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(Ultra-)long-acting insulin analogues versus NPH insulin (human isophane insulin) for adults with type 2 diabetes mellitus (Review)

Semlitsch T, Engler J, Siebenhofer A, Jeitler K, Berghold A, Horvath K

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[Intervention Review]

(Ultra-)long-acting insulin analogues versus NPH insulin (human isophane insulin) for adults with type 2 diabetes mellitus

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ABSTRACT

Background

Evidence that antihyperglycaemic therapy is beneficial for people with type 2 diabetes mellitus is conflicting. While the United Kingdom Prospective Diabetes Study (UKPDS) found tighter glycaemic control to be positive, other studies, such as the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, found the effects of an intensive therapy to lower blood glucose to near normal levels to be more harmful than beneficial. Study results also showed different effects for different antihyperglycaemic drugs, regardless of the achieved blood glucose levels. In consequence, firm conclusions on the effect of interventions on patient-relevant outcomes cannot be drawn from the effect of these interventions on blood glucose concentration alone. In theory, the use of newer insulin analogues may result in fewer macrovascular and microvascular events.

Objectives

To compare the effects of long-term treatment with (ultra-)long-acting insulin analogues (insulin glargine U100 and U300, insulin detemir and insulin degludec) with NPH (neutral protamine Hagedorn) insulin (human isophane insulin) in adults with type 2 diabetes mellitus.

Search methods

For this Cochrane Review update, we searched CENTRAL, MEDLINE, Embase, ICTRP Search Portal and ClinicalTrials.gov. The date of the last search was 5 November 2019, except Embase which was last searched 26 January 2017. We applied no language restrictions.

Selection criteria

We included randomised controlled trials (RCTs) comparing the effects of treatment with (ultra-)long-acting insulin analogues to NPH in adults with type 2 diabetes mellitus.

Data collection and analysis

Two review authors independently selected trials, assessed risk of bias, extracted data and evaluated the overall certainty of the evidence using GRADE. Trials were pooled using random-effects meta-analyses.

Main results

We identified 24 RCTs. Of these, 16 trials compared insulin glargine to NPH insulin and eight trials compared insulin detemir to NPH insulin. In these trials, 3419 people with type 2 diabetes mellitus were randomised to insulin glargine and 1321 people to insulin detemir. The duration of the included trials ranged from 24 weeks to five years. For studies, comparing insulin glargine to NPH insulin, target values ranged from 4.0 mmol/L to 7.8 mmol/L (72 mg/dL to 140 mg/dL) for fasting blood glucose (FBG), from 4.4 mmol/L to 6.6 mmol/L (80 mg/dL to 120 mg/dL) for nocturnal blood glucose and less than 10 mmol/L (180 mg/dL) for postprandial blood glucose, when applicable. Blood glucose and glycosylated haemoglobin A1c (HbA1c) target values for studies comparing insulin detemir to NPH insulin ranged from 4.0 mmol/L to 7.0 mmol/L (72 mg/dL to 126 mg/dL) for FBG, less than 6.7 mmol/L (120 mg/dL) to less than 10 mmol/L (180 mg/dL) for postprandial blood glucose, 4.0 mmol/L to 7.0 mmol/L (72 mg/dL to 126 mg/dL) for nocturnal blood glucose and 5.8% to less than 6.4% HbA1c, when applicable.

All trials had an unclear or high risk of bias for several risk of bias domains.

Overall, insulin glargine and insulin detemir resulted in fewer participants experiencing hypoglycaemia when compared with NPH insulin. Changes in HbA1c were comparable for long-acting insulin analogues and NPH insulin.

Insulin glargine compared to NPH insulin had a risk ratio (RR) for severe hypoglycaemia of 0.68 (95% confidence interval (CI) 0.46 to 1.01; P = 0.06; absolute risk reduction (ARR) −1.2%, 95% CI −2.0 to 0; 14 trials, 6164 participants; very low-certainty evidence). The RR for serious hypoglycaemia was 0.75 (95% CI 0.52 to 1.09; P = 0.13; ARR −0.7%, 95% CI −1.3 to 0.2; 10 trials, 4685 participants; low-certainty evidence). Treatment with insulin glargine reduced the incidence of confirmed hypoglycaemia and confirmed nocturnal hypoglycaemia.

Treatment with insulin detemir compared to NPH insulin found an RR for severe hypoglycaemia of 0.45 (95% CI 0.17 to 1.20; P = 0.11; ARR −0.9%, 95% CI −1.4 to 0.4; 5 trials, 1804 participants; very low-certainty evidence). The Peto odds ratio for serious hypoglycaemia was 0.16, 95% CI 0.04 to 0.61; P = 0.007; ARR −0.9%, 95% CI −1.1 to −0.4; 5 trials, 1777 participants; low-certainty evidence). Treatment with detemir also reduced the incidence of confirmed hypoglycaemia and confirmed nocturnal hypoglycaemia.

Information on patient-relevant outcomes such as death from any cause, diabetes-related complications, health-related quality of life and socioeconomic effects was insufficient or lacking in almost all included trials. For those outcomes for which some data were available, there were no meaningful differences between treatment with glargine or detemir and treatment with NPH. There was no clear difference between insulin-analogues and NPH insulin in terms of weight gain.

The incidence of adverse events was comparable for people treated with glargine or detemir, and people treated with NPH.

We found no trials comparing ultra-long-acting insulin glargine U300 or insulin degludec with NPH insulin.

Authors' conclusions

While the effects on HbA1c were comparable, treatment with insulin glargine and insulin detemir resulted in fewer participants experiencing hypoglycaemia when compared with NPH insulin. Treatment with insulin detemir also reduced the incidence of serious hypoglycaemia. However, serious hypoglycaemic events were rare and the absolute risk reducing effect was low. Approximately one in 100 people treated with insulin detemir instead of NPH insulin benefited.

In the studies, low blood glucose and HbA1c targets, corresponding to near normal or even non-diabetic blood glucose levels, were set. Therefore, results from the studies are only applicable to people in whom such low blood glucose concentrations are targeted. However, current guidelines recommend less-intensive blood glucose lowering for most people with type 2 diabetes in daily practice (e.g. people with cardiovascular diseases, a long history of type 2 diabetes, who are susceptible to hypoglycaemia or older people). Additionally, low-certainty evidence and trial designs that did not conform with current clinical practice meant it remains unclear if the same effects will be observed in daily clinical practice. Most trials did not report patient-relevant outcomes.

PLAIN LANGUAGE SUMMARY

(Ultra-)long-acting insulin analogues compared with NPH insulin (human isophane insulin) for adults with type 2 diabetes mellitus

Introduction

Type 2 diabetes mellitus is a progressive condition, meaning that ever more antihyperglycaemic medications are needed to achieve recommended glycosylated haemoglobin A1c (HbA1c) levels with increasing disease duration. The HbA1c test measures blood glucose levels over two to three months. Eventually, many people will require insulin treatment. Insulin treatment is frequently performed by administering human basal insulins once or twice daily. Basal insulins are long-acting insulins with delayed onset of action covering the basic insulin needs of the body. Fast-acting insulins are used to cover meals. The most common side effects of insulin treatment are low blood sugar (hypoglycaemia) and weight gain. Newer synthetic insulins, so-called (ultra-)long-acting insulin-analogues, have been developed with the intention of minimising side effects and allowing better blood glucose control.

Review question

We wanted to compare the effects of treatment with (ultra-)long-acting insulin analogues with NPH (neutral protamine Hagedorn) insulin (human isophane insulin).

Search date

The evidence is current to 5 November 2019.

