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REVIEW OF THE EVIDENCE COMPARING INSULIN (HUMAN OR ANIMAL) WITH ANALOGUE INSULINS

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Abbreviations

CI	confidence interval
HbA1c	haemoglobin A1c (glycosylated haemoglobin)
HR	hazard ratio
ICER	incremental cost-effectiveness ratio
LYG	life years gained
NPH	neutral protamine Hagedorn
OR	odds ratio
QALY	quality adjusted life year
RR	relative risk
WMD	weighted mean difference

Executive Summary

Background: The WHO has requested an assessment of the efficacy and safety of analogue insulins, in comparison to human or animal insulin, for the treatment of Type 1 and 2 diabetes. Given a recent comprehensive review of analogue insulins (Singh et al., 2009), the current review focused on updating the evidence available in the 2009 review.

Methods: A systematic review of the literature was conducted to obtain relevant trials of long-acting and rapid-acting analogue insulins in comparison to regular human or animal insulin published since the Singh et al (2009) review. Additional searches were also conducted to identify recent systematic reviews and meta-analyses, studies addressing the association between analogue insulins and cancer, as well as assessments of the cost-effectiveness of analogue insulins.

Results: A total of 35 comparative trials were identified as relevant, however only 8 of these included data that could be used to update the 2009 meta-analyses. Consequently, only 3 of the original comparison were able to be updated. The new data did not alter the conclusions of the Singh et al (2009) review, which indicated that analogue insulins had little advantage over conventional insulins in terms of glycaemic control or reduced hypoglycaemia. Statistically significant advantages associated with analogues are generally less than clinically important minimal differences, and advantages for occurrence of hypoglycaemia are not consistent across comparisons. Recent health technology assessments in the UK and Germany indicated no advantage for long-acting analogue insulins in Type 1 and 2 diabetes. Cost-effectiveness estimates of analogue insulins vary widely, from just over €500/QALY to over £412,000/QALY. Estimates indicating cost-effectiveness are generally specific to a particular population and regimen, while the broader and more comprehensive analyses indicate that analogue insulins appear to lack cost-effectiveness. Reviews of analogue use and cancer risk indicate increased cancer risk in some analyses and no difference with human insulins in other analyses – the methodological and statistical issues with these analyses indicate caution should be used in interpreting the results.

Conclusion: The evidence indicates that across Type 1 and 2 diabetes, for both rapid- and long-acting analogue insulins, there is no clear advantage over human insulins, with inconsistent statistically significant advantages and lack of clinically important benefits. Analogue insulins have not consistently been demonstrated to be cost-effective, and uncertainty remains regarding the association between analogue insulins and increased cancer risk.

1. Objective

To carry out a review of the evidence comparing insulin (human or animal) with analogue insulins, including a meta-analysis of comparative effectiveness and safety if sufficient data are available, as well as the preparation of GRADE tables.

Evidence addressing the cost-effectiveness of analogue insulins as well as the risk of malignancy associated with analogues was also assessed.

The following table provides a list of the analogue insulins and comparator insulins included in this review, as well as the international non-proprietary names (INN) and formulations of the insulins. A range of costs of the insulins and international availability is provided in Attachment 1.

Table 1: Insulins included in the review and INNs

Insulin	INN	Brand name	Formulations
Analogue insulins			
glargine	insulin glargine	Lantus	3mL cartridge 100 IU/mL 3mL cartridge 100IU/mL pre-filled pen 10mL vial 100 IU/mL
detemir	insulin detemir	Levemir	3mL cartridge 100IU/mL pre-filled pen
aspart	insulin aspart	Novorapid	3mL cartridge 100IU/mL pre-filled pen
lispro	insulin lispro	Humalog	3mL cartridge 100 IU/mL 3mL cartridge 100IU/mL pre-filled pen 10mL vial 100 IU/mL
glulisine	insulin glulisine	Apidra	3mL cartridge 100 IU/mL 3mL cartridge 100IU/mL pre-filled pen 10mL vial 100 IU/mL
Insulin			
NPH	insulin isophane	Humulin NPH, Protaphane	3mL cartridge 100 IU/mL 10mL vial 100 IU/mL
regular human insulin	insulin human	Actrapid, Humulin R	3mL cartridge 100 IU/mL 10mL vial 100 IU/mL

2. Methods

2.1 Identification of clinical evidence

2.1.1 Background

A comprehensive systematic review of analogue insulins by Singh et al was published in 2009. This review compared rapid and long-acting analogues with conventional insulins in Type 1, Type 2 and gestational diabetes. Data available as of April 2007, including a total of 68 trials using rapid-acting analogues and 49 trials using long-acting analogues, were used in the analyses. The key results are provided in Table 2 below, with GRADE tables provided in Attachment 4. For outcomes, the Singh et al (2009) review considered weighted mean difference (WMD) in HbA1c level at trial endpoint and the rate of hypoglycaemia (ie number of patients reporting hypoglycaemic events given total group N). Full details of outcomes are provided in Section 2.2.

Table 2: Results from the Singh et al (2009) systematic review of analogue insulins

Comparison	Number of trials/subjects	Results	
		Outcome	Difference (95% CI)
Rapid-acting – Type 1 adults			
lispro vs. regular human	22 trials/6021 subjects 10 trials/4502 subjects 4 trials/725 subjects	HbA1c: Severe hypo: Noct hypo:	WMD=-0.09 (-0.16,-0.02) RR=0.80 (0.67, 0.96) RR=0.51 (0.42, 0.62)
aspart vs. regular human	7 trials/3035subjects 4 trials/1814 subjects	HbA1c: Severe hypo:	WMD=-0.13 (-0.20,-0.07) RR=0.83 (0.65, 1.04)
Rapid-acting – Type 1 children and adolescents			
lispro vs. regular human (children)	4 trials/286 subjects 3 trials/222 subjects 3 trials/234 subjects	HbA1c: Severe hypo: Noct hypo:	WMD=0.14 (-0.18, 0.46) RR=0.69 (0.24, 2.01) RR=0.96 (0.74, 1.26)
lispro vs. regular human (adolescents)	1 trial/926 subjects 1 trial/926 subjects 1 trial/926 subjects	HbA1c: Severe hypo: Noct hypo:	WMD=-0.01 (-0.21, 0.19) RR=1.00 (0.29, 3.43) RR=0.61 (0.57, 0.64)
Long-acting – Type 1 adults			
glargine vs. NPH	11 trials/2728 subjects 7 trials/2227 subjects 5 trials/1943 subjects	HbA1c: Severe hypo: Noct hypo:	WMD=-0.11 (-0.21,-0.02) RR=0.82 (0.52, 1.29) RR=0.97 (0.87, 1.09)
detemir vs. NPH	7 trials/2558 subjects 7 trials/2442 subjects 6 trials/2311 subjects	HbA1c: Severe hypo: Noct hypo:	WMD=-0.06 (-0.13, 0.02) RR=0.74 (0.58, 0.96) RR=0.92 (0.85, 0.98)
detemir+aspart vs. NPH+regular human	1 trial/595 subjects 1 trial/595 subjects 1 trial/595 subjects	HbA1c: Severe hypo: Noct hypo:	WMD=-0.23 (-0.37,-0.09) RR=1.05 (0.56, 1.96) RR=0.65 (0.55, 0.77)
Long-acting – Type 1 children and adolescents			
glargine vs. NPH	4 trials/680 subjects 4 trials/727 subjects 1 trial/349 subjects	HbA1c: Severe hypo: Noct hypo:	WMD=-0.25 (-0.55, 0.05) RR=1.18 (0.59, 2.35) RR=0.71 (0.43, 1.18)
detemir vs. NPH	1 trial/347 subjects 1 trial/347 subjects 1 trial/347 subjects	HbA1c: Severe hypo: Noct hypo:	WMD=0.10 (-0.10, 0.30) RR=0.80 (0.50, 1.28) RR=0.85 (0.77, 0.94)
Rapid-acting – Type 2 adults			
lispro vs. regular human	11 trials/3093 subjects 2 trials/1622 subjects 1 trial/178 subjects	HbA1c: Severe hypo: Noct hypo:	WMD=-0.03 (-0.12, 0.06) RR=0.43 (0.08, 2.37) RR=1.63 (0.71, 3.73)
aspart vs. regular human	6 trials/1031 subjects 1 trial/121 subjects 1 trial/93 subjects	HbA1c: Severe hypo: Noct hypo:	WMD=-0.09 (-0.21, 0.04) RR=0.39 (0.11, 1.36) RR=0.65 (0.28, 1.53)
Long-acting – Type 2 adults			
glargine vs. NPH	1 trial/518 subjects 1 trial/518 subjects	HbA1c: Noct hypo:	WMD=0.28 (0.07, 0.49) RR=0.78 (0.62, 0.98)
glargine+orals vs. NPH+orals	9 trials/3397 subjects 7 trials/2866 subjects 7 trials/2532 subjects	HbA1c: Severe hypo: Noct hypo:	WMD=-0.05 (-0.13, 0.04) RR=0.66 (0.29, 1.48) RR=0.56 (0.47, 0.68)
detemir+orals vs. NPH+orals	3 trials/1159 subjects 2 trials/808 subjects 2 trials/808 subjects	HbA1c: Severe hypo: Noct hypo:	WMD=0.13 (0.03, 0.22) RR=0.75 (0.03, 20.01) RR=0.53 (0.31, 0.91)
detemir+aspart vs. NPH+aspart	1 trial/505 subjects	HbA1c:	WMD=0.10 (-0.18, 0.38)
detemir+aspart vs. NPH+regular human	1 trial/394 subjects 1 trial/394 subjects 1 trial/394 subjects	HbA1c: Severe hypo: Noct hypo:	WMD=0.06 (-0.31, 0.19) RR=1.02 (0.26, 4.02) RR=0.54 (0.30, 0.97)

WMD=weighted mean difference

For glycaemic control, as measured by HbA1c, the Singh et al (2009) review demonstrated statistically significant advantages for analogue insulins in a limited number of comparisons:

- lispro versus regular human insulin (WMD=-0.09; 95% CI: -0.16, -0.02); aspart versus regular human insulin (WMD=-0.13; 95% CI: -0.20, -0.07) in Type 1 adults;
- glargine versus NPH (WMD=-0.11; 95% CI: -0.21, -0.02); detemir and aspart versus NPH and regular insulin (WMD=-0.23; 95% CI: -0.37, -0.09) in Type 1 adults.

The authors of the review noted that all differences (eg -0.09%, -0.13%, -0.11%, which refer to trial endpoint differences in HbA1c level) were smaller than published minimal clinically important differences.

There were no statistically significant advantages for analogue insulins compared to regular insulins in Type 2 patients, while NPH demonstrated a statistically significant advantage over glargine in HbA1c (WMD=0.28; 95% CI: 0.07, 0.49) in Type 2 patients.

For hypoglycaemic events, there were statistically significant advantages for analogue insulins for both Type 1 and Type 2 patients for nocturnal hypoglycaemia, although results were not consistent across insulins (see table above).

The authors concluded that rapid and long-acting insulins contribute little benefit relative to conventional insulins in terms of glycaemic control or reduced hypoglycaemia, and that further long-term studies are required to determine whether analogue insulins reduce the risk of long-term complications of diabetes. The authors also noted that most of the analogue insulin trials had methodological limitations (eg only 10 of 177 included trials had adequate allocation concealment), thus increasing the potential for bias, particularly for patient-reported outcomes such as hypoglycaemia.

Given the breadth of the Singh et al (2009) review it was determined that the current review would focus on updating the analyses presented in the Singh et al (2009) systematic review.

A recent heath technology assessment (Waugh et al., 2010) focused on treatments for Type 2 patients and included an assessment of long-acting insulins. The authors reviewed five already published systematic reviews as well as five individual trials, and concluded that glycaemic control, as measured by HbA1c, was equivalent across glargine, detemir and NPH. While both glargine and detemir had advantages for the occurrence of hypoglycaemia, particularly nocturnal hypoglycaemia, the effect size was not clear in the published reviews.

The German Institute for Quality and Efficiency in Health care (IQWiG) published a report on long-acting analogue insulins for the treatment of Type 1 diabetes in 2010, with reports on long-acting analogues for Type 2 diabetes and rapid-acting analogues for Type 1 and Type 2 diabetes being

published in 2009, 2007 and 2005, respectively. While the full reports are provided in German only, English executive summaries are available online. The 2010 report states that due to the close relationship between hypoglycaemia and HbA1c value, conclusions regarding the benefit of an agent were drawn only on the basis of a conjoint assessment of both outcomes. The executive summary of the report does not provide any details on the format of the conjoint analyses. The conclusions drawn by the reports are as follows:

Long-acting analogues Type 1 patients (2010): for both insulin glargine and detemir compared to NPH in adult patients there was no proof of an advantage for the analogues when blood-glucose lowering (measured via HbA1c) and severe nocturnal or non-severe nocturnal hypoglycaemia were assessed conjointly. For children and adolescents there was no proof of an advantage with either analogues or NPH insulin in terms of hypoglycaemia and HbA1c values.

Long-acting analogues Type 2 patients (2009): for both glargine and detemir compared to NPH insulin, the report concluded that within the framework of intensified insulin therapy and within the framework of a treatment scheme with basal insulin and oral drugs, there is no proof of and additional benefit with analogues compared to NPH. There were some differences noted – a conjoint assessment of long-term blood glucose lowering (as measured by HbA1c) and severe hypoglycaemia indicated a superiority of morning glargine over evening NPH. In the comparison of detemir and NPH there were additional benefits associated with detemir with regard to the conjoint assessment of non-severe nocturnal hypoglycaemia and blood glucose lowering for once and twice daily administration, and for the conjoint assessment of non-severe overall hypoglycaemia and blood glucose lowering for twice daily administration.

