	Diabetes Quality of Life Clinical Trial Questionnaire (DQLCTQ)	N/I
Dailey 2004	Symptomatic: an event with clinical symptoms resulting from hypoglycaemia Nocturnal symptomatic: symptomatic hypoglycaemia occurring while the participant was asleep (between bedtime and rising in the morning)	N/I	N/I	N/I
Hermann 2013	N/D	N/I	N/I	N/I
NCT01650129	N/D	N/I	N/I	N/I
Pfützner 2013	N/I	N/I	N/I	N/I
Rayman 2007	All: symptoms considered to have resulted from hypoglycaemia Nocturnal: symptoms considered to have resulted from hypoglycaemia occurring between bedtime and rising in the morning	N/I	N/I	N/I
Ross 2001	All: blood glucose value less than 3 mmol/L or the development of 'typical' hypoglycaemic symptoms Severe: any hypoglycaemic	N/I	Diabetes quality of life (DQOL) questionnaire developed for the DCCT: 4 subscales: satisfaction, impact, social or	N/I

(*Continued*)

	event requiring assistance by another person, coma, or seizure		vocational worry, diabetes-related worry	
Z012 1997	All: sign or symptom normally associated with hypoglycaemia, or blood glucose value below 2.0 mmol/L (< 36 mg/dL) As part of safety assessment: number of people with glucagon injection by another person, coma due to hypoglycaemia, and IV glucose injection	N/I	N/I	N/I
Z014 1997	All: sign or symptom normally associated with hypoglycaemia, or blood glucose value below 2.0 mmol/L (< 36 mg/dL) As part of safety assessment: number of people with glucagon injection by another person, coma due to hypoglycaemia, and IV glucose injection	N/I	N/I	N/I

BG: blood glucose; **DCCT**: Diabetes Control and Complications Trial; **EQ-5D-3L**: Euro Q5 Questionnaire 3 level version; **HbA1c**: glycosylated haemoglobin A1c; **ICER**: incremental cost-effectiveness ratio; **N/D**: not defined; **N/I**: not investigated; **QALY**: quality-adjusted life year; **VAS**: visual analogue scale

Appendix 11. Adverse events (I)

Trial ID	Intervention(s) and comparator (s)	Randomised / safety (N)	Deaths (n/N)	All adverse events (n/N (%))	Severe, serious adverse events (n/N (%))	Attrition due to adverse events (n/N (%))	All hypoglycaemic episodes (n/N (%))	Severe hypoglycaemic episodes (n/N (%))
Altuntas 2003	I: insulin lispro	20	-	-	-	0/20	-	-
	C: RHI	20	-	-	-	0/20	-	-

(*Continued*)

Bastyr 2000	I: insulin lispro	186	2/186	-	2/186 (1)[a]	3/186 (2)	-[b]	-[c]
	C: RHI	189	0/189	-	0/189 (0)[a]	4/189 (2)	-[b]	-[c]
Dailey 2004	I: insulin glulisine	-/435	1/435	358/435 (82)	55/435 (13)	5/435 (1)	317/435 (73)[d]	6/416 (1)[d,e]
	C: RHI	-/441	2/441	351/441 (80)	51/441 (12)	6/441 (1)	322/441 (73)[d]	5/420 (1)[d,e]
	all:	878[f] /876	3/876	709/876 (81)	106/876 (12)	11/876 (1)	639/876 (73)[d]	11/836[d,e]
Hermann 2013	I: insulin aspart	18	-[g]	-	-	-[h]	-[i]	-
	C: RHI	11	-[g]	-	-	-[h]	-[i]	-
NCT016501	I: biphasic insulin aspart 50	58	0/58	53/58 (91)	5/58 (9)	2/58 (3)	40/58 (69)	2/58 (3)[j]
	C: biphasic human insulin 50/50	26[f] /25	0/25	22/25 (88)	1/25 (4)	1/25 (4)	16/25 (64)	1/25 (4)
Pfützner 2013	I1: insulin aspart	4	-[g]	-	-	-	-	-
	I2: insulin glulisine	4	-[g]	-	-	-	-	-
	C: RHI	4	-[g]	-	-	-	-	-
Rayman 2007	I: insulin glulisine	448	2/448	260/448 (58)	43/448 (10)[k]	9/448 (2)	140[l] /-[m] (33)	6/-[n] (1)
	C: RHI	444[o] /442	1/442	260/442 (59)	52/442 (12)[k]	3/442 (1)	144[l] /-[m] (33)	14/-[n] (3)
	All	892/890	3/890	520/890 (58)	95/890 (11)[k]	12/890 (1)	284/- (33)	20/- (-)
Ross 2001	I: insulin lispro	70	-	-	-	1/148 (1)	-	-