Background

It is unclear if or to what extent (ultra-)long-acting insulin analogues show more benefit or less harm compared to NPH insulin.

Study characteristics

All 24 included studies were randomised controlled trials (clinical studies in which people are randomly assigned to one of two or more treatment groups). Sixteen studies compared the long-acting insulin glargine to NPH insulin and eight studies compared the long-acting insulin detemir to NPH insulin. In these studies, 3419 people with type 2 diabetes mellitus were randomised to insulin glargine and 1321 people to insulin detemir. The duration of the studies ranged from 24 weeks to 5 years.

Key results

The different insulins reduced HbA1c by about the same amount.

Treatment with insulin glargine or insulin detemir instead of NPH insulin resulted in fewer people with hypoglycaemia. Treatment with insulin detemir reduced the risk of serious hypoglycaemia. However, serious hypoglycaemia occurred only rarely in the studies, in fewer than one in 100 people treated with insulin detemir and in about one in 100 people treated with NPH insulin. Approximately one in 100 people treated with insulin detemir instead of NPH insulin benefited.

Information on diabetes-related complications (such as heart disease, renal disease, damage to the retina of the eyes and amputations), death from any cause and health-related quality of life was scarce. When available, study results did not suggest clear differences between insulin analogues and NPH insulin.

There was no clear difference between insulin analogues and NPH insulin for side effects or weight gain.

None of the included studies reported on socioeconomic effects (such as costs of the intervention, absence from work, medication consumption).

Certainty of the evidence

In the studies, very low blood glucose and HbA1c target values were set. However, doctors often recommend higher targets for people with a long history of type 2 diabetes, who have had a heart attack or stroke, or who are old. With higher target values, hypoglycaemia occurs less frequently and more people need to be treated with insulin analogues instead of NPH insulin to prevent hypoglycaemia in one person. Therefore, study results are only applicable to people who are treated to such low blood glucose target values.

In many studies, an adequate adjustment of NPH insulin was not possible. However, doctors will do that in daily practice. Therefore, a further decrease in the benefit of insulin analogues is expected.

Treatment in all but one study lasted for 12 months or less. However, diabetes-related complications usually only develop over many years. Thus, most studies were unable to answer the important question whether treatment with different insulin preparations has different effects on diabetes-related complications. This means that potentially important differences between insulin analogues and NPH insulin were not detected.

All studies had problems in the way they were conducted.

SUMMARY OF FINDINGS

Summary of findings 1. Insulin glargine versus NPH insulin for type 2 diabetes mellitus

Insulin glargine vs NPH insulin for type 2 diabetes mellitus

Patient: participants with type 2 diabetes mellitus

Intervention: insulin glargine

Comparison: NPH insulin (human isophane insulin)

Outcomes	Risk for NPH insulin	Risk for insulin glargine	Relative effect (95% CI)	No of participants (trials)	Certainty of the evidence (GRADE)	Comments
Diabetes-related complications (1) Fatal MI (2) Fatal stroke (3) Progression in retinopathy (4) Amputations (5) ESRD Follow-up: 6 months to 36 weeks	(1) See comment (2) See comment **(3) 101 per 1000** (4) See comment (5) See comment	(1) See comment (2) See comment **(3) 104 per 1000** (60 to 178) (4) See comment (5) See comment	(1) + (2) See comment (3) **RR 1.03** (0.60 to 1.77) (4) + (5) See comment	(1) 934 (4 RCTs) (2) 934 (4 RCTs) (3) 1947 (5 RCTs) (4) 34 (1 RCT) (5) 34 (1 RCT)	(1) + (2) ⊕⊖⊖⊖ **Very low[a]** (3) ⊕⊖⊖⊖ **Very low[b]** (4) + (5) ⊕⊖⊖⊖ **Very low[c]**	(1) 1 trial reported 3/352 participants in the glargine 100 IU group vs 0/349 participants in the NPH group experienced fatal MI; 3 additional trials with 233 participants reported that no fatal MI occurred. (2) No fatal strokes occurred. (3) The 95% prediction interval ranged between 0.22 and 4.83. (4) + (5) 1 trial reported that no amputation or ESRD occurred.
Hypoglycaemic episodes (1) Severe hypoglycaemia (2) Serious hypoglycaemia (3) Confirmed hypoglycaemia (BG < 75 mg/dL) (4) Confirmed hypoglycaemia (BG < 55 mg/dL) (5) Confirmed nocturnal hypoglycaemia (BG < 75 mg/dL)	(1) **37 per 1000** (2) **27 per 1000** (3) **572 per 1000** (4) **180 per 1000** (5) **351 per 1000** (6) **115 per 1000**	(1) **25 per 1000** (17 to 37) (2) **20 per 1000** (14 to 29) (3) **526 per 1000** (486 to 578) (4) **159 per 1000** (146 to 173) (5) **274 per 1000** (239 to 312)	(1) **RR 0.68** (0.46 to 1.01) (2) **RR 0.75** (0.52 to 1.09) (3) **RR 0.92** (0.85 to 1.01) (4) **RR 0.88** (0.81 to 0.96) (5) **RR 0.78** (0.68 to 0.89)	(1) 6164 (14 RCTs) (2) 4685 (10 RCTs) (3) 4115 (7 RCTs) (4) 4388 (8 RCTs) (5) 4225 (8 RCTs)	(1) ⊕⊖⊖⊖ **Very low[d]** (2) ⊕⊕⊖⊖ **Low[e]** (3) ⊕⊖⊖⊖ **Very low[f]** (4) ⊕⊕⊕⊖ **Moderate[g]** (5) ⊕⊖⊖⊖ **Very low[f]**	(1) The 95% prediction interval ranged between 0.33 and 1.40. (2) The 95% prediction interval ranged between 0.48 and 1.16. (3) The 95% prediction interval ranged between 0.69 and 1.22. (4) The 95% prediction interval ranged between 0.79 and 0.98. (5) The 95% prediction interval ranged between 0.53 and 1.14.

(6) Confirmed nocturnal hypoglycaemia (BG < 55 mg/dL) Follow-up: 24 weeks to 5 years		(6) **85 per 1000** (74 to 98)	(6) **RR 0.74** (0.64 to 0.85)	(6) 4759 (8 RCTs)	(6) ⊕⊕⊕⊖ **Moderate**[g]	(6) The 95% prediction interval ranged between 0.62 and 0.88.
HRQoL Follow-up: 28 weeks to 48 weeks	See comment			1228 (3 RCTs)	⊕⊖⊖⊖ **Very low**[h]	3 trials reported no statically significant differences between glargine groups and NPH groups in HRQoL total scores (W-BQ22; EQ-5) or any subscales.
All-cause mortality Follow-up: 24 weeks to 5 years	**8 per 1000**	**9 per 1000** (5 to 15)	**Peto OR 1.06** (0.62 to 1.82)	6173 (14 RCTs)	⊕⊕⊖⊖ **Low**[i]	—
AEs other than hypoglycaemia (1) SAE (2) Overall AE (3) AE leading to discontinuation Follow-up: 24 weeks to 5 years	(1) **135 per 1000** (2)**662 per 1000** (3) **17 per 1000**	(1) **132 per 1000** (117 to 148) (2) **669 per 1000** (649 to 682) (3)**20 per 1000** (14 to 30)	(1) **RR 0.98** (0.87 to 1.10) (2) **RR 1.01** (0.98 to 1.03) (3) **RR 1.21** (0.84 to 1.76)	(1) 5499 (13 RCTs) (2) 6170 (14 RCTs) (3) 6149 (13 RCTs)	(1) + (2) (+3) ⊕⊕⊕⊖ **Moderate**[j]	(1) The 95% prediction interval ranged between 0.86 and 1.12. (2) The 95% prediction interval ranged between 0.99 and 1.03. (3) The 95% prediction interval ranged between 0.79 and 1.84.
Socioeconomic effects	Not reported					
HbA1c Follow-up: 24 weeks to 5 years	The mean change in HbA1c ranged across control groups from –2.12% to +0.1%	The mean change in HbA1c in the intervention groups was **0.07% lower** (0.18% lower to 0.03% higher)	—	5809 (16 RCTs)	⊕⊕⊖⊖ **Low**[k]	The 95% prediction interval ranged between –46% and 0.32%.