Rapid-acting analogues Type 1 patients (2007): for adult patients, given the lack of data or poor-quality data, the benefit of insulin aspart compared to regular human insulin in adult patients is not proven. For insulin lispro, the evidence indicates similar results between lispro and regular human insulin, and for glulisine, given the lack of data there is no evidence of an additional benefit with insulin glulisine. For children and adolescents the benefit of aspart and lispro is unclear.

Rapid-acting analogues Type 2 patients (2005): there is no convincing evidence of superiority of analogues compared to regular human insulin for Type 2 patients.

Overall, the reports indicate that there are no distinct advantages for analogue insulins for Type 1 and 2 patients, with the exception of some benefits in Type 2 patients for long-acting analogues. It should be noted that the reports on rapid-acting insulins are a few years old and will not contain current data.

In 2009 the Canadian Optimal Medication Prescribing and Utilization

Service (COMPUS), a service of the Canadian Agency for Drugs and Technology in Health (CADTH) published a report on the optimal prescribing and use of analogues insulins. For Type 1 and 2 patients the report recommended the use of NPH over long-acting analogues, and also recommended the use of regular human insulin over rapid-acting analogues in Type 2 patients. For Type 1 patients, the use of rapid-acting analogues or regular human insulin was recommended, with analogues suggested for use in adolescent Type 1 patients (COMPUS 2009). The report made the following recommendations:

2.1.2 Search strategy

The search focused on evidence available from April 2007 to December 2010. Medline, Embase and the Cochrane Library were searched for relevant trials comparing regular human or animal insulin and analogue insulins. The currently available analogue insulins included in the searches were glargine, detemir, lispro, aspart and glulisine. As well as trial evidence, assessments of cost-effectiveness and malignancy were also sought.

2.2 Statistical analysis

Meta-analyses were conducted using StatsDirect software, version 2.7.8. Data was combined using a random-effects model and heterogeneity was assessed using the I^2 statistic.

The outcomes assessed were HbA1c and hypoglycaemia. For HbA1c the analyses used weighted mean difference (WMD) which is a measure of effect size used when an outcomes is continuous. The mean differences between the groups are weighted to account for different sample size and different precision between trials. For HbA1c the WMD provides an estimate of the difference in HbA1c level of the analogue and human insulin groups at trial endpoint. As WMD is an absolute figure the units remain the same as the original HbA1c measure, in this case a percentage. Therefore, when comparing glargine and NPH, a WMD of -0.09 indicates that based on the trials included in the meta-analysis, HbA1c was, on average, 0.09 lower for glargine than for NPH – so if HbA1c is 7.89% for detemir-treated patients then HbA1c for glargine-treated patients would be 7.80%.

For hypoglycaemia, a dichotomous outcome, the number of patients in each treatment group reporting a hypoglycaemic event was used, with the analyses reporting relative risk, ie the risk of an event relative to exposure.

3. Literature searches

The literature searches returned 633 articles (duplicates removed). These articles were reviewed and 35 trials, along with 20 reviews, 16 articles addressing cancer risk and 11 articles assessing cost-effectiveness were selected as relevant. Comparative trials were assessed to determine if they included required data for further analyses.

4. Available evidence

Of the 35 identified trials, only 8 included data that could be included in meta-analyses,

eg endpoint HbA1c and standard deviation; number of patients with hypoglycaemic events. Some of these trials were excluded as they were publications of data already included in the Singh et al (2009) review or were comparisons of other treatment regimens. Consequently, only 3 comparisons that were made in the Singh et al (2009) review could be updated (see Section 5.1). For the trials that provided comparisons of analogue insulins and regular human insulin with HbA1c and/or hypoglycaemic outcomes, a summary of individual trial results is provided in Attachment 2. This summary includes trials that provided data which could be used in further analyses and those which did not provide such data. Trials which compared analogues or did not include HbA1c or hypoglycaemic outcomes are not included in the summary.

Recent systematic reviews and meta-analyses are summarised in Section 5.2, a summary of articles addressing cost-effectiveness of analogue insulins is provided in Section 5.3 and a summary of available data on cancer and analogue insulins is provided in Section 5.4.

4.1 Quality of evidence

The quality of the evidence, both the evidence identified in the current review as well as the evidence in published reviews, is generally low. Attachment 4 contains GRADE evidence profiles for the comparisons included in the Singh et al (2009) review – all comparisons received a low or very low rating as none of the included trails were double-blinded, allocation concealment was seldom described and most trials were industry-sponsored, suggesting possible publication bias. Given the lack of blinding, trials are open to bias, particularly for patient-reported outcomes such as hypoglycaemia. Previous reviews (Siebenhofer et al., 2006; Horvath et al., 2007; Singh et al., 2009) have all noted the low quality and methodologic limitations of most analogue insulin trials.

The trials identified in the current search are of similar quality, as all were open-label trials (see Table A2.1 in Attachment 2) with a concordant increase in risk of bias. In addition, the varying treatment regimens and patient populations of the trials, as well as the relatively short duration of the trials (12 weeks to 24 months, with most trials <36 weeks) suggest that the results should be interpreted with caution.

5. Results

5.1 Updated comparisons

Table 3 provides a summary of updated meta-analyses results, with original results from the Singh et al (2009) review also provided. Forest plots and bias plots for the updated analyses are in Attachment 3.

Table 3: Original and updated meta-analysis results

Comparison	Outcome	Singh 2009 results Difference (95% CI)	Updated results Difference (95% CI)
Long-acting – Type 1 adults			
glargine vs. NPH	HbA1c: Severe hypo: Noct hypo:	WMD=-0.11 (-0.21,-0.02) RR=0.82 (0.52, 1.29) RR=0.97 (0.87, 1.09)	•no new data available for analysis
detemir vs. NPH	HbA1c: Severe hypo: Noct hypo:	WMD=-0.06 (-0.13, 0.02) RR=0.74 (0.58, 0.96) RR=0.92 (0.85, 0.98)	WMD=-0.08 (-0.15, -0.01); I^2=0% RR=0.45 (0.28, 0.72); 1^2=84.3%
Rapid-acting – Type 2 adults			
lispro vs. regular	HbA1c:	WMD=-0.03 (-0.12, 0.06)	•no new data available for

Comparison	Outcome	Singh 2009 results Difference (95% CI)	Updated results Difference (95% CI)
human	Severe hypo: Noct hypo:	RR=0.43 (0.08, 2.37) RR=1.63 (0.71, 3.73)	analysis
aspart vs. regular human	HbA1c: Severe hypo: Noct hypo:	WMD=-0.09 (-0.21, 0.04) RR=0.39 (0.11, 1.36) RR=0.65 (0.28, 1.53)	WMD=-0.10 (-0.21, 0.03); I^2=43.5%
Long-acting – Type 2 adults			
glargine+orals vs. NPH+orals	HbA1c: Severe hypo: Noct hypo:	WMD=-0.05 (-0.13, 0.04) RR=0.66 (0.29, 1.48) RR=0.56 (0.47, 0.68)	WMD=-0.001 (-0.11, 0.11); I^2=52.4%

The addition of new data did not change most outcomes, with the only change in terms of statistical significance being an advantage for detemir compared to NPH insulin in Type 1 adult patients (WMD=-0.08; 95% CI: -0.15, -0.01), however as with other statistically significant results this difference is less than accepted minimal clinically important differences in HbA1c (eg 10% improvement, Majumdar et al., 2005).

Additional analyses pooling together all analogues were also undertaken. Where possible, trials published since the Singh et al (1999) review were included. Results of these comparisons for HbA1c are provided in Table 4, with forest plots and bias plots provided in Attachment 3.

Table 4: Comparisons using pooled analogues

Comparison	Outcome	Difference (95% CI)
Type 1 adults		
glargine and detemir vs. NPH	HbA1c	WMD=-0.09 (-0.15, -0.03) I^2=19.5%
lispro and aspart vs. regular human insulin	HbA1c	WMD=-0.12 (-0.16, -0.07) I^2=0%
Type 2 adults		
glargine and detemir vs. NPH	HbA1c	WMD=0.03 (-0.05, 0.12) I^2=51.8%
lispro and aspart vs. regular human insulin	HbA1c	WMD=-0.08 (-0.16, 0.01) I^2=39.6%

Pooling the analogues did not change the results when compared to NPH or regular human insulin with the exception of the loss of statistical significance for the advantage of NPH over long-acting analogues in Type 2. The results of these analyses should be interpreted with caution given that the included trials are quite different in terms of duration, patient population, study design as well as additional insulins or oral agents used. The analyses for Type 2 patients had relatively high levels of heterogeneity with 1^2=51.8% for long-acting insulins and 1^2=39.6% for rapid-acting insulins.

Short-acting insulin glulisine, which demonstrated no significant differences in HbA1c or occurrence of hypoglycaemia in a 2006 review (Siebenhofer et al) was not included in the Singh et al (2009) review and given lack of new evidence has not been assessed in the current review.

5.2 Published systematic reviews and meta-analyses

Table 5 provides a summary of recent systematic reviews and meta-analyses published from 2007 to December 2010.

Table 5: Published systematic reviews and meta-analyses

Review	Comparison	Number of trials/patients	Results	
			HbA1c	Hypoglycaemia
Waugh 2010	Type 2 - glargine and detemir vs. NPH	5 systematic reviews, 5 individual trials	•no differences between glargine, detemir and NPH	•advantages for glargine and detemir vs. NPH, particularly nocturnal hypos
Home 2010	Type 2 – glargine+orals vs. NPH+orals	5 trials, 2711 patients	•decrease -1.12% glargine, -1.03% for NPH, difference not reported	•risk of severe nocturnal hypos glargine vs. NPH OR=0.52; p=0.0498
Singh 2009	Type 1 and 2 – analogues vs. regular human insulin, rapid and long-acting	68 trials rapid-acting analogues and 49 trials long-acting analogues	•statistically significant advantages for lispro and aspart vs. regular human insulin in Type 1 adults and for glargine vs. NPH and detemir+aspart vs. NPH and regular human insulin in Type 1 adults; no differences considered clinically important •no statistically significant differences between analogues and regular insulin in Type 2 patients; NPH demonstrated significant advantage over glargine	•statistically significant advantages for analogues vs. regular human insulin for Type 1 and 2 patients for nocturnal hypoglycaemia
Horvath 2009	Type 2 – glargine vs. NPH and detemir vs. NPH	8 trials	•no differences between glargine or detemir and NPH	•statistically significant advantages for glargine and detemir vs. NPH for symptomatic, overall and nocturnal hypoglycaemia, no significant differences for severe hypoglycaemia
Jacobsen 2009	Type 1 – rapid-acting analogues vs. human		•statistically significant reduction in HbA1c for rapid-acting analogues, but minor clinical improvement	•reduced risk for hypos with rapid-acting analogues
Rogoz 2009	Type 2 – glargine+orals vs. premix human insulin	3 trials, 637 patients	•greater reduction for glargine+orals than premix human with WMD=-0.33 (95% CI: -0.50, -0.16)	•all hypos RR=0.90 (95% CI: 0.78, 1.04)
Davidson 2009	Type 2 – biphasic aspart vs. biphasic human insulin	9 trials, 1674 patients	•treatment difference 0.04 (95% CI: -0.02, 0.10)	•overall hypos RR=1.08 (95% CI: 0.94, 1.24) •nocturnal hypos RR=0.50 (95% CI:

Review	Comparison	Number of trials/patients	Results	
			HbA1c	**Hypoglycaemia**
				0.38, 0.67)
Van Avendonk 2009	Type 2 – all treatments	78 trials	•long-acting analogues plus orals similar HbA1c to NPH and orals	
Rys 2009	Type 1 – rapid-acting analogues vs. regular human insulin	12 trials, 3553 patients	•aspart lower HBa1c than regular human with WMD=-0.14 (95% CI: -0.20, -0.07)	•significant reduction in nocturnal hypos with aspart RR=0.67 (95% CI: 0.54, 0.83)
Heller 2009	Type 1 and 2 – aspart vs. regular human insulin (basal NPH with both)	10 trials, 3727 patients	•significant advantage in HbA1c for aspart with difference of -0.10 (95% CI: -0.15, -0.04)	•overall and symptomatic hypos similar, nocturnal hypos lower with aspart RR=0.76 (95% CI: 0.67, 0.85)
Lee 2009	Type 2 – glargine+orals vs. NPH+orals (patients <65 and >65 years)	4 trials	•similar HbA1c reductions for younger patients (<65 years); significantly greater HbA1c reductions for glargine vs. NPH for older patients	•rate of nocturnal hypos less with glargine (p<0.01)
Hermansen 2009	Type 1 – detemir vs. NPH (both with bolus insulin)	7 trials	•difference in HbA1c favouring detemir (-0.10; p=0.02)	•rate of hypos 19% less for detemir vs. NPH (p<0.0001)
Monami 2009	Type 1 – glargine or detemir vs. NPH	20 trials, 6178 patients	•long-acting analogues had significant reduction in HbA1c vs. NPH (difference=-0.07; 95% CI: -0.13, -0.01)	•reduced risk for nocturnal hypos (OR=0.69; 95% CI: 0.55, 0.86) and severe hypos (OR=0.73; 95% CI: 0.60, 0.89) for long-acting analogues vs. NPH
Mannucci 2009	Type 2 – short-acting analogues vs. human insulin	13 trials	•significant reduction in HbA1c for analogues vs. human insulin 0.4 (95% CI: 0.1, 0.6)	•no difference between analogues and human insulin for severe hypos (OR=0.61; 955 CI: 0.25, 1.45)
Bazzano 2008	Type 2 – glargine vs. NPH	12 trials, 4385 patients	•mean net change in HbA1c NPH vs. glargine 0.08% (95% CI: -0.04, 0.21)	•no significant differences in confirmed or severe hypos
Mullins 2007	Type 1 and 2 – glargine vs. NPH	11 trials, 5074 patients	NR – only used to adjust for hypos	•unadjusted risk of hypos lower for glargine compared to NPH, -6.1% for all hypos, -21.6% for confirmed, -23.9% for severe (all p<0.05) •when adjusted using HbA1c as covariate, risks were 9.1% all hypos (p<0.05), 26.6% for confirmed hypos (p<0.001) and 30.0% for severe hypos (p=0.08)