(*Continued*)

	C: RHI	78	-	-	-		-	-
Z012 1997	I: insulin lispro	72	0/72	-	0/72 (0)	0/72 (0)	-[p]	-[q]
	C: RHI	73	0/73	-	0/73 (0)	1/73 (1)	-[p]	-[q]
Z014 1997	I: insulin lispro	73	0/73	-	3/73 (4)	3/73 (4)	-[r]	-[s]
	C: RHI	77	0/77	-	0/77 (0)	3/77 (4)	-[r]	-[s]

[a] Excluding hyper- and hypoglycaemic events
[b] Events/participant/30 days (mean ± standard deviation) at study end: 0.9 ± 2.1 (lispro) vs 0.8 ± 1.9 (RHI); P = 0.39
[c] Inconsistent with other numbers presented in the same table in NCT01650129
[d] Based on author's response in IQWIG 2005
[e] Only for the period month 4 to study end
[f] One participant did not receive treatment
[g] Not explicitly reported, but likely zero
[h] Not explicitly reported, but the results sections leads us to assume that there were no dropouts
[i] Number of participants with up to three episodes per year: aspart: 5/18, RHI: 3/11
[j] RHI: coma: 2 participants; IV glucose: 1 participant, glucagon: 1 participant; lispro: coma: 0 participants, IV glucose: 1 participant, glucagon: 1 participant
[k] Inconsistent with information from IQWIG 2005: serious adverse events (other than severe hypo- and hyperglycaemia): 38 (8.5%) and 40 (9.0%); adding the number of serious hypoglycaemia (6 and 14) to these numbers results in a higher number than what was reported in Rayman 2007
[l] Months 4 to 6 only, according to IQWIG 2005, 226 (glulisine) and 240 (RHI) participants with at least one episode over a period of 6 months
[m] The number of participants presented in table 4 of the publication cannot be correct (Rayman 2007)
[n] According to IQWIG 2005, the total number of participants should be 448 and 442 (deducted from percentage numbers presented in the original study report), but in the same table, it is also reported that there are 21 and 8 missing values
[o] Two participants did not receive treatment
[p] Events/participant/30 days (mean ± standard deviation) at study end: 2.1 ± 3.2 (lispro) vs 2.5 ± 4.6 (RHI); P = 0.51
[q] RHI: coma: 1 participant; IV glucose: 2 participants, glucagon: 0 participants; lispro: coma: 1 participant, IV glucose: 2 participants, glucagon: 0 participants
[r] Events/participant/30 days (mean ± standard deviation) at study end: 0.8 ± 2.3 (lispro) vs 0.8 ± 2.1 (RHI); P = 0.65
[s] RHI: coma: 2 participants; IV glucose: 1 participant, glucagon: 0 participants; lispro: coma: 1 participant, IV glucose: 1 participant, glucagon: 0 participants
-: denotes not reported
C: comparator; **I**: intervention; **RHI**: regular human insulin; **IV**: intravenous

Appendix 12. Adverse events (II)

Trial ID	Intervention(s) and comparator(s)	Randomised / safety (N)	Hypoglycaemic episodes, severe nocturnal (n/N (%))	Hypoglycaemic episodes, SAE (n/N (%))	Hypoglycaemic episodes, nocturnal (n/N (%))	Hyperglycaemic/ketoacidotic episodes (n/N (%))
Altuntas 2003	I: insulin lispro	20	-	-	-	-
	C: RHI	20	-	-	-	-
Bastyr 2000	I: insulin lispro	186	-	-	-	3/186 (2)
	C: RHI	189	-	-	-	3/189 (2)
Dailey 2004	I: insulin glulisine	-/435	-	-	89/416[a,b]	-
	C: RHI	-/441	-	-	103/420[a,b]	-
	All	878[c]/876	-	-	192/836[a,b]	-
Hermann 2013	I: insulin aspart	18	-	-	-	-
	C: RHI	11	-	-	-	-
NCT01650129	I: biphasic insulin aspart 50	58	-	-	-	-
	C: biphasic human insulin 50/50	26	-	-	-	-
Pfützner 2013	I_1: insulin aspart	4	-	-	-	-
	I_2: insulin glulisine	4	-	-	-	-
	C: RHI	4	-	-	-	-
Rayman 2007	I: insulin glulisine	448	3/-[d] (1)	-	95/-[d] (21)	-
	C: RHI	444[c]/442	5/-[d] (1)	-	100/-[d] (23)	-
Ross 2001	I: insulin lispro	70	-	-	-	-
	C: RHI	78	-	-	-	-
Z012 1997	I: insulin lispro	72	-	-	-	0/72 (0)