AE: adverse event; **BG:** blood glucose; **CI:** confidence interval; **EQ-5(D):** EuroQol 5 (Dimension); **ESRD:** end-stage renal disease; **HbA1c:** glycosylated haemoglobin A1c; **HRQoL:** health-related quality of life; **MD:** mean difference; **MI:** myocardial infarction; **NPH:** neutral protamine Hagedorn; **OR:** odds ratio; **RCT:** randomised controlled trial; **RR:** risk ratio; **SAE:** serious adverse event; **W-BQ22:** Well-Being Questionnaire (22 items).

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 three levels because of risk of bias and serious imprecision (very sparse data) – see Appendix 1.
[b]Downgraded three levels because of risk of bias, inconsistency and imprecision – see Appendix 1.
[c]Downgraded three levels because of indirectness and serious imprecision (very sparse data) – see Appendix 1.
[d]Downgraded three levels because of risk of bias, imprecision and inconsistency – see Appendix 1.
[e]Downgraded two levels because of risk of bias and imprecision – see Appendix 1.
[f]Downgraded three levels because of risk of bias, inconsistency and imprecision – see Appendix 1.
[g]Downgraded one level because of risk of bias – see Appendix 1.
[h]Downgraded three levels because of risk of bias and serious imprecision – see Appendix 1.
[i]Downgraded two levels because of risk of bias and imprecision – see Appendix 1.
[j]Downgraded one level because of imprecision – see Appendix 1.
[k]Downgraded two levels because of inconsistency and imprecision – see Appendix 1.

Summary of findings 2. Insulin detemir versus NPH insulin for type 2 diabetes mellitus

Insulin detemir vs NPH insulin for type 2 diabetes mellitus

Patient: participants with type 2 diabetes mellitus

Intervention: insulin detemir

Comparison: NPH insulin (human isophane insulin)

Outcomes	Risk for NPH insulin	Risk for insulin detemir	Relative effect (95% CI)	No of participants (trials)	Certainty of the evidence (GRADE)	Comments
Diabetes-related complications (1) Fatal MI (2) Fatal stroke (3) Progression in retinopathy (4) Amputations (5) ESRD	(1) + (2) See comment **(3) 25 per 1000** (4) + (5) See comment	(1) + (2) See comment **(3) 37 per 1000** (17 to 82) (4) + (5) See comment	(1) + (2) See comment (3) **RR 1.50** (0.68 to 3.32) (4) + (5) See comment	(1) + (2) 271 (1 RCT) (3) 972 (2 RCTs) (4) + (5) 271 (1 RCT)	(1) + (2) + (3) + (4) + (5) ⊕⊖⊖⊖ **Very low**[a]	(1) + (2) 1 trial reported that no fatal MI or fatal stroke occurred. (3) – (4) + (5) 1 trial reported that no amputation or ESRD occurred.

Follow-up: 24 weeks to 26 weeks						
Hypoglycaemic episodes (1) Severe hypoglycaemia (2) Serious hypoglycaemia (3) Confirmed hypoglycaemia (BG < 75 mg/dL) (4) Confirmed hypoglycaemia (BG < 55 mg/dL) (5) Confirmed nocturnal hypoglycaemia (BG < 75 mg/dL) (6) Confirmed nocturnal hypoglycaemia (BG < 55 mg/dL) Follow-up: 24 weeks to 7 months	(1) **17 per 1000** (2) **11 per 1000** (3) **562 per 1000** (4) **493 per 1000** (5) **309 per 1000** (6) **40 per 1000**	(1) **8 per 1000** (3 to 21) (2) **2 per 1000** (0 to 7) (3) **410 per 1000** (343 to 484) (4) **237 per 1000** (158 to 350) (5) **176 per 1000** (145 to 210) (6) **13 per 1000** (6 to 25)	(1) **RR 0.45** (0.17 to 1.20) (2) **Peto OR 0.16** (0.04 to 0.61) (3) **RR 0.73** (0.61 to 0.86) (4) **RR 0.48** (0.32 to 0.71) (5) **RR 0.57** (0.47 to 0.68) (6) **RR 0.32** (0.16 to 0.63)	(1) 1804 (5 RCTs) (2) 1777 (5 RCTs) (3) 1718 (4 RCTs) (4) 1718 (4 RCTs) (5) 1718 (4 RCTs) (6) 1718 (4 RCTs)	(1) ⊕⊖⊖⊖ **Very low**[b] (2) ⊕⊕⊖⊖ **Low**[c] (3) ⊕⊕⊖⊖ **Low**[d] (4) + (5) + (6) ⊕⊕⊖⊖ **Low**[e]	(1) The 95% prediction interval ranged between 0.09 and 2.21. (2) – (3) The 95% prediction interval ranged between 0.36 and 1.48. (4) The 95% prediction interval ranged between 0.20 and 1.13. (5) The 95% prediction interval ranged between 0.39 and 0.84. (6) The 95% prediction interval ranged between 0.07 and 1.42.
Health-related quality of life Follow-up: 26 weeks to 36 weeks	See comment			873 (3 RCTs)	⊕⊖⊖⊖ **Very low**[b]	3 trials reported no statically significant difference between detemir groups and NPH groups in HRQoL total scores (ITR-QOLN; DHP-2; SF-36) or any subscales.
All-cause mortality Follow-up: 24 weeks to 48 weeks	**5 per 1000**	**4 per 1000** (1 to 13)	**Peto OR 0.74** (0.20 to 2.65)	2328 (8 RCTs)	⊕⊕⊖⊖ **Low**[f]	—
AEs other than hypoglycaemia (1) SAE (2) Overall AE (3) AE leading to discontinuation Follow-up: 24 weeks to 48 weeks	(1) **71 per 1000** (2)**611 per 1000** (3) **18 per 1000**	(1) **62 per 1000** (45 to 85) (2) **629 per 1000** (586 to 678) (3)**22 per 1000** (12 to 40)	(1) **RR 0.88** (0.64 to 1.20) (2) **RR 1.03** (0.96 to 1.11) (3) **RR 1.22** (0.67 to 2.25)	(1) 2328 (8 RCTs) (2) 2328 (8 RCTs) (3) 2328 (8 RCTs)	(1) + (2) (+3) ⊕⊖⊖⊖ **Moderate**[g]	(1) The 95% prediction interval ranged between 0.60 and 1.30. (2) The 95% prediction interval ranged between 0.94 and 1.13. (3) The 95% prediction interval ranged between 0.57 and 2.62.

Socioeconomic effects	Not reported					
HbA1c Follow-up:	The mean change in HbA1c ranged across control groups from –1.9% to –0.32%	The mean change in HbA1c in the intervention groups was **0.13% higher** (0.02% lower to 0.28% higher)	—	2233 (7 RCTs)	⊕⊕⊖⊖ **Low**[h]	The 95% prediction interval ranged between –0.28% and 0.54%.