Review	Comparison	Number of trials/patients	Results	
			HbA1c	Hypoglycaemia
Gough 2007	Type 1 and 2 – rapid and long-acting analogues vs. regular human insulin		•advantages for analogues compared to human insulin, with "modest" benefits	
Duckworth 2007	Type 2 – glargine vs. NPH (mono or with orals)	6 trials	•similar reductions in HbA1c with glargine and NPH	•nocturnal hypos less frequent with glargine vs. NPH
Gonzalez-Blanco 2010	Type 1 pregnant women – lispro vs. regular insulin	5 trials	First tri: MD=-0.33 (95% CI: -0.59, -0.08) Second tri: MD=-0.51 (95% CI: -0.83, -0.20) Third tri: MD=-0.17 (95% CI: -0.38, 0.03)	NR
Matyas 2009	Gestational diabetes – rapid-acting analogues vs. regular human insulin	3 trials, 134 patients	•no significant differences in HbA1c	•data for perinatal hypos reported in one trial, 0% in both treatment arms

5.3 Cost-effectiveness

Table 6 provides a summary of the recent evidence addressing the cost-effectiveness of analogue insulins. Most cost-effectiveness analyses use the IMS-CORE Diabetes Model, an internet-based Monte Carlo simulation model designed to assess long-term costs and outcomes of both Type 1 and 2 diabetes. The recent Waugh et al (2010) health technology assessment of Type 2 diabetes treatment uses the UKPDS Outcomes Model, also a simulation model.

The ICERs vary widely, both within and across diabetes types and comparisons. For example, Gschwend et al (2009) estimated an ICER of €519 per QALY gained for Type 1 patients using detemir in France, while Cameron et al (2009) estimated an ICER of $CAN387,729 per QALY gained for Type 1 patients using detemir in Canada. ICERs for Type 2 patients were less than $CAN30,000/QALY for rapid-acting analogues (Cameron et al., 2009) and ranged from $CAN130,865/QALY to £412,000/QALY (Waugh et al., 2010) for long-acting analogues.

All analyses were sensitive to changes in hypoglycaemic event rates and utility values. For example, in the Valentine et al (2010) Type 1 analysis comparing detemir and NPH, if the change in hypoglycaemia event rate was assumed to be equal between detemir and NPH the ICER increased to SEK579,835/QALY ($USD87,415) from a base case value of SEK49,757/QALY ($USD7501).

All models used different sources of clinical trial data, with some using data that indicated no difference between analogue and regular human insulin in terms of HbA1c reduction, and others using data indicating advantages for analogues insulins. The differences in hypoglycaemia rates used and the utility values applied differed across models – these factors likely contribute to the wide range in ICERs, given that HbA1c and hypoglycaemia are the drivers of the models, however firm conclusions cannot be drawn given that the models cannot be closely examined. Country

perspectives would also have an impact.

Table 6: Summary of available cost-effectiveness analyses for analogue insulins

Study	Comparison	Design	Results
Type 1 and 2			
Cameron 2009	•rapid-acting analogues vs. regular human insulin •long-acting analogues vs. NPH	•cost-effectiveness analyses using IMS-CORE Diabetes Model •clinical data obtained from CADTH meta-analyses •Canadian perspective	**Type 1** •aspart dominant vs. regular human insulin •lispro ICER vs. regular human insulin $28,996 per QALY gained •glargine ICER vs. NPH $87,932 per QALY gained •detemir ICER vs. NPH $387,729 per QALY gained **Type 2** •aspart ICER vs. regular human insulin $22,488 per QALY gained lispro ICER vs. regular human insulin $130,865 per QALY gained •glargine ICER vs. NPH $642,994 per QALY gained •detemir less effective and more costly than NPH
Type 1			
Valentine 2010	•detemir vs. NPH, both combined with aspart	•cost-effectiveness analysis, using published clinical trial data and IMS-CORE Diabetes Model •Markov model using Monte Carlo simulation •Swedish setting	•ICER SEK49,757 per QALY gained (equivalent to $USD7501) and SEK 190,208 ($USD28,675) per LYG •clinical data obtained from one trial showing an advantage for detemir for both HbA1c and hypos •model sensitive to HbA1c effect and hypos. If change in hypo rate was assumed to be equal for detemir and NPH, ICER increases to SEK579,835 ($87,415) per QALY gained
Gschwend 2009	•detemir vs. NPH, using basal-bolus regimen	•cost-effectiveness analysis, using published clinical trial data and IMS-CORE Diabetes Model •Markov model using Monte Carlo simulation •Belgian, French, German, Italian and Spanish settings	•cost-savings for detemir vs. NPH in Belgium, Germany and Spain •ICER of €519 per QALY gained in France and €3,256 in Italy •model sensitive to hypoglycaemic rates. For example, if no difference in major hypos was assumed, ICER increased to €7,393 in Germany (detemir dominant in base case)
Type 2			
Waugh 2010	•glargine vs. NPH and detemir vs. NPH, all with orals or bolus insulin	•cost-effectiveness analysis, using meta-analysis of 5 trials included in the Waugh review •UKPDS Outcomes model which is a patient-level simulation model, with male and female populations run separately	•glargine vs. NPH ICER ranging from £280,000 to £320,000 per QALY gained •detemir vs. NPH ICER ranging from £188,000 to £412,000 per QALY gained

Tunis 2010	•glargine+orals vs. regular human premixed insulin in Type 2 patients in Canada	•cost-effectiveness analysis, using published clinical trial data and IMS-CORE Diabetes Model •Markov model using Monte Carlo simulation •cost/LYG and cost/QALY	•ICER $6750 per life year gained and $7923 per QALY gained •results sensitive to disutilities for hypos, effect of glargine and orals on HbA1c and acquisition costs of glargine, eg if glargine HbA1c effect decreased 10%, ICER increased to $27,137; if glargine acquisition cost increased 10%, ICER increased to $23,444; if utility for major hypos changed to -0.0121 from -0.00153 in base case and all hypos changed to -0.0052 the ICER decreases to $1,174

A review published in 2008 (Brixner and McAdam-Marx) summarised the cost-effectiveness of analogue insulins, focusing on studies conducted in the US (other countries were included) between 2004 and 2007. The ICERs estimated in the included studies were generally lower than those presented in Table 6 above, ranging from $4882/QALY to $<$39,052/QALY. The studies included in the Brixner and McAdam-Marx (2008) review are briefly summarised in the table below.

Table 7: Summary of cost-effectiveness analyses for analogue insulins from Brixner and McAdam-Marx (2008) review

Study	Comparison/location	Cost per QALY
Palmer 2004	•detemir vs. NPH in Type 1 •UK	•£19,285 for detemir vs. NPH
Lammert 2004	•biphasic aspart vs. biphasic regular human insulin •Europe	•€5,000 to €14,068 for biphasic aspart vs. biphasic human
Valentine 2006	•detemir vs. NPH in Type 1 •US	•$USD14,974 for detemir vs. NPH
Grima 2007	•glargine vs. NPH Type 1 and 2 •Canada	•$CAN20,799 for Type 1 and $CAN8618 for Type 2 for glargine vs. NPH
McEwan 2007	•glargine vs. NPH Type 1 and 2 •UK	•£2695 to £10,943 for Type 1 and <£20,000 for Type 2 for glargine vs. NPH
Palmer 2007	•detemir+aspart vs. NPH+regular human insulin in Type 1 •UK	•£2500 for detemir+aspart vs. NPH+human
Valentine 2007	•Type 2 patients switching to detemir (with or without orals) from NPH (with or without orals) •US	•$USD6269 for detemir

5.4 Malignancy

The association between the use of insulin and potential increased risk for malignancy experienced a considerable surge in attention in 2009 with the publication of a number of studies indicating increased risk of malignant cancer with the use of analogue insulins, in particular glargine (Hemkens et al., 2009; Jonasson et al., 2009). Other publications indicated no increased risk with analogue insulins (eg Currie et al., 2009; Colhoun 2009). The German Institute for Quality and Efficiency in Health Care subsequently recommended that "…as long as reliable studies do not prove the safety of glargine compared to human insulin, the drug should only be used

if there are particularly important reasons for doing so" (https://www.iqwig.de/insulin-analogue-glargine-possibly-increases.879.en.html?random=5edd36).

A number of studies, as well as editorial pieces, have subsequently been published. Editorial and opinion pieces are not included in the table below, however these outline the methodological and statistical issues which result in conflicting views of the evidence (Simon 2010; Nagel et al., 2010; Johnson and Yasui 2010; Grouven et al., 2010; Hernandez-Diaz and Adami 2010; Hemkens 2010).

Table 8 provides a summary of the available evidence addressing malignancy associated with analogue insulins.

Table 8: Available evidence addressing risk of cancer associated with analogue insulins

Trial	Comparison/ design	Number of trials	Number of subjects	Cancer
Hemkens 2009	•regular human insulin vs. aspart, lispro or glargine – Type 1 and 2 patients •observational cohort study	1	127,031	•dose-dependent increase in cancer risk was found for glargine (p<0.0001), with adjusted HR=1.09 (95% CI: 1.00, 1.19) for 10 IU/day and HR=1.31 (95% CI: 1.20, 1.42) for dose of 50 IU/day •no increased cancer risk was found for aspart or lispro
Jonasson 2009	•glargine vs. other insulin types – Type 1 and 2 patients •observational cohort study	1	114,841	•users of insulin glargine alone had increased risk for breast cancer (RR=1.99; 95% CI: 1.31, 3.03) with no other types of cancer indicating an increased risk
Currie 2009	•analogue insulin, human insulin, oral agents – type 1 and 2 patients •retrospective cohort study	1	62,809	•use of analogue insulin was not associated with increased risk of cancer compared to human insulin with HR=1.24 (95% CI: 0.90, 1.70)
Colhoun 2009	•glargine vs. other insulins – Type 1 and 2 patients •retrospective review	1	36,254	•patients receiving any insulin glargine had same incidence rate for all cancers as those receiving glargine (HR=1.02; 95% CI: 0.77, 1.36). •no increase in breast cancer rate associated with glargine (HR=1.49; 95% CI: 0.79, 2.83) however insulin glargine only users had a higher rate of breast cancer then those using non-insulin glargine only (HR=3.39; 95% CI: 1.46, 7.85)
Home 2009	•glargine vs. comparator (insulin and orals) – Type 1 and 2 •retrospective review of sanofi-aventis' pharmacovigilance database	31	10,880	•malignant cancer reported by 45 glargine patients (0.8%) and 46 comparator patients (0.9%) with RR=0.90; 955 CI: 0.60, 1.36) •skin cancer reported by 12 patients with 16 events on glargine and 6 patients with 7 events on comparator (RR=1.85; 95% CI: 0.69, 4.92) •colon and rectal cancer 6 glargine patients vs. 10 comparator patients (RR=0.55; 95% CI: 0.20, 1.52) •breast cancer 4 glargine patients vs. 6 comparator patients (RR=0.62; 95% CI:

Trial	Comparison/ design	Number of trials	Number of subjects	Cancer
				0.17, 2.18) •gastrointestinal tract six glargine patients vs. 4 comparator patients (RR=1.38; 95% CI: 0.39, 4.90) •authors conclude glargine was not associated with increased risk of cancer
Rosenstock 2009	•glargine vs. NPH – Type 2 •open-label safety study designed to assess ocular complications of diabetes	1	1017	•number of patients with neoplasms 57 (11.2%) for glargine and 62 (12.3%) for NPH with RR= 0.90 (95% CI: 0.64, 1.26) •malignant breast tumour cases: 3 in glargine group vs. 5 in NPH group with RR=0.59 (95% CI: 0.14, 2.44)
Dejgaard 2009	•detemir vs. NPH and glargine – Type 1 and 2 •IPD meta-analysis of Novo Nordisk-sponsored trials	16	3983	•patients treated with detemir had lower incidence of cancer compared to those treated with NPH (OR=2.44; 95% CI: 1.01, 5.89) and a similar incidence compared to those treated with glargine (OR=1.47; 95% CI: 0.55, 3.94)

The results of the available studies vary, with two large observational studies (Hemkens et al., 2009; Jonasson et al., 2009) indicating an increased risk of cancer associated with insulin glargine, and other studies indicating no increased cancer risk associated with analogue insulins. The presented results should be interpreted with caution, given the methodological sand statistical issues associated with the available analyses,

6. Discussion

While there are a number of new trials (post 2007) available assessing analogue insulins in comparison to regular human insulin, there is little data available within these trials to update previous meta-analyses. For the analyses that could be updated there was little change in results, which demonstrated little or no differences between analogue and regular human insulins.

In analyses that indicated statistically significant advantages for analogue insulins for glycaemic control, the differences between analogues and regular human insulin remain very small (ie 0.09%) and do not constitute clinically important differences. Consequently, the available evidence indicates that analogue insulins have no advantage over regular human insulins for the outcome of glycaemic control.