(*Continued*)

	C: RHI	73	-	-	-	1/73 (1)
Z014 1997	I: insulin lispro	73	-	-	-	1/73 (1)
	C: RHI	77	-	-	-	1/77 (1)

[a] Based on author's response in IQWIG 2005
[b] Only for the period month 4 to study end
[c] Two participants not exposed to treatment
[d] According to IQWIG 2005, the total number of participants should be 448 and 442 (deducted from percentage numbers presented in the original study report), but in the same table it is also reported that there are 21 and 8 missing values
-: denotes not reported
C: comparator; **I**: intervention; **RHI**: regular human insulin; **SAE**: serious adverse events

Appendix 13. Survey of trial investigators providing information on included trials and trials awaiting classification

Trial ID	Study author contacted	Study author replied	Study author asked for additional information	Study author provided data
Altuntas 2003	28 November 2012	No answer	N/A	N/A
Bastyr 2000	28 November 2012	No answer	N/A	N/A
Dailey 2004	28 November 2012	No answer	N/A	N/A
Hermann 2013	21 November 2012	Yes	Yes	The author provided additional information regarding the design of the trial
NCT01650129	5 March 2013	No answer	N/A	N/A
Pfützner 2013	22 January 2013[a]	No answer	N/A	N/A
Rayman 2007	28 November 2012	No answer	N/A	N/A
Ross 2001	28 November 2012	No answer	N/A	N/A
Z012 1997	28 November 2012	No answer	N/A	N/A
Z014 1997	28 November 2012	No answer	N/A	N/A
NCT01500850	13 November 2017	No answer	N/A	N/A

(*Continued*)

[a] We contacted the 'ikfe CRO GmbH', which forwarded our request to Dr Pfützner
N/A: not applicable

Appendix 14. Health-related quality of life: instruments

Instrument	Dimensions (subscales) (no. of items)	Validated instrument	Answer options	Scores	Minimum score Maximum score	Weighting of scores	Direction of scales	Minimum important difference
Diabetes quality of life (DQOL) questionnaire (S) (used in Ross 2001)	Satisfaction (18) Impact (23) Social or vocational worry (7) Diabetesrelated worry (7)	Yes	5-point scale	Overall score Scores for each subscale	Minimum index: 1 Maximum index: 5	No	Lower index score means better assessment	-
Diabetes Quality of Life Clinical Trial Questionnaire (DQLCTQ) (S) (used in Bastyr 2000)	General health (1) Comparative health (1) Physical functioning (6) Global role functioning (2) Social functioning (1) General social functioning (1) Energy or fatigue (5) Health distress (6) Mental health (5) Diabetes quality	Yes	100-point scale	Overall score Scores for each domain	Minimum index: 0.1 Maximum index: 1.0	No	Higher index score means better assessment	-

(*Continued*)

	of life (59) Hypoglycemic fear survey (17) Treatment satisfaction (3) Treatment flexibility (10) Social stigma (4) Symptom frequency and bothersomeness (14) Self-efficacy (3) Background factors (4)							

-: denotes not reported
G: generic; **S**: specific; **SF**: short-form health survey; **VAS**: visual analogue scale

Appendix 15. Checklist to aid consistency and reproducibility of GRADE assessments

Short-acting insulin analogues vs regular human insulin		**All-cause mortality**	**Macrovascular complications**	**Microvascular complications**	**Severe hypoglycaemic episodes**	**HbA1c**	**Adverse events other than severe hypoglycaemic episodes (all non-severe hypoglycaemic events)**	**Health-related quality of life**	**Socioeconomic effects**
Trial limitations (risk of bias)[a]	Was random sequence generation used	Yes	N/A	N/A	Yes	Yes	Yes	Yes	N/A