AE: adverse event; **BG:** blood glucose; **CI:** confidence interval; **DHP-2:** Diabetes Health Profile 2; **ESRD: e**nd-stage renal disease; **HbA1c:** glycosylated haemoglobin A1c; **HRQoL:** health-related quality of life; **ITR-QOLN:** insulin therapy-related quality of life at night; **MD:** mean difference; **MI:** myocardial infarction; **NPH:** neutral protamine Hagedorn; **OR:** odds ratio; **RR:** risk ratio; **SAE:** serious adverse event; **SF-36:** 36-item Short Form Health Survey.

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 three levels because of risk of bias and serious imprecision (very sparse data) – see Appendix 2.
[b]Downgraded three levels because of risk of bias and serious imprecision – see Appendix 2.
[c]Downgraded two levels because of risk of bias and imprecision – see Appendix 2.
[d]Downgraded two levels because of risk of bias and inconsistency – see Appendix 2.
[e]Downgraded two levels because risk of bias and imprecision – see Appendix 2.
[f]Downgraded two levels because of serious imprecision – see Appendix 2.
[g]Downgraded one level because of imprecision – see Appendix 2.
[h]Downgraded two levels because of inconsistency and imprecision – see Appendix 2.

BACKGROUND

Description of the condition

Type 2 diabetes mellitus is a metabolic disorder characterised by relative insulin deficiency resulting from a reduced sensitivity of tissues to insulin, impaired insulin secretion by pancreatic β-cells, or both (ADA 2020). This in turn leads to chronic hyperglycaemia (i.e. elevated levels of plasma glucose) with disturbances in carbohydrate, fat and protein metabolism (ADA 2020). Long-term complications of diabetes mellitus include retinopathy, nephropathy, neuropathy and increased risk of cardiovascular disease (CVD) (ADA 2020).

Description of the intervention

Type 2 diabetes mellitus is a progressive disease that causes a decline in pancreatic β-cell function. Thus, at some point during the course of the disease, treatment with oral glucose-lowering agents or other non-insulin glucose-lowering agents may not suffice, and exogenous insulin will be necessary to achieve the desired glucose levels. At this stage, treatment with intermediate or long-acting insulins is one of the recommended treatment options (ADA 2020).

Historically, intermediate- and long-acting insulin preparations were obtained by crystallising either protamine (NPH type) or zinc (Lente type). Treatment with these basal insulins, however, has drawbacks. Achieving lower blood glucose levels carries an increased risk of hypoglycaemia (Ahrén 2013). As NPH is associated with a pronounced insulin peak following injection and variable absorption (Heinemann 2000; Lepore 2000), targeting for lower glycosylated haemoglobin A1c (HbA1c) levels is often difficult and leads to a higher incidence of hypoglycaemic events (Ahrén 2013).

To provide insulin with a more suitable physiological time course to people with diabetes mellitus, so-called insulin analogues have been developed. Insulin analogues are insulin-like molecules, engineered on the basis of the molecular structure of human insulin by changing the amino acid sequence and physiochemical properties. Four such (ultra-)long-acting insulin analogues – insulin detemir (Levemir), insulin glargine U100 (Lantus), insulin degludec (Tresiba) and insulin glargine U300 (Toujeo) – are currently available on the market.

Adverse effects of the intervention

Compared to human insulin, some insulin analogues have shown higher mitogenic potency and insulin-growth factor binding affinity in vitro and animal studies (Grant 1993; Jorgensen 1992; King 1985; Kurtzhals 2000). These effects differ depending on the insulin analogue, but results provided in these studies are unable to clarify their relevance for people with diabetes mellitus. The American and European pharmaceutical registration bodies, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have commented on the mitogenic and carcinogenic potency of long-acting insulin analogues and concluded that there appear to be few detrimental effects (EMA 2003; EMA 2004; EMA 2012; FDA 2000; FDA 2005). One cohort study based on data from a large German statutory insurance fund found a dose-dependent increase in cancer risk for treatment with insulin glargine compared with human insulin (Hemkens 2009).

Epidemiological investigations indicate that higher blood glucose concentrations are associated with a higher risk of developing micro- and macrovascular diabetic complications (Adler 1997; Klein 1995; Turner 1998). The United Kingdom Prospective Diabetes Study (UKPDS) showed that lowering blood glucose to near normal levels might reduce microvascular complications (Holman 2008; UKPDS-33 1998; UKPDS 34 1998). However, evidence that the effects of antihyperglycaemic therapy on macrovascular complications and mortality is positive, is conflicting. Several studies investigating the effects of tight versus less tight glycaemic control have not shown a clear reduction in the risk of macrovascular complications (ACCORD 2008; ADVANCE 2008; Duckworth 2009; Kooy 2009). Furthermore, investigations into different pharmacological interventions have shown a reduction in the risk of complications without a significant simultaneous change in blood glucose concentrations (Marso 2016; Zinman 2015), while others have reported an increase in the risk of mortality and macrovascular complications despite a substantial decrease in blood glucose levels (ACCORD 2008; Singh 2007). In consequence, firm conclusions on the effect of interventions on patient-relevant outcomes cannot be drawn from the effect of these interventions on blood glucose concentrations alone.

The new long- and ultra-long-acting insulins are usually more expensive than NPH insulin. While price differences may not be a problem for health services in high-income countries, they may be important in low- and middle-income countries.

How the intervention might work

Based on the altered time-action profiles of insulin analogues, several possible advantages in the therapy of people with type 2 diabetes mellitus have been suggested. For instance, it has been hypothesised that the longer action (lower fasting plasma glucose) and the less pronounced peak (less hypoglycaemia, especially during the night) will enable both HbA1c and the risk of hypoglycaemia to be reduced. It has also been suggested that the use of Insulin glargine or detemir may improve patient's health-related quality of life and treatment satisfaction.

Why it is important to do this review

The aim of the original Cochrane Review was to systematically review the clinical efficacy and safety of insulin glargine and detemir in the treatment of people with type 2 diabetes mellitus. Although their pharmacokinetic profiles appeared to indicate that long-acting insulin analogues improved the insulin therapy of people with type 2 diabetes mellitus, their superiority in a clinical setting had still to be confirmed. This is an update of the original Cochrane Review which was necessary because new trials on the topic have been published and new ultra-long-acting insulin analogues – insulin degludec and insulin glargine U300 – have been launched on the market since publication of the original review.

OBJECTIVES

To compare the effects of long-term treatment with (ultra-)long-acting insulin analogues (insulin glargine U100 and U300, insulin detemir and insulin degludec) with NPH insulin (human isophane insulin) in adults with type 2 diabetes mellitus.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs).

Reports for which no full publication existed were only considered for inclusion in this review if the available information met the publication criteria in the CONSORT statement.

Types of participants

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

Types of interventions

We had intended to compare the following interventions with the comparator.

Only trials reporting on subcutaneously administered insulin were considered for inclusion in this review.

Intervention

- Long-acting insulin analogues (insulin glargine U100 or insulin detemir) or ultra-long-acting insulin analogues (insulin glargine U300 or insulin degludec).

Comparator

- NPH insulin

Interventions in both intervention and comparator groups had to be the same to enable fair comparisons.

Minimum duration of intervention

We considered studies with a minimal duration of 24 weeks. In case of a cross-over design, each of the periods had to last at least 24 weeks.

Minimum duration of follow-up

Minimal duration of follow-up was 24 weeks. In case of a cross-over design, duration of follow-up for each of the periods had to be at least 24 weeks.

We defined extended follow-up periods (also called open-label extension studies) as the follow-up of participants once the original trial as specified in the trial protocol had been terminated. However, such studies are frequently of an observational nature and were only evaluated in case of adverse events (Buch 2011; Megan 2012).