Regarding the occurrence of hypoglycaemic events, analogue insulins appear to have statistically significant advantages compared to regular human insulins, but these advantages are not consistent across types of insulin (rapid or long-acting) or types of diabetes, and the clinical importance of these differences is not clear. In addition, many trials which demonstrated a difference between analogue insulin and regular human insulin for the occurrence of hypoglycaemia excluded patients with a history of recurrent major hypoglycaemia (Singh et al., 2009), therefore it may not be appropriate to assume such advantages will be observed across all patients.

It should be noted that the trials assessing analogue insulins are of relatively low quality, given the lack of blinding of participants and outcome assessors, with resultant potential for

bias with patient-reported outcomes (ie hypoglycaemia). Also, most trials are linked to the pharmaceutical industry, suggesting that there may be some degree of publication bias.

Cost-effectiveness estimates of analogue insulins vary widely, from just over €500 to greater than £412,000 per QALY gained. Estimates indicating cost-effectiveness are generally specific to a particular population and regimen, however the broader and more comprehensive analyses indicate that analogue insulins appear to lack cost-effectiveness.

Recent reviews of the potential link between analogue insulin use and cancer raise a number of methodological and statistical questions and indicate that further evidence is required before firm conclusions can be drawn.

There remains a lack of evidence addressing longer-term outcomes of diabetes such as mortality and long-term complications. Given the lack of clear benefits for analogue insulins for glycaemic control as well as the inconsistent and clinically debatable benefits for occurrence of hypoglycaemia, along with concerns about trial quality, the current evidence does not indicate a strong advantage for analogue insulins compared to regular human insulin for both Type 1 and 2 diabetes.

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Attachment 1: International availability and costs

Table A1.1 provides the manufacturer and countries the analogue and human insulins are registered in. Availability could not be determined for a number of countries, particularly African and South Pacific countries.

Table A1.1: International availability and manufacturer

Insulin	Manufacturer	Countries/regions registered in
glargine	sanofi-aventis	EU - Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom; Switzerland, USA, Canada, Australia, New Zealand, Singapore, China, Hong Kong, Indonesia, Malaysia, Philippines, Taiwan, Vietnam, Korea, Japan, Russia, India,
detemir	Novo Nordisk	
aspart	Novo Nordisk	
lispro	Eli Lilly	
glulisine	sanofi-aventis	
NPH	Novo Nordisk, Eli Lilly	
regular human insulin	Novo Nordisk, Eli Lilly	

Table A1.2 provides the costs for the different formulations of the analogue and human insulins. As the costs of the insulins are not readily available, costs are only provided for Australia, New Zealand, Canada and the USA, with costs for the latter two sourced from online pharmacies.

Table A1.2: Insulin costs

Insulin	Country	Cost		
		3mL cartridge	3mL pre-filled pen	10mL vial
glargine	Australia	$432.72 (5)	$432.72 (5)	NA
	New Zealand	$94.50 (5)	$94.50 (5)	$63.00 (1)
	USA	NA	NA	$118.99 (1) $553.30 (5)
	Canada	$98.49 to $128.00 (5)	NA	NA
detemir	Australia	$432.72 (5)	$432.72 (5)	NA
	USA	NA	NA	$120.44 (1) $558.74 (5)
	Canada	$144.99 (5)	$164.99 (5)	$134.99 (1)
aspart	Australia	$264.22 (5)	$264.22 (5)	$159.27 (5)
	New Zealand	$51.19 (5)	NA	$30.03 (1)
	USA	$216.99 (5)	$239.99 (5)	
	Canada	$73.99 (5)	$74.99 (5)	$40.74 (1)
lispro	Australia	$264.22 (5)	$264.22 (5)	$159.27 (5)
	New Zealand	$59.52 (5)	NA	$34.92 (1)
	USA	$215.99 (5)	$225.99 (5)	$125.99 (1) $566.62 (5)
	Canada	$68.52 (5)	$68.52 (5)	$34.99 (1) $154.49 (5)
glulisine	Australia	$264.22 (5)	$264.22 (5)	$159.27 (5)
	New Zealand	$46.07 (5)	$46.07 (5)	$27.03 (1)
	USA	$203.64	NA	$109.99 (1) $513.30 (5)
	Canada	$68.00 (5)	$77.99 (5)	$63.99 (1)
NPH	Australia	$224.32 (5)	NA	$133.82 (5); $172.02 (5)
	New Zealand	$29.86 (5)	$29.86 (5)	$17.68 (1)
	USA	NA	NA	$72.99 (1) $318.28 (5)

Insulin	Country	Cost		
		3mL cartridge	**3mL pre-filled pen**	**10mL vial**
	Canada	$54.59 (5)	$53.01 (5)	$34.49 (1) $119.99 (5)
regular human insulin	Australia	$224.32 (5)	NA	$133.82 (5)
	New Zealand	$42.66 (5)	NA	$25.26 (1)
	USA	NA	NA	$72.99 (1) $318.28 (5)
	Canada	$56.99 (5)	$324.00 (15)	$217.25 (5)

NA=not available (price)
Source: Canada: http://www.pharmacychecker.com
USA: http://www.drugstore.com/prescriptions/qxc10663
Australia: http://www.pbs.gov.au/pbs/home
New Zealand: http://www.pharmac.govt.nz/Schedule

Attachment 2: Individual trial results

Table A2.1: Available evidence and outcomes

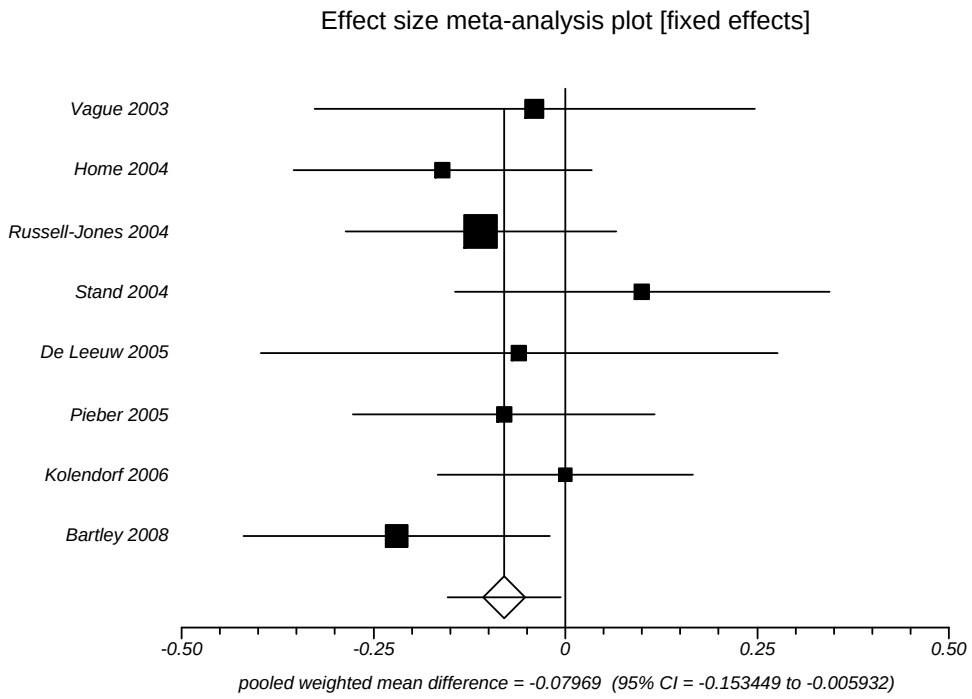
Trial	Comparison/design	N	HbA1c	Hypoglycaemia
Long-acting Type 1				
Bolli 2009	•glargine+lispro vs. NPH+lispro – Type 1 adults •randomised, open-label	175	•glargine 7.26%, NPH 7.26%, p=0.9982, •decrease -0.56% for both glargine and NPH	•serious nocturnal hypos glargine decrease -0.19 episodes/patient/month vs. NPH decrease -0.10 episodes/patient/month, with no difference between groups (p=0.383) •serious hypos glargine decrease -0.54 episodes/patient/month vs. NPH decrease -0.54 episodes/patient/month, with no difference between groups (p=0.993)
Chatterjee 2007	•glargine+aspart vs. NPH+aspart – Type 1 adults •open-label, cross-over	60	•glargine 8.07% vs. NPH 8.26%, difference -0.19% (95% CI: -0.36, -0.01), p=0.04	•all hypos glargine 80.7% vs. NPH 77.2%, p=0.63
Bartley 2008	•detemir+aspart vs. NPH+aspart – Type 1 adults •randomised, open-label	495	•detemir 7.36% vs. NPH 7.58%, mean difference -0.22% (95% CI: -0.41, -0.03), p=0.022 •decrease of -0.94% for detemir and -0.72% for NPH	•all hypos detemir 26.2 episodes/patient/year vs. NPH 36.0 RR=0.74 (95% CI: 0.51, 1.07) •nocturnal hypos detemir 3.4 episodes/patient/year vs. NPH 6.4 RR=0.54 (95% CI: 0.40, 0.71)
Hassan 2008	•glargine+aspart vs. NPH+aspart – Type 1 children •randomised, open-label	36	glargine 6.7% vs. NPH 7.6%, p=0.29	•no events with glargine, 3 with NPH
Robertson 2007	•detemir+aspart vs. NPH+aspart – Type 1 children •randomised, open-label	347	•detemir 8.0% vs. NPH 7.9%, mean difference 0.1%	•nocturnal hypos RR=0.74 (95% CI 0.55, 0.99), p=0.041
Long-acting Type 2				
Rosenstock 2009	•glargine+orals or bolus insulin vs. NPH+orals or bolus insulin – Type 2 adults •randomised, open-label	1017	•glargine vs. NPH difference 0.19% (90% CI: 0.02, 0.36)	•severe hypos glargine 5 vs. NPH 28 (p<0.03) •nocturnal hypos glargine 221 vs. NPH 620 (p<0.001) •overall hypos glargine 682 vs. NPH 1019 (p<0.004)
Montanana 2008	•detemir+aspart vs. NPH+aspart – Type 2 •randomised, open-label	271	•detemir 7.8% vs. NPH 7.8%, difference NS	•detemir vs. NPH all hypos RR=0.62, p<0.0001 •nocturnal hypos RR=0.43, p<0.0001
Davies 2008	•detemir+orals vs. NPH+orals – Type 2 adults •randomised, open-label	476	•detemir 6.6%, NPH 6.5%, difference NS	•risk of overall hypoglycaemia 47% lower with detemir
De Mattia 2009	•glargine+orals vs. NPH+orals – Type 2	20	•glargine decrease -1.7%, NPH	•glargine 1.04 episodes/patient/month and

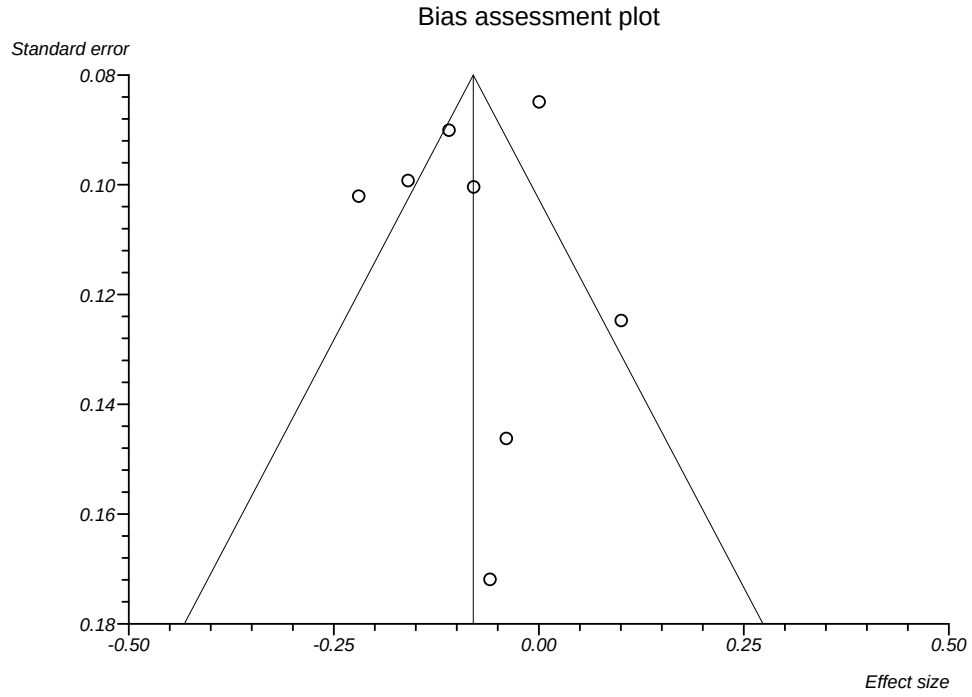
Trial	Comparison/design	N	HbA1c	Hypoglycaemia
	adults •randomised, open-label, cross-over		decrease -1.6%, difference NS	NPH 2.12 episodes/patient/ month
Rapid-acting Type 1				
Pankowska 2010	•NPH+aspart vs. NPH+regular human vs. CSII aspart – Type 1 children •randomised, open-label	61	•NPH+aspart 7.6%, NPH+human 7.6%, CSII aspart 7.6%	•NPH+aspart minor hypos 21 episodes/year, NPH+human 18 episodes/year, CSII aspart 20 episodes/year
Danne 2007	•NPH+aspart vs. NPH+regular human – Type 1 children •randomised, open-label, cross-over	26	•no significant difference with HbA1c 7.7% with aspart and 7.6% with regular human insulin	•no difference in occurrence of hypoglycaemia with RR=1.06 (95% CI: 0.96, 1.17)
Rapid-acting Type 2				
Chlup 2007	•aspart vs. regular human insulin – Type 2 •open-label, patients switched from regular human to aspart	57	•HbA1c decreased to 7.5% with aspart from 8.4% at baseline	•no change in occurrence of hypoglycaemia with use of aspart
Gao 2008	•premix lispro vs. premix regular human – Type 2 adults •randomised, open-label, cross-over	120	•lispro 7.59% vs. human 7.61% (p=0.581)	•no difference in hypo rate (p=0.401)
Biphasic insulins Type 2				
Li 2009	•premix lispro vs. premix regular human – Type 2 adults •randomised, open-label, cross-over	117	•lispro 7.91% vs. human 7.96%; difference -0.05% (95% CI: -0.20, 0.10) therefore non-inferior	•lispro 0.34 episodes/patient/ month vs. human 0.37, difference NS
Clements 2008	•premix aspart vs. premix regular human – Type 2 adults •randomised, open-label	664	•aspart 8.35% vs. human 8.67%, difference -0.32, p<0.0001	•aspart 0.1 major events/subject year vs. human 0.1 •aspart 29.83 all episodes/year vs. human 20.14 all episodes/year; RR=1.48 (95% CI: 1.16, 1.89)
Yamada 2007	•premix lispro vs. premix regular human – Type 2 adults •randomised, open-label	30	•lispro 7.24 vs. human 7.29 (p<0.05)	NR
Dashora 2009	•premix aspart vs. premix regular human – Type 2 adults •randomised, open-label, cross-over	38	NR	•aspart 42% experiencing hypos vs. human 43%, difference NS
Miyashita 2008	•premix aspart vs. basal NPH+aspart – Type 2 adults •randomised, open-label	42	•premix aspart 7.4% vs. NPH 6.9%; percent change premix aspart -14.7% vs. NPH -17.8%, p=0.32	NR