(*Continued*)

	(i.e. no potential for selection bias)?							
	Was allocation concealment used (i.e. no potential for selection bias)?	Yes			Yes	Yes	Yes	Yes
	Was there blinding of participants and personnel (i.e. no potential for performance bias) , or outcome not likely to be influenced by lack of blinding?	Yes			No ()	Unclear	No ()	No ()
	Was there blinding of outcome assessment (i.e. no potential for detection bias), or was outcome measurement not likely to be influenced by lack of blinding?	Yes			No ()	Yes	No ()	No ()

(*Continued*)

	Was an objective outcome used?	Yes		Yes	Yes	Unclear	Yes
	Were more than 80% of participants enrolled in trials included in the analysis (i.e. no potential reporting bias)?[b]	Yes		Yes	Yes	Yes	Unclear
	Were data reported consistently for the outcomes of interest (i.e. no potential selective reporting)?	Yes		Yes	Yes	Yes	Yes
	No other biases reported (i.e. no potential of other bias)?	Unclear		Unclear	Unclear	Unclear	Yes
	Did the trials end up as scheduled (i.e. not stopped early)?	Yes		Yes	Yes	Yes	Yes
Inconsistency[c]	Point estimates did not vary	N/A		N/A	Yes	Yes	N/A

(*Continued*)

	widely?							
	To what extent did confidence intervals overlap (substantial: all confidence intervals overlapped at least one of the included trials' point estimate; some: confidence intervals overlapped but not all overlapped at least one point estimate; no: at least one outlier: where the confidence intervals of some of the trials do not overlap with those of most included trials)?	N/A			N/A	Substantial	Some	N/A
	Was the direction of effect consistent?	Unclear			N/A	No ()	No ()	N/A
	What was the magnitude of statistical heterogene-	Low			N/A	Low	Low	N/A

(*Continued*)

	ity (as measured by I^2) - low (I^2 < 40%), moderate (I^2 40% to 60%), high I^2 > 60%)?							
	Was the test for heterogeneity statistically significant (P < 0.1)?	Not statistically significant			N/A	Not statistically significant	Not statistically significant	N/A
Indirectness	Were the populations in included trials applicable to the decision context?	Highly applicable			Highly applicable	Highly applicable	Highly applicable	Highly applicable
	Were the interventions in the included trials applicable to the decision context?	Highly applicable			Highly applicable	Highly applicable	Highly applicable	Highly applicable
	Was the included outcome not a surrogate outcome?	Yes			Yes	Unclear	No ()	Unclear
	Was the outcome timeframe sufficient?	Sufficient			Sufficient	Sufficient	Sufficient	Sufficient

(*Continued*)

	Were the conclusions based on direct comparisons?	Yes		Yes	Yes	Yes	Yes
Imprecision[d]	Was the confidence interval for the pooled estimate not consistent with benefit and harm?	No ()		N/A	No ()	Unclear	N/A
	What is the magnitude of the median sample size (high: 300 participants, intermediate: 100 to 300 participants, low: < 100 participants)?[b]	Intermediate		Intermediate	Intermediate	Intermediate	Intermediate
	What was the magnitude of the number of included trials (large: > 10 trials, moderate: 5 to 10 trials, small: < 5 trials)?[b]	Moderate		Moderate	Moderate	Moderate	Small ()
	Was the outcome a com-	No ()		Yes	N/A	Yes	N/A

(*Continued*)

	mon event (e.g. occurs more than 1/100)?							
Publication bias[e]	Was a comprehensive search conducted?	Yes			Yes	Yes	Yes	Yes
	Was grey literature searched?	Yes			Yes	Yes	Yes	Yes
	Were no restrictions applied to study selection on the basis of language?	Yes			Yes	Yes	Yes	Yes
	There was no industry influence on trials included in the review?	No ()			No ()	No ()	No ()	No ()
	There was no evidence of funnel plot asymmetry?	N/A			N/A	N/A	N/A	N/A
	There was no discrepancy in findings between published and unpublished trials?	N/A			N/A	N/A	N/A	N/A

(*Continued*)