Types of outcome measures

We did not exclude trials solely based on their outcome measures. In case none of our primary or secondary outcomes were reported, we planned to provide at least some basic information in an additional table.

Primary outcomes

- Diabetes-related complications.
- Hypoglycaemic episodes.
- Health-related quality of life.

Secondary outcomes

- All-cause mortality.
- Adverse events other than hypoglycaemia.
- Socioeconomic effects.
- HbA1c.

Method of outcome measurement

- Diabetes-related complications: such as renal failure, amputation, blindness or deterioration in retinopathy, myocardial infarction, stroke, heart failure, revascularisation procedures.
- Hypoglycaemic episodes: number of severe (as defined in the studies), serious (as defined in the studies), confirmed (as defined in the studies) and confirmed nocturnal hypoglycaemic episodes (as defined in the studies).
- Health-related quality of life: evaluated using a validated instrument such as the 36-item Short Form (SF-36) or EuroQol 5 Dimension (EQ-5D).
- All-cause mortality: defined as death from any cause and measured at any time after participants had been randomised to intervention or comparator groups.
- Adverse events other than hypoglycaemia: such as cancer incidence, skin reactions and measured at any time after participants had been randomised to intervention or comparator groups.
- Socioeconomic effects: such as direct costs defined as admission or readmission rates, mean length of stay, visits to general practitioner, accident/emergency visits; medication consumption; indirect costs defined as resources lost due to illness by the participant or a family member.
- HbA1c: measured in % or mmol/mol.

Timing of outcome measurement

- Diabetes-related complications, hypoglycaemic episodes, all-cause mortality, adverse events other than hypoglycaemia, socioeconomic effects: measured at any time after participants had been randomised to intervention or comparator groups.
- Health-related quality of life: measured at the latest time point of measurement during follow-up.
- HbA1c: measured as change between baseline and end of follow-up.

Search methods for identification of studies

Electronic searches

Searches for the previous review version were conducted to 11 December 2006. For this update, we revised the search strategies.

We searched the following sources without restrictions on the language of publication:

- from 1 September 2006 to 26 January 2017 (for detailed search strategies, see Appendix 3):
    - Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO) (searched 26 January 2017);

- MEDLINE Ovid (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present) (searched 26 January 2017);
- Embase Ovid (1974 to 2017 Week 04) (searched 26 January 2017);
- ClinicalTrials.gov (www.clinicaltrials.gov) (searched 26 January 2017);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/trialsearch/) (searched 26 January 2017);

- from 1 January 2017 to 5 November 2019 (for detailed search strategies, see Appendix 4):
  - CENTRAL via the CRSO (searched 5 November 2019);
  - MEDLINE Ovid (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present) (searched 5 November 2019);
  - ClinicalTrials.gov (www.clinicaltrials.gov) (searched 5 November 2019);
  - WHO ICTRP (www.who.int/trialsearch/) (searched 5 November 2019).

Searching other resources

We tried to identify other potentially eligible trials or ancillary publications by searching the reference lists of included trials, systematic reviews, meta-analyses and health technology assessment reports. Inquiries were directed to the two main pharmaceutical companies producing long-acting insulin analogues (Sanofi, Novo Nordisk). In addition, we contacted authors of potentially relevant and included trials to obtain additional information on the retrieved trials and to determine if further trials existed that we might have missed.

We also searched the databases of regulatory agencies (EMA and FDA) (Hart 2012; Schroll 2015).

We considered additional information based on original trial reports published in a report by the German Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) (IQWiG 2009), which we defined as grey literature. This report was cited as an additional source. In terms of inconsistency between journal publications and the IQWiG report 2009, data from the IQWiG report were used preferentially, since these data were based on original trial reports and therefore deemed more reliable.

We did not use abstracts or conference proceedings for data extraction because this information source does not fulfil the CONSORT requirements which is "an evidence-based, minimum set of recommendations for reporting randomized trials" (CONSORT; Scherer 2018).

Data collection and analysis

Selection of studies

Two review authors (JE and TS or KH) independently scanned the abstract, title or both, of every record we retrieved in the literature searches, to determine which trials we should assess further. We obtained the full text of all potentially relevant records. We resolved any disagreements through consensus or by recourse to a third review author (JE, KH, TS, KJ). If we could not resolve a disagreement, we categorised the trial as a 'study awaiting classification' and contacted the trial authors for clarification. We present an adapted PRISMA flow diagram to show the process of trial selection (Liberati 2009).

Data extraction and management

For trials that fulfilled our inclusion criteria, two review authors (JE, KH, TS, KJ) independently extracted key participant 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, by consultation with a third review author (JE, KH, TS, KJ) (for details, see Characteristics of included studies table; Table 1; Appendix 5; Appendix 6; Appendix 7; Appendix 8; Appendix 9; Appendix 10; Appendix 11; Appendix 12; Appendix 13; Appendix 14, Appendix 15; Appendix 16; Appendix 17; Appendix 18; Appendix 19; Appendix 1; Appendix 2; Appendix 20).

We provided information on potentially relevant ongoing trials, including the trial identifier in the Characteristics of ongoing studies table and in Appendix 10 'Matrix of trial endpoint (publications and trial documents)'. We tried to find the protocol for each included trial and we reported primary, secondary and other outcomes in comparison with data in publications in Appendix 10.

We emailed all authors of included trials to enquire whether they would be willing to answer questions on their trials. We presented the results of this survey in Appendix 19. We then asked for relevant missing information on the trial from the primary trial author(s), where necessary.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents or multiple reports of a primary trial, we maximised the information yielded by collating all available data and we used the most complete data set aggregated across all known publications. We listed 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. Furthermore, 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 trial registers

If data from included trials were available as study results in clinical trial 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 trial register but no additional information (study results, publication or both) was available, we added this trial to the Characteristics of excluded studies table.

Assessment of risk of bias in included studies

Two review authors (JE, KH, TS, KJ) independently assessed the risk of bias for each included trial. We resolved disagreements by consensus or by consulting a third review author (JE, KH, TS, KJ).

In the case 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 study publications, study protocols or other sources, we contacted the study authors for more detail to request missing data on 'Risk of bias' items.

We used the Cochrane 'Risk of bias' assessment tool (Higgins 2019a), to assign assessments of low, high or unclear risk of bias (for details, see Appendix 5; Appendix 6). 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 2019a).

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 and investigator-assessed and adjudicated outcome measures.

We considered the following self-reported outcomes.

- Diabetes-related complications, reported by participants.
- Hypoglycaemia, when measured by participants.
- Health-related quality of life.
- Adverse events other than hypoglycaemia, as reported by participants.

We considered the following outcomes to be investigator-assessed.

- Diabetes-related complications, evaluated/as measured by trial personnel.
- Hypoglycaemia, when measured by trial personnel.
- All-cause mortality.
- Adverse events other than hypoglycaemia, as measured by trial personnel.
- Socioeconomic effects.
- HbA1c.

Risk of bias for a study 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 study. In case of high risk of selection bias, we marked all endpoints investigated in the associated study as being at high risk. Otherwise, we did not perform a summary assessment of the risk of bias across all outcomes for a study.