Trial	Comparison/design	N	HbA1c	Hypoglycaemia
Masuda 2008	•premix lispro vs. basal NPH+lispro – Type 2 adults •randomised, open-label	28	•premix lispro 6.9% vs. NPH 6.6%, difference NR	•premix lispro 3.07 events/patient vs. NPH 3.86, difference NS

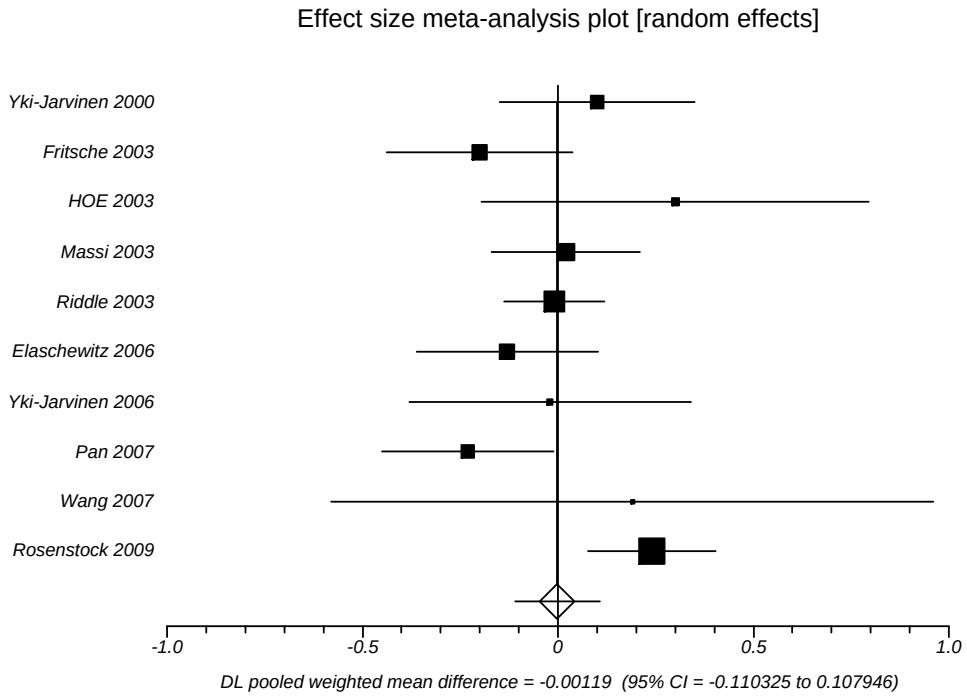
Attachment 3: Forest plots and bias plots for updated meta-analyses

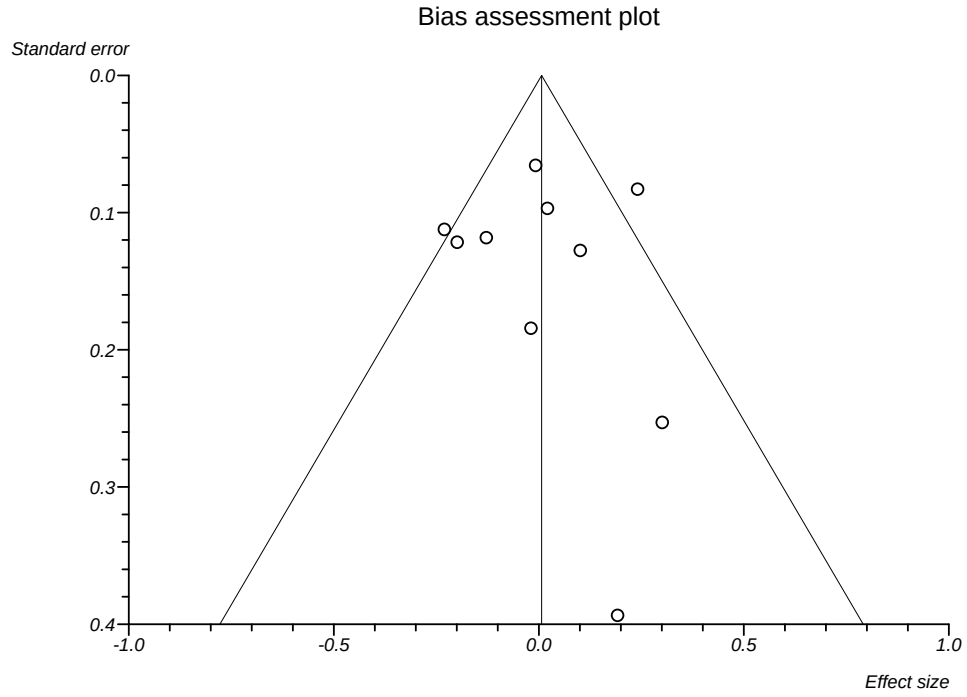
Long-acting Type 1:





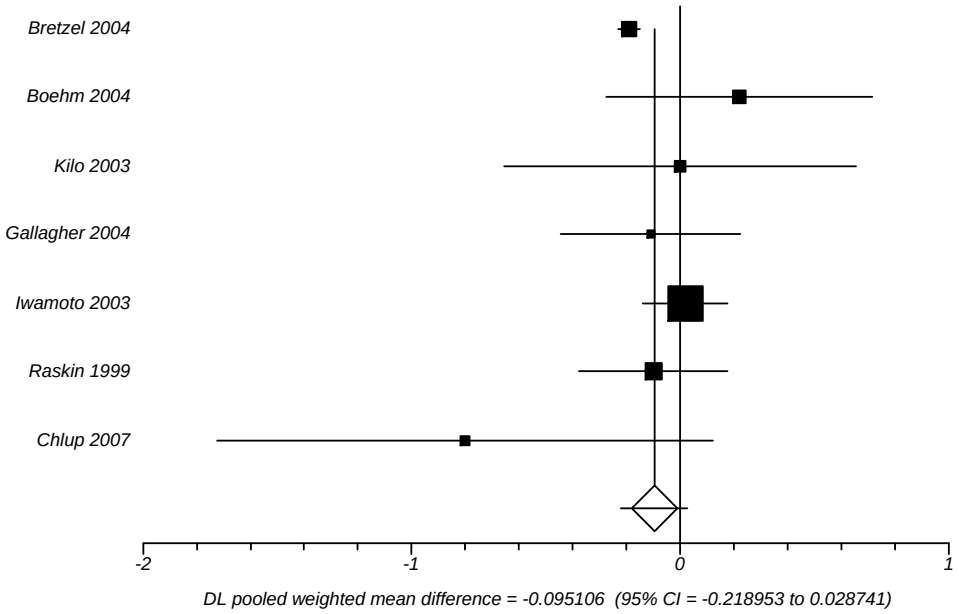
Long-acting Type 2:



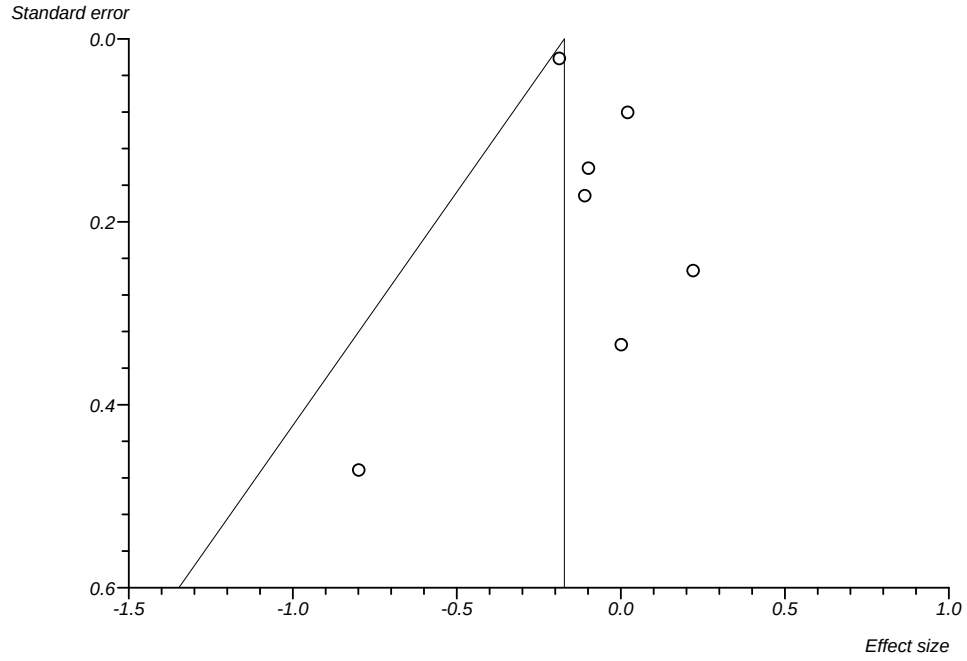


Rapid-acting Type 2:

Effect size meta-analysis plot [random effects]