[a] Questions on risk of bias are answered in relation to the majority of the aggregated evidence in the meta-analysis rather than to individual trials
[b] Depends on the context of the systematic review area
[c] Questions on inconsistency are primarily based on visual assessment of forest plots and the statistical quantification of heterogeneity, based on I^2
[d] When judging the width of the confidence interval, it is recommended to use a clinical decision threshold to assess whether the imprecision is clinically meaningful
[e] Questions address comprehensiveness of the search strategy, industry influence, funnel plot asymmetry and discrepancies between published and unpublished trials
(): key item for potential downgrading the certainty of the evidence (GRADE) as shown in the footnotes of the 'Summary of finding' table(s)
HbA1c: glycosylated haemoglobin A1c; **N/A**: not applicable

WHAT'S NEW

Date	Event	Description
1 November 2018	New search has been performed	This review is an update of the former review 'Short-acting insulin analogues versus regular human insulin in patients with diabetes mellitus', which has been withdrawn and split into two Cochrane Reviews on short-acting insulin analogues versus regular human insulin for type 1 and type 2 diabetes mellitus

HISTORY

Review first published: Issue 12, 2018

Date	Event	Description
21 September 2005	New search has been performed	This review is an update of the review published in 2004, Issue 4 (second update) A highly sensitive search applying the same search strategy as used for the original review was performed from 01 October 2003 to 21 September 2005 (adding the search terms for glulisine, which is new on the market): 386 potentially relevant abstracts were identified and screened. 375 of these were excluded by consensus. Eleven publications were potentially appropriate for this review, 4 of which were excluded by consensus because they were not randomised, had no comparable insulin regimens, or analogues were not compared with regular insulin. Finally, seven new studies fulfilled the inclusion criteria. For further details, see figure 9 presenting the flow chart according to the QUOROM statement

(*Continued*)

		After including the 7 new studies in the analyses, the conclusion from the first review remained unchanged
31 December 2003	New search has been performed	first update

CONTRIBUTIONS OF AUTHORS

Birgit Fullerton (BF) - update of the review: literature screening, data extraction, data analysis, manuscript draft, and review of manuscript

Andrea Siebenhofer (AS) - update of the review: protocol development, literature screening, review of manuscript

Klaus Jeitler (KJ) - update of the review: protocol development, searching for trials, literature screening, review of manuscript

Karl Horvath (KH) - update of the review: literature screening, review of manuscript

Thomas Semlitsch (TS) - update of the review: literature screening, review of manuscript

Andrea Berghold (AB): initial review: protocol development, data analysis, development of final review; update of the review: data analysis, review of manuscript

Ferdinand M Gerlach (FMG): protocol development, development of final review

DECLARATIONS OF INTEREST

BF: none known.

AS: was involved in the preparation of a report on the effects of long-acting insulin analogues versus other basal insulins in the therapy of patients with type 1 and type 2 diabetes mellitus for IQWiG, the German Institute for Quality and Efficiency in Health Care.

KJ: was involved in the preparation of the reports on short-acting insulin analogues for the treatment of diabetes mellitus for the Institute for Quality and Efficiency in Health Care.

KH: has received payment for lectures, travel/accommodations/meeting expenses and consultancy from various sources (Novo Nordisk, Novartis, Medtronic, Eli Lilly, Sanofi Aventis, Merck Sharp & Dohme, AstraZeneca).

TS: none known.

AB: none known.

FMG: none known.

SOURCES OF SUPPORT

Internal sources

- Medical University of Graz, Austria.

In-kind office equipment

- Institute of General Practice, Goethe University Frankfurt, Germany.

In-kind office equipment

External sources

- Institute for Quality and Efficiency in Health Care (IQWiG), Germany.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Several methodological improvements such as the integration of a summary of findings table as demanded by the CMED Group were implemented in this review update.

A major change from the original review was that now trials had to have a minimum duration of intervention of 24 weeks, compared with four weeks in the former Cochrane Review. Because we focused our review update on patient-important outcome measures, such as microvascular and macrovascular complications, a longer time period of interventions appeared meaningful. This also concurs with the requirement of the European Medicines Agency for confirmatory trials in the treatment of diabetes mellitus (EMA 2002).

NOTES

The former Cochrane Review 'Short-acting insulin analogues versus regular human insulin in patients with diabetes mellitus' (Siebenhofer 2006), has been withdrawn and split into the following Cochrane reviews: 'Short-acting insulin analogues versus regular human insulin for adults with type 1 diabetes mellitus' and 'Short-acting insulin analogues versus regular human insulin for adult, non-pregnant persons with type 2 diabetes mellitus'.