Risk of bias for an outcome within a study and across domains

We assessed the risk of bias for an outcome measure by including all entries relevant to that outcome (i.e. both study-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 studies and across domains

To facilitate our assessment of the certainty of the evidence for key outcomes, we assessed risk of bias across studies and domains for the outcomes included in the 'Summary of findings' tables. We defined the evidence as being at low risk of bias when most information came from studies at low risk of bias, unclear risk of bias when most information came from studies at low or unclear risk of bias and high risk of bias when a sufficient proportion of information came from studies 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 odds ratio (OR) with 95% confidence intervals (CI). For continuous outcomes measured on the same scale (e.g. weight loss in kilograms), we estimated the intervention effect using the mean difference (MD) with 95% CI. For continuous outcomes measuring the same underlying concept (e.g. health-related quality of life) but using different measurement scales, we intended to calculate the standardised mean difference with 95% CI. We also planned to express time-to-event data as a hazard ratio with 95% CI.

Unit of analysis issues

We intended to consider 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 more than once (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 because the same set of participants was included in multiple comparisons (Higgins 2019b).

We planned to reanalyse cluster-RCTs that had not appropriately adjusted for potential clustering of participants within clusters in their analyses. Variance in the intervention effects would have been inflated by a design effect. Calculation of a design effect would have involved estimation of an intracluster correlation (ICC). We would have obtained estimates of ICCs through contact with authors, or imputed them using estimates from other included trials that reported ICCs, or using external estimates from empirical research (e.g. Bell 2013). We also planned to examine the impact of clustering using sensitivity analyses.

Dealing with missing data

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

In trials where the standard deviation (SD) of the outcome was not available at follow-up or could not be recreated, we standardised using the mean of the pooled baseline SD from those trials in which this information was reported.

Where included trials did not report means and 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 investigated the impact of imputation on meta-analyses by performing sensitivity analyses and we reported which trials were included with imputed SDs per outcome.

Assessment of heterogeneity

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

We identified heterogeneity (inconsistency) by visually inspecting the forest plots and by using a standard Chi^2 test with a significance level of $\alpha = 0.1$ (Deeks 2019). In view of the low power of this test, we also considered the I^2 statistic – which quantifies inconsistency across studies – to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003). When we identified heterogeneity, we attempted to determine possible reasons for this by examining individual characteristics of the study and subgroups.

Assessment of reporting biases

If we included 10 or more studies that investigated a particular outcome, we planned to use funnel plots to assess small-study effects. Several explanations may account for funnel plot asymmetry, including true heterogeneity of effect with respect to study size, poor methodological design (and hence bias of small studies) and selective non-reporting (Kirkham 2010). Therefore, we interpreted the results carefully (Sterne 2011).

Data synthesis

We planned to undertake (or display) a meta-analysis only if participants, interventions, comparisons and outcomes were judged to be sufficiently similar to ensure an answer that was clinically meaningful. For the outcome HbA1c, we used the change between baseline and end of follow-up for the comparison between the two groups. MDs were calculated using a random-effects model for the meta-analysis. In some studies, the mean change and its variance for each group were presented in the published report of the trial. In other cases where these estimates were not reported, we had to calculate appropriate variances, if possible, from other statistics presented. The same approach was used for the outcome weight gain (change in body mass index (BMI)). Furthermore, we looked at different episodes of hypoglycaemia (severe, serious, less than 70 mg/dL to 75 mg/dL, less than 50 mg/dL to 55 mg/dL, nocturnal less than 70 mg/dL to 75 mg/dL, nocturnal less than 50 mg/dL to 55 mg/dL) and serious adverse events. For the meta-analysis of severe and serious hypoglycaemic episodes, we used Peto's OR method, since the event rates were low.

We interpreted random-effects meta-analyses with due consideration for the whole distribution of effects and planned to present a prediction interval (Borenstein 2017a; Borenstein 2017b; Higgins 2009). A prediction interval requires at least three studies to be calculated and specifies a predicted range for the true treatment effect in an individual study (Riley 2011). In addition, we performed statistical analyses according to the statistical guidelines presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2019).

Subgroup analysis and investigation of heterogeneity

We expected the following characteristics to introduce clinical heterogeneity, and planned to carry out the following subgroup analyses for the primary outcomes including investigation of interactions.

- Different additional antihyperglycaemic therapy such as oral antidiabetic drugs (OADs) versus insulin.
- NPH once daily versus NPH twice or three times daily.

Sensitivity analysis

We intended to perform sensitivity analyses for the primary outcomes to explore the influence of the following factors (when applicable) on effect size by restricting analysis to the following:

- Published trials.
- Taking into account risk of bias, as specified in the Assessment of risk of bias in included studies section.
- Very long or large trials to establish the extent to which they dominated the results.
- Trials using the following filters: diagnostic criteria, imputation, language of publication, source of funding (industry versus other) or country.

We also tested the robustness of results by repeating the analyses using different measures of effect size (RR, OR, etc.) and different statistical models (fixed-effect and random-effects models).

Certainty of the evidence

We present the overall certainty of the evidence for each outcome specified below, according to the GRADE approach, which takes into account issues related to internal validity (risk of bias, inconsistency, imprecision, publication bias) and external validity (such as directness of results). Two review authors (JE, KH, TS, KJ) independently rated the certainty of the evidence for each outcome. We resolved any differences in assessment by discussion or by consultation with a third review author (JE, KH, TS, KJ).

We included appendices entitled 'Checklist to aid consistency and reproducibility of GRADE assessments' (Appendix 1; Appendix 2), to help with standardisation of the 'Summary of findings' tables (Meader 2014). Alternatively, we planned to use the GRADEpro GDT software and would have presented evidence profile tables as an appendix (GRADEpro GDT). If meta-analysis was not possible, we presented the results in a narrative format in the 'Summary of findings' table. We justified all decisions to downgrade the certainty of the evidence using footnotes, and we made comments to aid the reader's understanding of the Cochrane Review when necessary.

'Summary of findings' tables

We presented a summary of the evidence in 'Summary of findings' tables. This provides key information about the best estimate of the magnitude of effect, in relative terms and as absolute differences for each relevant comparison of alternative management strategies; the numbers of participants and studies addressing each important outcome; and a rating of overall confidence in effect estimates for each outcome. We created the 'Summary of findings' tables using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2019), along with Review Manager 5 software (Review Manager 2020).

Interventions presented in the 'Summary of findings' tables were long-acting insulin analogues (insulin glargine U100 or insulin detemir). The comparator was NPH insulin.
We reported the following outcomes, listed according to priority.

- Diabetes-related complications.
- Hypoglycaemic episodes.
- Health-related quality of life.
- All-cause mortality.
- Adverse events other than hypoglycaemia.
- Socioeconomic effects.
- HbA1c.