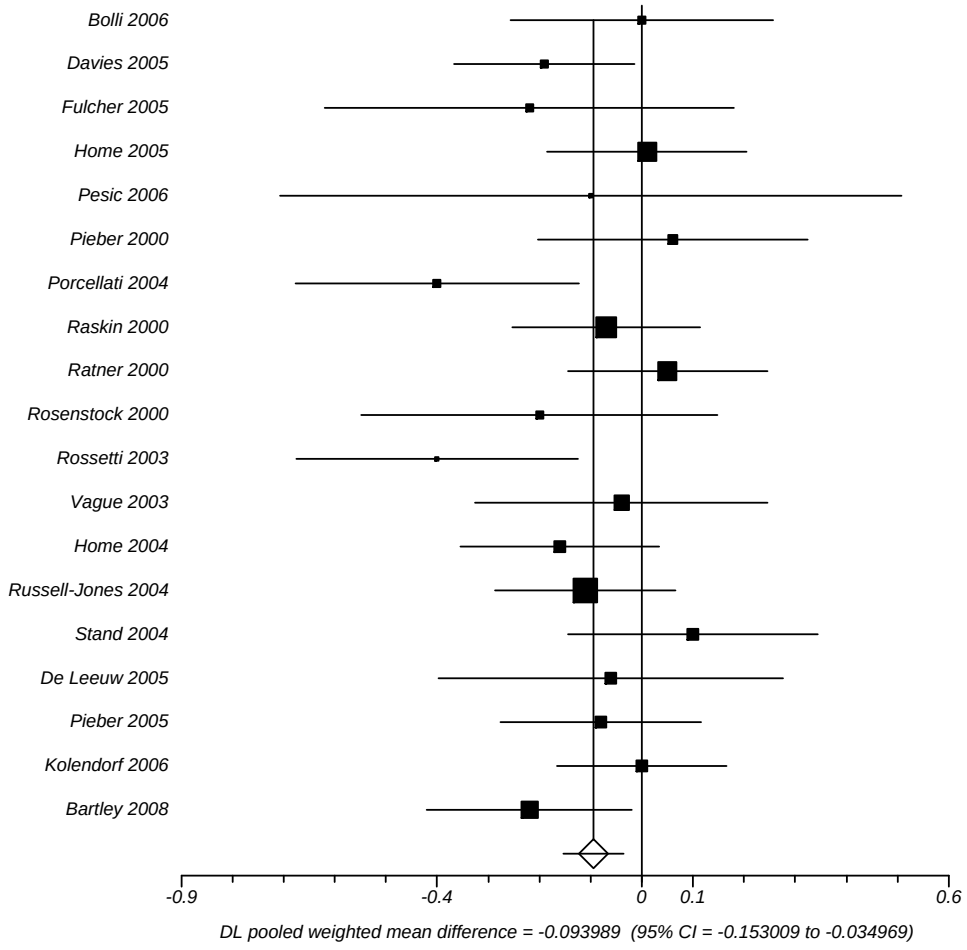


Bias assessment plot

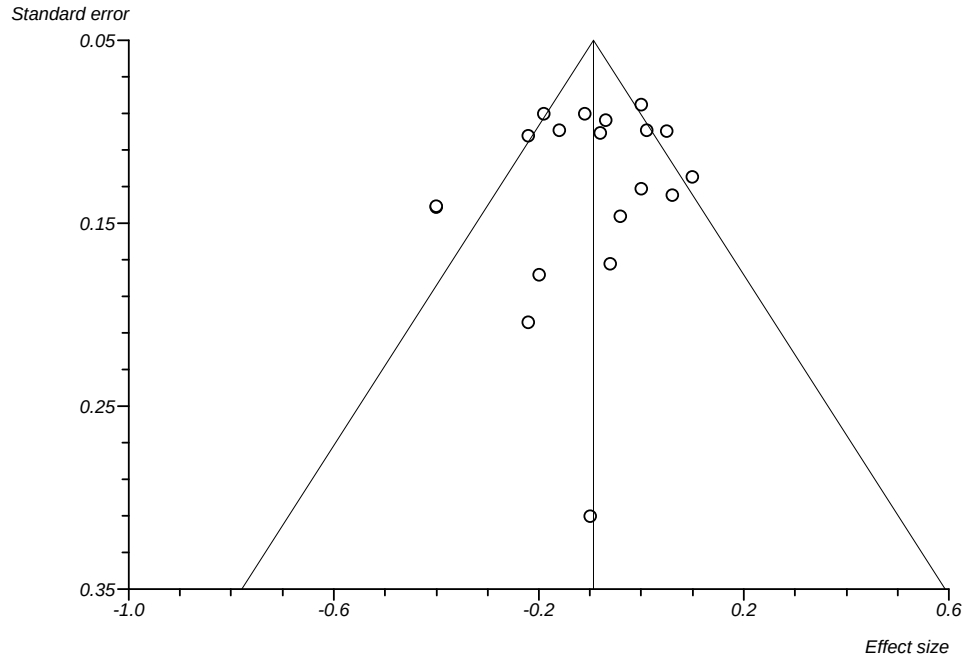


Glargine and detemir combined vs. NPH – Type 1:

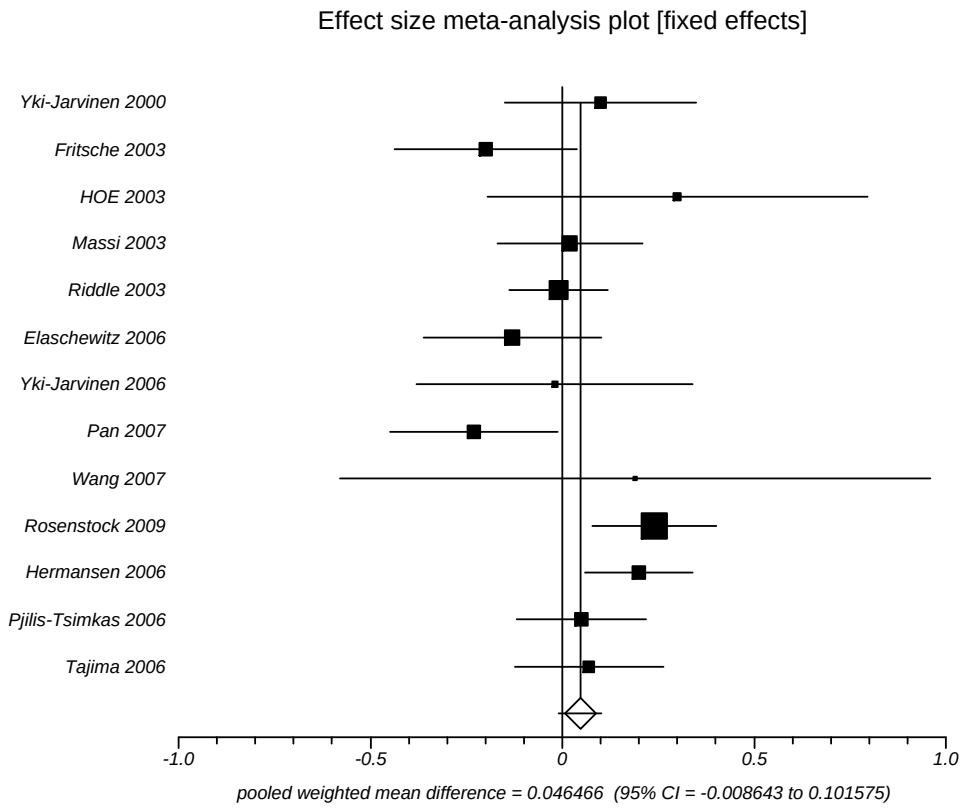
Effect size meta-analysis plot [random effects]

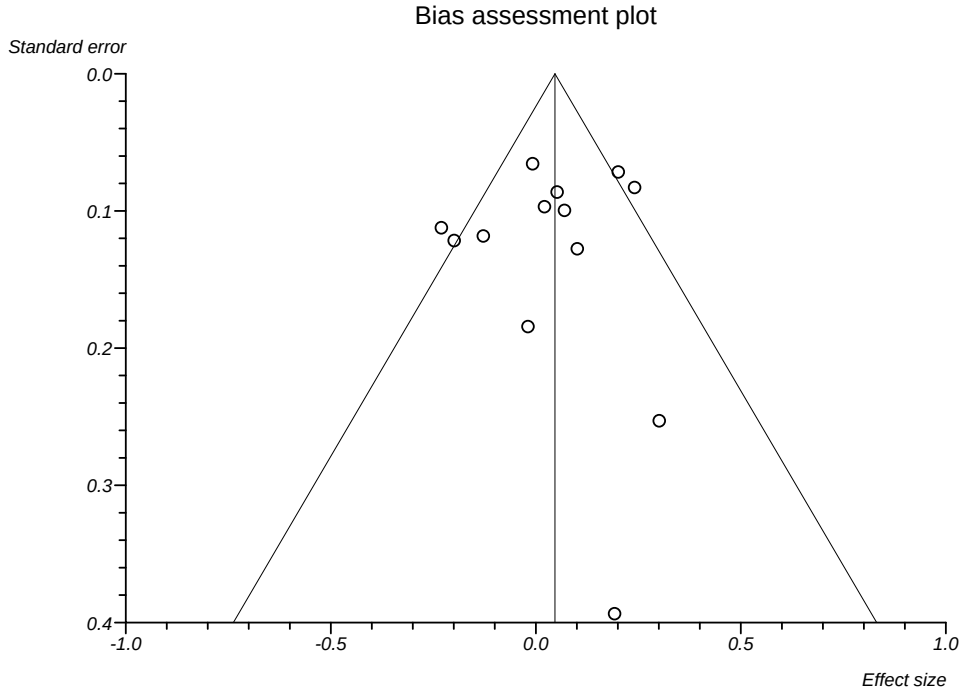


Bias assessment plot

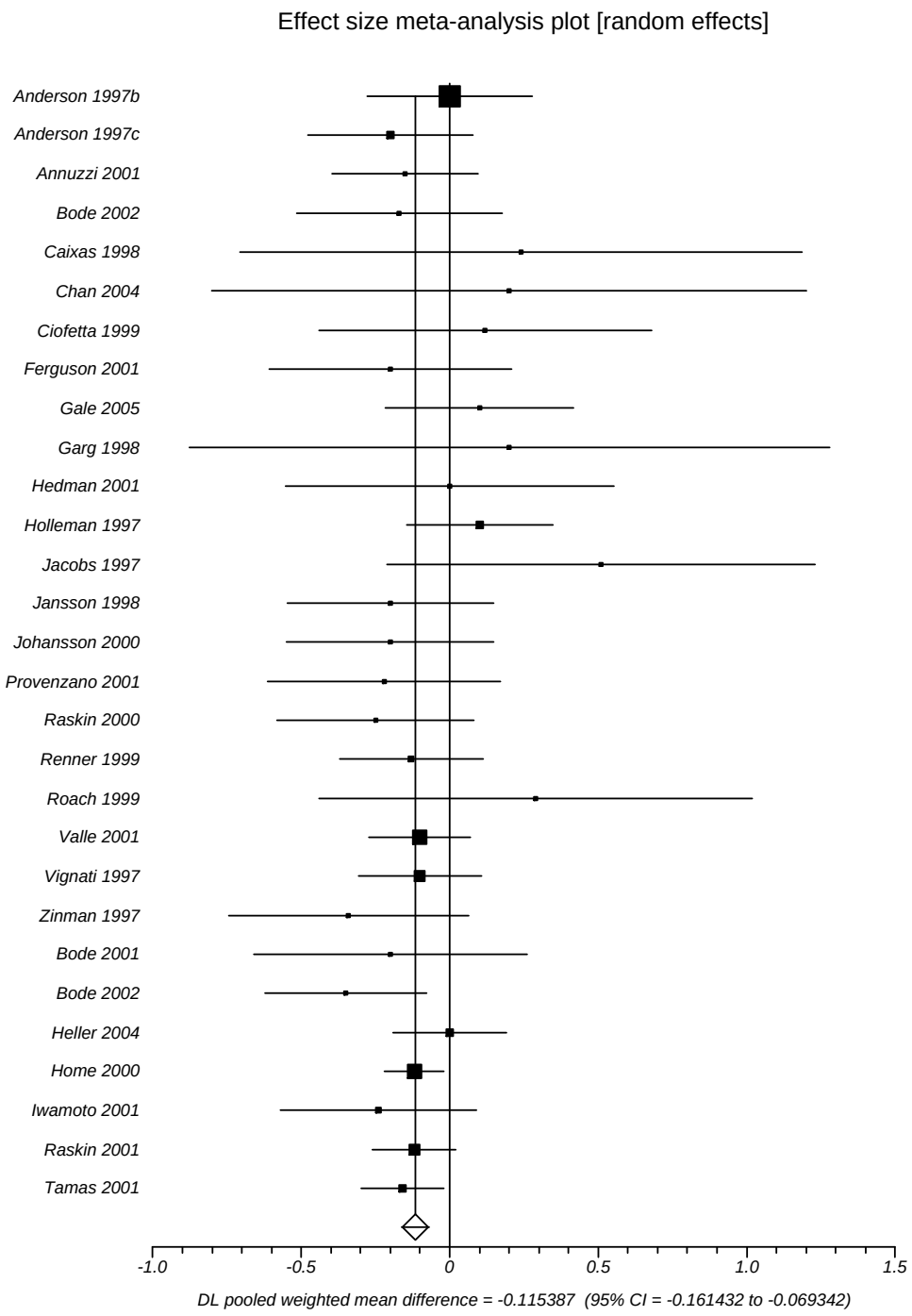


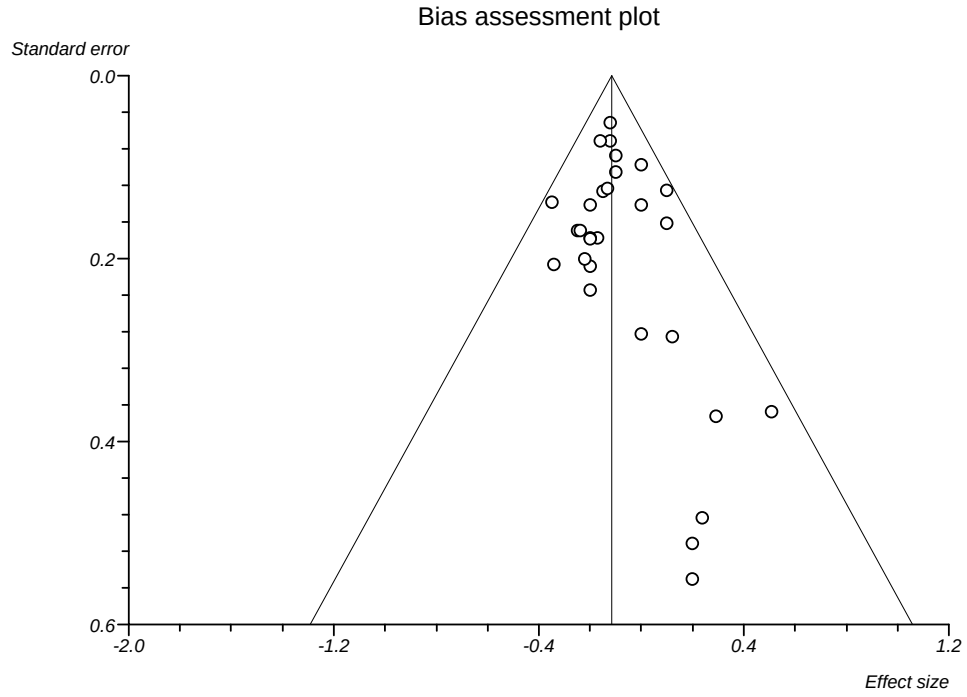
Glargine and detemir combined vs. NPH – Type 2:



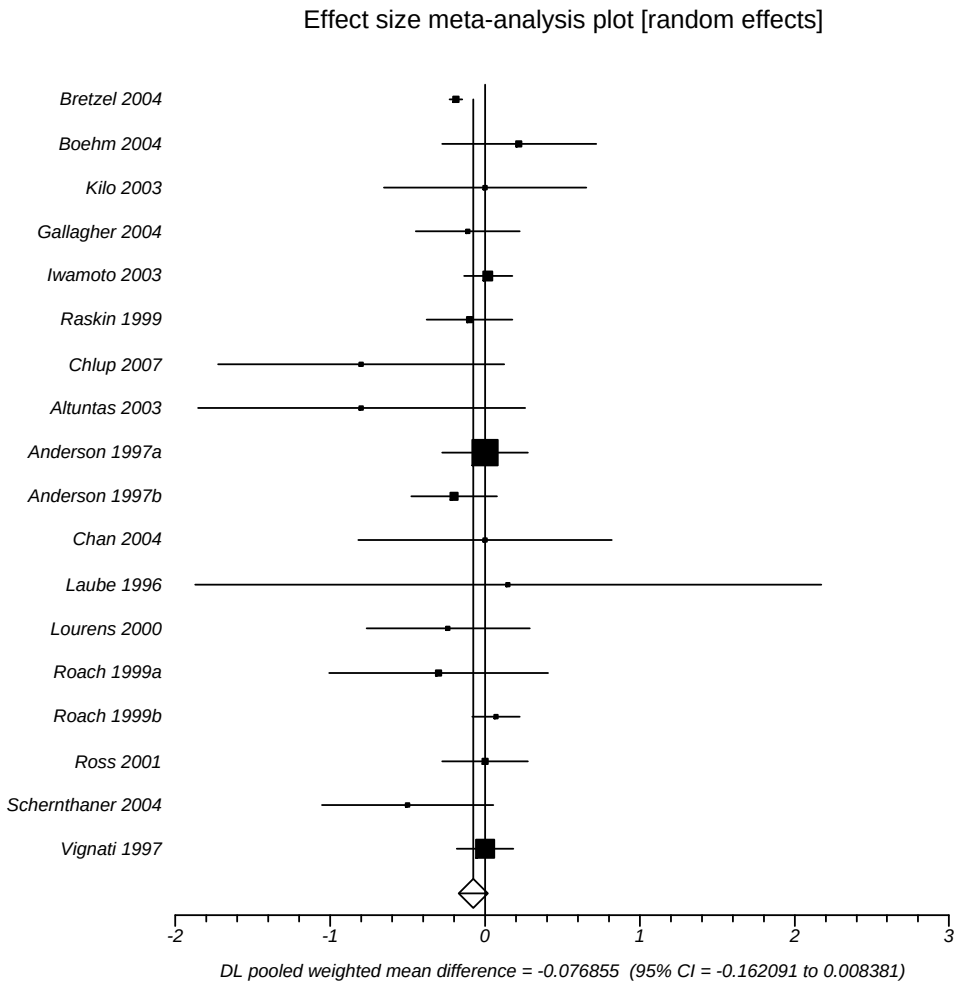


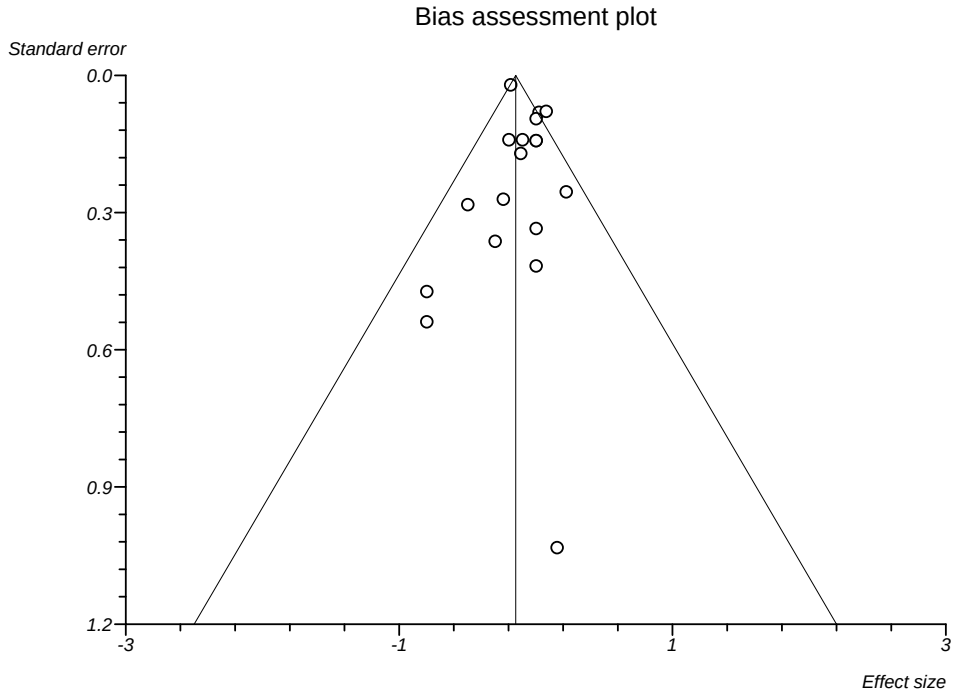
Aspart and lispro combined vs. regular human insulin – Type 1:





Aspart and lispro combined vs. regular human insulin – Type 2:




Bias assessment plot
Standard error
0.0
0.3
0.6
0.9
1.2
-3
-1
1
3
Effect size

Attachment 4: GRADE tables

Author(s): P. Whyte
Date: 2011-01-28
Question: Should lispro vs regular human insulin be used in Type 1 adults?
Settings: International
Bibliography: Singh 2009

Table G1: Lispro vs. regular human insulin – Type 1 adults

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	lispro	regular human insulin	Relative (95% CI)	Absolute		
HbA1c (Better indicated by lower values)												
22	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	2984	3037	-	0.09 lower (0.16 to 0.02 lower)[3]	⊕OOO VERY LOW	CRITICAL
severe hypoglycaemia												
10[4]	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	0/0 (0%)[6]	0%	RR 0.80 (0.67 to 0.96)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕OOO VERY LOW	CRITICAL
nocturnal hypoglycaemia												
4[7]	randomised trials	very serious[5]	serious[8]	no serious indirectness	no serious imprecision	reporting bias[2]	0/0 (0%)[9]	0%	rate ratio 0.51 (42 to 0.62)	0 fewer per 1000 (from 0 more to 0 fewer)	⊕OOO VERY LOW	CRITICAL

[1] No trials were double-blinded and allocation concealment only adequately described for 2 trials; randomisation method described in only 4 trials, blinding of outcome assessor not reported across trials.
[2] Most trials are industry-sponsored.
[3] Difference would not be considered clinically meaningful.
[4] Anderson 1997, Bode 2002, Ciofetta 1999, Vignati 1997, Valle, 2001, Ferguson 2001, Gale 2000, Hedman 2001, Linkeschova 2003, Raskin 2001.
[5] No trials were double-blinded, allocation concealment unclear and randomisation not described.
[6] Numbers with event not provided for groups, only total N of 4502 for both lispro and regular human insulin groups combined.
[7] Bode 2002, Roach 1999, Gale 2000, Holleman 1997.
[8] Significant heterogeneity with I^2=73.1%.
[9] Numbers with event not provided for groups, only total N of 725 for both lispro and regular human insulin combined.

Author(s): P. Whyte
Date: 2011-02-04
Question: Should lispro vs regular human insulin be used in Type 1 children and adolescents?
Settings: International
Bibliography: Singh 2009

Table G2: Lispro vs. regular human insulin in Type 1 children and adolescents

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	lispro	regular human insulin	Relative (95% CI)	Absolute		
HbA1c (Better indicated by lower values)												
4[1]	randomised trials	very serious[2]	serious[3]	no serious indirectness	no serious imprecision	reporting bias[4]	0[5]	0[5]	-	0.14 higher (0.18 lower to 0.46 higher)	⊕OOO VERY LOW	CRITICAL
severe hypoglycaemia (children)												
3[6]	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[4]	0/0 (0%)[8]	0%	RR 0.69 (0.24 to 2.01)	0 fewer per 1000 (from 0 fewer to 0 more)	⊕OOO VERY LOW	CRITICAL
nocturnal hypoglycaemia (children)												
3[9]	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[4]	0/0 (0%)[10]	0%	RR 0.69 (0.24 to 2.01)	0 fewer per 1000 (from 0 fewer to 0 more)	⊕OOO VERY LOW	CRITICAL
severe hypoglycaemia ((adolescents)												
1[11]	randomised trials	very serious[12]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/0 (0%)[10]	0%	RR 1.00 (0.29 to 3.43)	0 fewer per 1000 (from 0 fewer to 0 more)	⊕⊕OO LOW	CRITICAL
nocturnal hypoglycaemia ((adolescents)												
1[11]	randomised trials	very serious[12]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/0 (0%)[10]	0%	rate ratio 0.61 (0.57 to 0.64)	0 fewer per 1000 (from 0 fewer to 0	⊕⊕OO LOW	CRITICAL

										fewer)		

[1] Fairchild 2000, Tupola 2001, Deeb 2001, Ford-Adams 2003.
[2] No trials were double-blinded and allocation concealment only adequately described for 1trial; blinding of outcome assessor not reported across trials.
[3] Moderate degree of heterogeneity with I^2=45.3%.
[4] Most trials were industry-sponsored.
[5] N of lispro and regular human insulin groups not provided in review; total N was 286.
[6] Tubiana-Rufi 2004, Deeb 2001, Ford-Adams 2003.
[7] No trials were double-blinded, allocation concealment unclear in 2 of 3 trials, randomisation not described across trials and outcome assessors not blinded.
[8] Numbers were not provided, only total N for both lispro and regular human insulin groups (n=222).
[9] Fairchild 2000, Tupola 2001, Ford-Adams 2003.
[10] Numbers were not provided, only total N for both lispro and regular human insulin groups (n=234).
[11] Holcombe 2002.
[12] Trial was not blinded, allocation concealment was unclear, blinding of outcome assessors not reported and randomisation methods not reported.

Author(s): P. Whyte
Date: 2011-02-05
Question: Should lispro vs regular human insulin be used in Type 2 patients?
Settings: International
Bibliography: Singh 2009

Table G3: Lispro vs. regular human insulin – Type 2 patients

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	lispro	regular human insulin	Relative (95% CI)	Absolute		
HbA1c (Better indicated by lower values)												
11[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	2984	3037	-	0.03 higher (0.12 lower to 0.06 higher)	⊕OOO VERY LOW	CRITICAL
severe hypoglycaemia												
2[4]	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	0/0 (0%)[6]	0%	RR 0.43 (0.08 to 2.37)	0 fewer per 1000 (from 0 fewer to 0 more)	⊕OOO VERY LOW	CRITICAL
nocturnal hypoglycaemia												
1[7]	randomised trials	very serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/0 (0%)[9]	0%	RR 1.63 (0.71 to 3.63)	0 more per 1000 (from 0 fewer to 0 more)	⊕⊕OO LOW	CRITICAL

[1] Altuntas 2003, Anderson 1997a, Anderson 1997b, Chan 2004, Laube 1998, Lourens 2000, Roach 1999a, Roach 1999b, Ross 2001, Schemthaner 2004, Vignati 1997.
[2] No trials were double-blinded, none described method of randomisation, allocation concealment was unclear across trials and blinding of outcome assessors was not reported or not used.
[3] Most trials were industry-sponsored.
[4] Anderson 1997, Roach 1999.
[5] Trials were not blinded, method of randomisation not described, allocation concealment unclear and blinding of outcome assessors not reported or not used.
[6] N with event and N in each group not provided in review, total N=1622.
[7] Roach 1999.
[8] Trial was not blinded, randomisation method not described, allocation concealment unclear and outcome assessors not blinded.

[9] N with event and N in each group not provided in review, total N=178.

Author(s): P. Whyte
Date: 2011-02-05
Question: Should aspart vs regular human insulin be used in Type 1 adults?
Settings: International
Bibliography: Singh 2009

Table G4: Aspart vs. regular human insulin – Type 1 adults

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	aspart	regular human insulin	Relative (95% CI)	Absolute		
HbA1c (Better indicated by lower values)												
7[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	1892	1143	-	0.13 lower (0.2 to 0.07 lower)	⊕OOO VERY LOW	CRITICAL
severe hypoglycaemia												
4[4]	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	0/0 (0%)[6]	0%	RR 0.83 (0.65 to 1.04)	0 fewer per 1000 (from 0 fewer to 0 more)	⊕OOO VERY LOW	CRITICAL

[1] Bode 2001, Bode 2002, Heller 2004, Home 2000, Iwamoto 2001, Raskin 2001, Tamas 2001.
[2] Only 1 of 7 trials was double-blinded, most had unclear allocation concealment, randomisation methods were not described and blinding of outcome assessors either not reported or not used.
[3] Most trials were industry-sponsored.
[4] Bode 2002, Iwamoto 2003, Home 1998, Home 2000.
[5] Only 1 of 4 trials had blinding, allocation concealment was unclear, randomisation method was not described across trials and blinding of outcome assessors was not reported or not used.
[6] Number of patients with events and number in each group not provided, only overall N provided (N=1814).

Author(s): P. Whyte
Date: 2011-02-05
Question: Should aspart vs regular human insulin be used in Type 2 patients?
Settings: International
Bibliography: Singh 2009

Table G5: Aspart vs. regular human insulin – Type 2 patients

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	aspart	regular human insulin	Relative (95% CI)	Absolute		
HbA1c (Better indicated by lower values)												
6[1]	randomised trials	very serious[2]	serious[3]	no serious indirectness	no serious imprecision	reporting bias[4]	615	416	-	0.09 lower (0.21 lower to 0.04 higher)	⊕OOO VERY LOW	CRITICAL
severe hypoglycaemia												
1[5]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/0 (0%)[6]	0%	RR 0.39 (0.11 to 1.36)	0 fewer per 1000 (from 0 fewer to 0 more)	⊕⊕OO LOW	CRITICAL
nocturnal hypoglycaemia												
1[7]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/0 (0%)[8]	0%	RR 0.65 (0.28 to 1.53)	0 fewer per 1000 (from 0 fewer to 0 more)	⊕⊕OO LOW	CRITICAL

[1] Boehm 2004, Bretzel 2004, Gallagher 2005, Iwamoto 2003, Kilo 2003, Raskin 1999.
[2] Trial was not double-blinded, allocation concealment was unclear and it was not reported if outcome assessors were blinded.
[3] Heterogeneity was relatively high, with I^2=47.1%.
[4] Most trials were industry-sponsored.
[5] Boehm 2004.
[6] N with event and N in each group not provided in review, total N=121.
[7] Kilo 2003.
[8] N with event and N in each group not provided in review, total N=93.