RESULTS

Description of studies

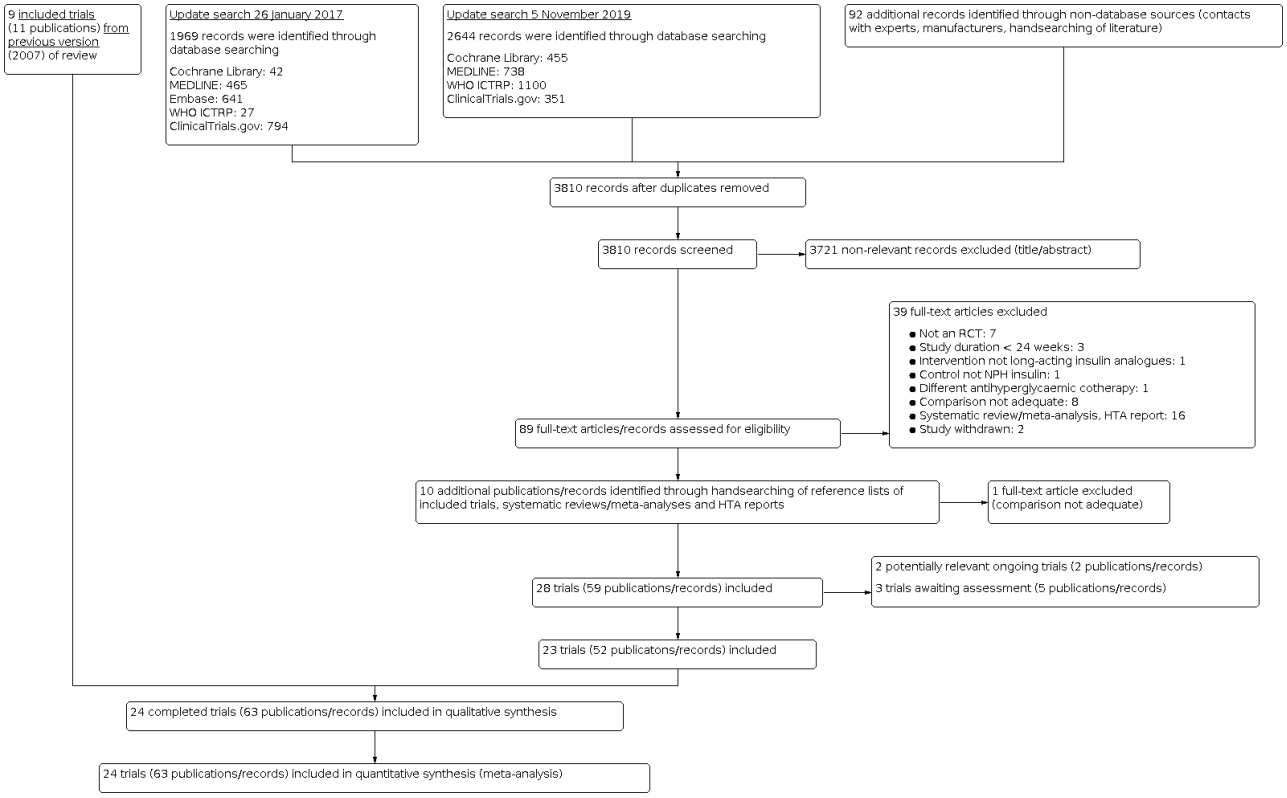
For a detailed description of trials, see Table 1, and the Characteristics of included studies, Characteristics of excluded studies, Characteristics of studies awaiting classification, and Characteristics of ongoing studies tables.

Results of the search

Using the described strategies, the update searches in 2017 yielded 1969 and in 2019 yielded 2644 results. We identified 92 additional records including the IQWiG report through non-database sources (IQWiG 2009). After deduplication, 3810 records remained.

After reading the 3810 abstracts, we excluded 3721 articles by consensus as irrelevant to the question under review, leaving 89 articles for further examination. We identified 10 additional publications by handsearching the reference lists of included trials, systematic reviews/meta-analyses and Health Technology Assessment (HTA) reports or databases from regulatory agencies. After screening the full text of the selected 99 publications and after contacting authors of potentially relevant studies, 28 studies (59 articles/records) met the inclusion criteria. Two of these studies (two records) were potentially relevant ongoing trials and three trials (five records) were classified as studies awaiting assessment. Finally, incorporating 15 additional studies with the nine studies from the previous version of the review, in this review update 24 completed trials (63 articles/records) could be included. For further details see flow diagram in Figure 1.

Figure 1. Trial flow diagram; HTA: health technology assessment; RCT: randomised controlled trial.



Included studies

A detailed description of the characteristics of included trials is presented elsewhere (see Characteristics of included studies table and Appendix 7; Appendix 8; Appendix 9). The following is a short overview.

Source of data

The results of 20 trials were at least partially published in scientific journals between 2000 and 2019. For three of the trials, information and results were mostly obtained from entries in ClinicalTrials.gov and from pharmaceutical manufacturers' study reports. For 14 trials, we relied on additional information that was based on the original study reports published in a report by the Institute for Quality and Efficiency in Health Care (IQWiG 2009). For one trial, the

IQWiG report was the only available source of data. We contacted authors of all studies that were not included in the IQWiG report to request missing data or clarify issues regarding the methodology of the trial. Nine of the authors replied but only two of them provided information that was relevant to the review. All other authors were contacted during the preparation of the IQWiG report and their replies incorporated in the IQWiG report, where relevant (see Appendix 19).

Comparisons

Glargine U300 versus NPH

We found no trials comparing glargine U300 with NPH insulin.

Glargine versus NPH

Sixteen trials compared NPH to insulin glargine (Berard 2015; Eliaschewitz 2006; Fritsche 2003; Hermanns 2015; Home 2015; Hsia 2011; Kawamori 2003; Massi 2003; NCT00687453; Pan 2007; Betônico 2019; Riddle 2003; Rosenstock 2001; Rosenstock 2009; Yki-Järvinen 2006; Yokoyama 2006).

Glargine was given once daily in all trials and was generally administered shortly before retiring to bed (Berard 2015; Eliaschewitz 2006; Home 2015; Massi 2003; NCT00687453; Pan 2007; Riddle 2003; Rosenstock 2001; Rosenstock 2009; Yki-Järvinen 2006). Three trials administered glargine in the morning (Kawamori 2003; Betônico 2019; Yokoyama 2006). Two further trials had two interventional arms, of which one involved taking glargine at bedtime and one in the morning (Fritsche 2003; NCT00687453). Both intervention arms were compared with NPH. In one trial, glargine could be administered at any time, as long as it was at the same time each day (Hermanns 2015).

Most trials administered NPH once daily, either shortly before retiring to bed (Eliaschewitz 2006; Fritsche 2003; Home 2015; Hsia 2011; Massi 2003; Pan 2007; Riddle 2003; Yki-Järvinen 2006; Yokoyama 2006), or in the morning (Kawamori 2003). Three trials gave NPH once daily at bedtime and once more in the morning if blood glucose targets were not met (Berard 2015; Hermanns 2015; Rosenstock 2001). Two trials compared insulin glargine to NPH insulin both at bedtime and in the morning (NCT00687453; Rosenstock 2009). One trial administered NPH three times daily, at breakfast, lunch and bedtime (Betônico 2019).

Three trials administered short-acting insulins (either regular insulin or short-acting insulin analogues) at mealtimes in addition to glargine and NPH (Betônico 2019; Rosenstock 2001; Yokoyama 2006). In nine trials, concomitant medication to lower blood glucose consisted only of OADs (Eliaschewitz 2006; Fritsche 2003; Hsia 2011; Kawamori 2003; Massi 2003; NCT00687453; Pan 2007; Riddle 2003; Yki-Järvinen 2006). In the four remaining trials, additional blood glucose lowering medication included OADs and, if necessary, short-acting insulins (Berard 2015; Hermanns 2015; Rosenstock 2009; Yokoyama 2006).

All 16 trials used insulin glargine U100.

Detemir versus NPH

Eight trials compared NPH insulin to insulin detemir (Fajardo Montañana 2008; Haak 2005; Hermansen 2006; Kobayashi 2007 A; Kobayashi 2007 B; NN304-1337; NN304-1808; NN304-3614).

Five of these trials administered detemir and NPH once daily, either shortly before retiring to bed (Fajardo Montañana 2008; Kobayashi 2007 B; NN304-1337; NN304-3614), or in the morning (NN304-1808). Two trials gave detemir and NPH at bedtime and, if necessary, in the morning (Haak 2005; Kobayashi 2007 A), and study gave them at bedtime and in the morning (Hermansen 2006).