Author(s): P. Whyte
Date: 2011-02-05
Question: Should glargine vs NPH be used in Type 1 adults?[1]
Settings: International
Bibliography: Singh 2009

Table G6: Glargine vs. NPH in type 1 adults (with bolus insulin)

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	glargine	NPH	Relative (95% CI)	Absolute		
HbA1c (Better indicated by lower values)												
11[2]	randomised trials	very serious[3]	no serious inconsistency[4]	no serious indirectness	no serious imprecision	none	1358	1370	-	0.11 lower (0.21 to 0.02 lower)[5]	⊕⊕OO LOW	CRITICAL
severe hypoglycaemia												
7[6]	randomised trials	very serious[3]	no serious inconsistency[7]	no serious indirectness	no serious imprecision	none	0/0 (0%)[8]	0%	RR 0.82 (0.52 to 1.29)	0 fewer per 1000 (from 0 fewer to 0 more)	⊕⊕OO LOW	CRITICAL
nocturnal hypoglycaemia												
5[9]	randomised trials	very serious[3]	serious[10]	no serious indirectness	no serious imprecision	none	0/0 (0%)[11]	0%	RR 0.97 (0.87 to 1.09)	0 fewer per 1000 (from 0 fewer to 0 more)	⊕OOO VERY LOW	CRITICAL

[1] All long-acting insulins were administered with bolus insulin, either regular human or rapid-acting analogues.
[2] Bolli 2006, Davies 2005, Fulcher 2005, Home 2005, Pesic 2006, Pieber 2000, Porcellati 2004, Raskin 2000, Ratner 2000, Rosenstock 2000, Rossetti 2003.
[3] No trials were double-blind, randomisation methods were described for only one trial, allocation concealment was unclear across all trials except one and blinding of outcome assessors was either not reported or not used.
[4] Some heterogeneity, with I^2=38.9%.
[5] While statistically significant, the difference in HbA1c is less than a clinically important minimal difference.
[6] Davies 2005, Pieber 2000, Raskin 2000, Home 2005, Porcellati 2004, Ratner 2000, Rossetti 2003.
[7] Some heterogeneity, with I^2=33.0%.
[8] N with event and N in each group not provided in review, total N=2227.
[9] Pieber 2000, Raskin 2000, Fulcher 2005, Hershon 2004, Home 2005.
[10] Significant heterogeneity with I^2=65.6%

[11] N with event and N in each group not reported in review, total N=1943.

Author(s): P. Whyte
Date: 2011-02-06
Question: Should glargine vs NPH be used in Type 1 children and adolescents?[1]
Settings: International
Bibliography: Singh 2009

Table G7: Glargine vs. NPH in Type 1 children and adolescents (with bolus insulin)

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	glargine	NPH	Relative (95% CI)	Absolute		
HbA1c (Better indicated by lower values)												
4[2]	randomised trials	very serious[3]	serious[4]	no serious indirectness	no serious imprecision	none	0[5]	0[5]	-	0.25 lower (0.55 lower to 0.05 higher)	⊕OOO VERY LOW	CRITICAL
severe hypoglycaemia												
4[6]	randomised trials	very serious[3]	no serious inconsistency[7]	no serious indirectness	no serious imprecision	none	0/0 (0%)[8]	0%	RR 1.18 (0.59 to 2.35)	0 more per 1000 (from 0 fewer to 0 more)	⊕⊕OO LOW	CRITICAL
nocturnal hypoglycaemia												
1[9]	randomised trials	very serious[10]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/0 (0%)[11]	0%	RR 0.71 (0.43 to 1.18)	0 fewer per 1000 (from 0 fewer to 0 more)	⊕⊕OO LOW	CRITICAL

[1] All long-acting insulins used with bolus insulin, wither regular human or rapid-acting analogues.
[2] Mianowska 2006, Chase 2006, Kawamura 2005, Schober 2002.
[3] None of the trials were double-blind, with randomisation method not described, allocation concealment unclear across trials and blinding of outcome assessors either not reported or not used.
[4] Significant heterogeneity with I^2=61.8%.
[5] N in each group not provided in review, total N=680.
[6] Mianowska 2006, Chase 2006, White 2006, Schober 2002.

[7] Some heterogeneity with I^2=48.0%.
[8] N with event and N in each group not provided by review, total N=727.
[9] Schober 2002.
[10] Trial was not double-blinded, randomisation method not described and allocation concealment unclear.
[11] N with event and N in each group not provided in review, total N=349.

Author(s): P. Whyte
Date: 2011-02-06
Question: Should glargine + orals vs NPH + orals be used in Type 2 patients?
Settings: International
Bibliography: Singh 2009

Table G8: Glargine + orals vs. NPH + orals in Type 2

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	glargine + orals	NPH + orals	Relative (95% CI)	Absolute		
HbA1c (Better indicated by lower values)												
9[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	1689	1708	-	0.05 lower (0.13 lower to 0.04 higher)	⊕OOO VERY LOW	CRITICAL
severe hypoglycaemia												
7	randomised trials	very serious[4]	serious[5]	no serious indirectness	no serious imprecision	reporting bias[3]	0/0 (0%)[6]	0%	RR 0.66 (0.29 to 1.48)	0 fewer per 1000 (from 0 fewer to 0 more)	⊕OOO VERY LOW	CRITICAL
nocturnal hypoglycaemia												
7[7]	randomised trials	very serious[4]	no serious inconsistency[8]	no serious indirectness	no serious imprecision	reporting bias[3]	0/0 (0%)	0%	RR 0.56 (0.47 to 0.68)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕OOO VERY LOW	CRITICAL

[1] Yki-Jarvinen 2000, Fritsche 2003, HOE 2003, Massi Benedetti 2003, Riddle 2003, Eliaschewitz 2006, Yki-Jarvinen 2006, Pan 2007, Wang 2007.
[2] None of the trials were double-blinded, allocation concealment unclear across trials, blinding of outcome assessor either not reported or not used, only 5 trials provided description of method of randomisation.

[3] Most trials are industry-sponsored.
[4] None of the trials were double-blinded, allocation concealment unclear across trials, blinding of outcome assessor either not reported or not used, only 4 trials provided description of method of randomisation.
[5] Significant heterogeneity with I^2=64.3%.
[6] N with event and N in each group not provided in review, total N=2866.
[7] Eliaschewitz 2006, Pan 2007, Wang 2007, Fritsche 2003, Massi Benedetti 2003, Yki-Jarvinen 2000, HOE 2003.
[8] Some heterogeneity with I^2=32.3%.

Author(s): P. Whyte
Date: 2011-02-06
Question: Should detemir vs NPH be used in Type 1 adults?[1]
Settings: International
Bibliography: Singh 2009

Table G9: Detemir vs. NPH in Type 1 adults (with bolus insulin)

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	detemir	NPH	Relative (95% CI)	Absolute		
HbA1c (Better indicated by lower values)												
7[2]	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1539	1019	-	0.06 lower (0.13 lower to 0.02 higher)	⊕⊕OO LOW	CRITICAL
severe hypoglycaemia												
7[4]	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/0 (0%)[5]	0%	RR 0.74 (0.58 to 0.96)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕OO LOW	CRITICAL
nocturnal hypoglycaemia												
6[6]	randomised trials	very serious[3]	no serious inconsistency[7]	no serious indirectness	no serious imprecision	none	0/0 (0%)[8]	0%	RR 0.92 (0.85 to 0.98)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕OO LOW	CRITICAL

[1] All long-acting insulins were administered with bolus insulin, either regular human or rapid-acting analogues.
[2] Vague 2003, Home 2004, Russell-Jones 2004, Standl 2004, De Leeuw 2005, Pieber 2005, Kolendorf 2006.

[3] None of the trials were double-blind, allocation concealment was unclear across trials, method of randomisation not described for all trials and blinding of outcome assessors was not reported or not used.
[4] De Leeuw 2005., Hermansen 2004, Home 2004, Pieber 2005, Russell-Jones 2004, Standl 2004, Vague 2003.
[5] N with event and N in each group not provided in review, total N=2442.
[6] Kolendorf 2006, De Leeuw 2005, Pieber 2005, Russell-Jones 2004, Standl 2004, Vague 2003.
[7] Some heterogeneity with I^2=32.2%.
[8] N with event and N in each group not provided in review, total N=2311.

Author(s): P. Whyte
Date: 2011-02-06
Question: Should detemir vs NPH be used in Type 1 children and adolescents?[1]
Settings: Europe and Israel
Bibliography: Singh 2009

Table G10: Detemir vs. NPH in Type 1 children and adolescents (with bolus insulin)

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	detemir	NPH	Relative (95% CI)	Absolute		
HbA1c (Better indicated by lower values)												
1[2]	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0[4]	0	-	0.10 higher (0.1 lower to 0.3 higher)	⊕⊕OO LOW	CRITICAL
severe hypoglycaemia												
1[2]	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/0 (0%)[5]	0%	RR 0.80 (0.5 to 1.28)	0 fewer per 1000 (from 0 fewer to 0 more)	⊕⊕OO LOW	CRITICAL
nocturnal hypoglycaemia												
1[2]	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/0 (0%)[5]	0%	RR 0.85 (0.77 to 0.94)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕OO LOW	CRITICAL

[1] Long-acting insulins used with bolus insulin, either regular human or rapid-acting analogues.
[2] Robertson 2007.

[3] Trial was not double-blinded, randomisation method not described and outcome assessors not blinded.
[4] N in each group not provided in review, total N=347.
[5] N with event and N in each group not provided in review, total N=347.

Author(s): P. Whyte
Date: 2011-02-06
Question: Should detemir + orals vs NPH + orals be used in Type 2 patients?
Settings: International
Bibliography: Singh 2009

Table G11: Detemir + orals vs. NPH + orals in type 2 patients

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	detemir + orals	NPH + orals	Relative (95% CI)	Absolute		
HbA1c (Better indicated by lower values)												
3[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	579	580	-	0.13 higher (0.03 to 0.22 higher)	⊕OOO VERY LOW	CRITICAL
severe hypoglycaemia												
2[4]	randomised trials	very serious[2]	serious[5]	no serious indirectness	no serious imprecision	reporting bias[3]	0/0 (0%)[6]	0%	RR 0.75 (0.03 to 20.01)	0 fewer per 1000 (from 0 fewer to 0 more)	⊕OOO VERY LOW	CRITICAL
nocturnal hypoglycaemia												
2[4]	randomised trials	very serious[2]	serious[7]	no serious indirectness	no serious imprecision	reporting bias[3]	0/0 (0%)[6]	0%	RR 0.53 (0.31 to 0.91)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕OOO VERY LOW	CRITICAL

[1] Hermansen 2006, Philis-Tsimikas 2006, Tajima 2006.
[2] None of the trials were double-blinded, randomisation not described across trials, outcome assessors not blinded.
[3] Most trials are industry-sponsored.
[4] Hermansen 2006, Philis-Tsimikas 2006.
[5] Significant heterogeneity with I^2=68.8%.
[6] N with event and N in each group not provided in review, total N=808.
[7] Significant heterogeneity with I^2=51.6%.

Author(s): P. Whyte
Date: 2011-02-06
Question: Should detemir + aspart vs NPH + aspart be used in Type 2 patients?
Settings: Europe
Bibliography: Singh 2009

Table 12: Detemir + aspart vs. NPH + aspart in Type 2 patients

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	detemir + aspart	NPH + aspart	Relative (95% CI)	Absolute		
HbA1c (Better indicated by lower values)												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias	341	164	-	0.10 higher (0.18 lower to 0.38 higher)	⊕OOO VERY LOW	CRITICAL
nocturnal hypoglycaemia												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	52/341 (15.2%)	38/164 (23.2%)	RR 0.66 (0.45 to 0.96)	79 fewer per 1000 (from 9 fewer to 127 fewer)	⊕⊕OO LOW	CRITICAL
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		

[1] Haak 2005.
[2] Trial was not double-blinded, randomisation method was not described, allocation concealment was unclear and blinding of outcome assessor was not reported.

Author(s): P. Whyte
Date: 2011-02-06
Question: Should detemir + aspart vs NPH + regular human insulin be used in Type 2 patients?
Settings: Europe
Bibliography: Singh 2009

Table G13: Detemir + aspart vs. NPH + regular human insulin in Type 2 patients

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	detemir + aspart	NPH + regular human insulin	Relative (95% CI)	Absolute	Quality	Importance
HbA1c (Better indicated by lower values)												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias	195	199	-	0.06 higher (0.31 lower to 0.19 higher)	⊕OOO VERY LOW	CRITICAL
severe hypoglycaemia												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2/195 (1%)	0%	RR 1.02 (0.26 to 4.02)	0 more per 1000 (from 0 fewer to 0 more)	⊕⊕OO LOW	CRITICAL
nocturnal hypoglycaemia												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	31/195 (15.9%)	0%	RR 0.54 (0.3 to 0.97)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕OO LOW	CRITICAL

[1] Raslova 2004
[2] Trial was not double-blinded, randomisation method not described, allocation concealment unclear and outcome assessors not blinded.