Four studies gave OADs as concomitant medication to lower blood glucose (Hermansen 2006; Kobayashi 2007 B; NN304-1337; NN304-1808), three studies gave of insulin aspart at mealtimes (Haak 2005; Kobayashi 2007 A; NN304-3614), and one study gave a combination of insulin aspart and OADs (Fajardo Montañana 2008).

Deglutec versus NPH

We found no trials comparing insulin degludec with NPH insulin.

Overview of trial populations

Glargine versus NPH

Overall, 6330 people with type 2 diabetes mellitus were randomised to the different comparison groups. Individual sample sizes ranged from 24 to 1024 participants per study. Between 60% and 95% of randomised participants finished the trials.

Detemir versus NPH

Overall, 2347 people with type 2 diabetes mellitus were randomised to the different comparison groups. Individual sample sizes ranged from 60 to 505 per study. Between 48% and 95% of participants finished the trial.

Trial design

Glargine versus NPH

Fourteen trials had a parallel design (Berard 2015; Eliaschewitz 2006; Fritsche 2003; Home 2015; Hsia 2011; Kawamori 2003; Massi 2003; NCT00687453; Pan 2007; Riddle 2003; Rosenstock 2001; Rosenstock 2009; Yki-Järvinen 2006; Yokoyama 2006), and two had a cross-over design (Hermanns 2015; Betônico 2019). Seven trials had a superiority design (Hermanns 2015; Home 2015; Massi 2003; Riddle 2003; Rosenstock 2001; Yki-Järvinen 2006; Yokoyama 2006), and seven trials had an equivalence/non-inferiority design (Eliaschewitz 2006; Fritsche 2003; Kawamori 2003; NCT00687453; Pan 2007; Betônico 2019; Rosenstock 2009). The latter was unclear in two trials (Berard 2015; Hsia 2011).

Eleven trials had a multicentre design with the number of centres ranging from seven to 111 (Eliaschewitz 2006; Fritsche 2003; Hermanns 2015; Home 2015; Kawamori 2003; Massi 2003; Pan 2007; Riddle 2003; Rosenstock 2001; Rosenstock 2009; Yki-Järvinen 2006). Eight trials involved more than 50 centres (Eliaschewitz 2006; Fritsche 2003; Home 2015; Kawamori 2003; Massi 2003; Riddle 2003; Rosenstock 2001; Rosenstock 2009).

Neither participants nor study personnel or outcome assessors were reported to be blinded in any of the trials.

Trials were performed between 1997 and 2016. This information was not available for seven trials (Berard 2015; Eliaschewitz 2006; Kawamori 2003; Pan 2007; Rosenstock 2001; Yki-Järvinen 2006; Yokoyama 2006).

The mean duration of intervention was identical to the mean duration of follow-up in all trials and ranged from six to 60 months.

Seven trials had formal run-in periods ranging from two to 12 weeks (Fritsche 2003; Home 2015; Hsia 2011; NCT00687453; Riddle 2003; Yki-Järvinen 2006; Yokoyama 2006).

Two trials were terminated early, one because of a lack of funding (Hsia 2011), and one for unspecified reasons (NCT00687453).

Detemir versus NPH

All trials had a parallel design and all but three had a non-inferiority design. Of these three trials, two had a superiority design (Fajardo Montañana 2008; NN304-3614), and in one trial, the design was unclear (NN304-1337).

Seven trials were multicentre where the number ranged from five to 65. For one trial, no information on the number of trial centres was available (NN304-1337).

Neither participants nor study personnel or outcome assessors were reported to be blinded in any of the trials.

Trials were performed between 2003 and 2010. For two trials, no information on when the trials were performed was available (Haak 2005; NN304-1337).

The mean duration of intervention was similar to the mean duration of follow-up in all trials and ranged from 24 to 48 weeks.

One trial had a formal run-in period of two weeks' duration (NN304-1337).

NN304-1808 was discontinued prematurely because of recruitment problems.

Settings

Glargine versus NPH

Some information on settings was available for six trials: two trials were conducted in a speciality primary care clinic (Hsia 2011; NCT00687453), one in university hospital facilities (Betônico 2019), two in outpatient facilities (Hermanns 2015; Yokoyama 2006), and one in an inpatient and outpatient care facility (Kawamori 2003).

Detemir versus NPH

No information was available for any of the trials.

Participants

Glargine versus NPH

Only people with type 2 diabetes mellitus were included. Major exclusion criteria were insulin therapy before the initiation of the trial in six trials (Eliaschewitz 2006; Fritsche 2003; Hermanns 2015; Massi 2003; Riddle 2003; Yki-Järvinen 2006), use of insulin analogues in one trial (Rosenstock 2009), and severe diabetic retinopathy in eight trials (Home 2015; Hsia 2011; Kawamori 2003; Massi 2003; NCT00687453; Pan 2007; Rosenstock 2009; Yki-Järvinen 2006). The mean duration of diabetes at baseline ranged from eight to 19 years. Participants were mostly of white ethnicity (for those publications with no information on the ethnic composition of the study population, it was inferred from the study locations), with mean age ranging from 50 to 62 years. The proportion of women in the comparison groups varied between 25% and 77%. Most participants were overweight, with mean BMI ranging from 23 kg/m^2 to 35 kg/m^2. None of the trials were performed on pharmaco-naive people (i.e. people whose treatment consisted only of dietary changes, exercise or both). Metabolic control in participants ranged from 6.9% (51 mmol/mol) to 9.6% (81 mmol/mol) HbA1c at baseline. Two trials including 515 participants were conducted in low- and middle-income countries (Eliaschewitz 2006; Betônico 2019). In addition, three further trials had study centres in low- and middle-income countries (Home 2015; Massi 2003; Pan 2007). Two trials conducted in the USA were specifically designed to investigate the effects of glargine versus NPH in low-income inner-city ethnic minorities (Hsia 2011; NCT00687453).

Detemir versus NPH

Only people with type 2 diabetes mellitus were included. Major exclusion criteria were severe retinopathy (Fajardo Montañana 2008; Haak 2005; Hermansen 2006; Kobayashi 2007 A; NN304-1337; NN304-1808; NN304-3614), and recurrent major hypoglycaemia (Haak 2005; Hermansen 2006; Kobayashi 2007 A; NN304-1337; NN304-1808). Mean duration of diabetes ranged from about 10 to 17 years. Participants were mostly of white or Asian ethnicity (for those publications with no information on the ethnic composition of the study population, it was inferred from the study locations), with mean age ranging from 55 to 78 years in the various comparison groups. Most participants were overweight, with BMI ranging from 22 kg/m^2 to 32 kg/m^2. The proportion of women varied from 29% to 62% in the different comparison groups. None of the studies were performed on pharmaco-naive people. Metabolic control in participants ranged from 7.6% to 9.5% HbA1c at baseline. One trial was partly conducted in a low-income country, in Puerto Rico as well as the USA (NN304-1337). All other trials were carried out in Europe and Japan.

Diagnosis

Glargine versus NPH

In one trial, the diagnosis of type 2 diabetes was made according to American Diabetes Association (ADA) criteria valid at the time (Betônico 2019), and in one further trial in accordance with WHO criteria (Pan 2007). For all other trials, the exact criteria used to diagnose type 2 diabetes mellitus were unclear.

Detemir versus NPH

In two trials, the diagnosis of type 2 diabetes was made in accordance with the ADA criteria valid at the time (Haak 2005; NN304-1808). For all other trials, the exact diagnostic criteria used to diagnose type 2 diabetes mellitus were unclear.

Interventions

Glargine versus NPH

All insulins were administered subcutaneously in all included trials. Dosages of investigative drugs and concomitant medications varied between trials and participants. None of the included trials were placebo controlled.

While administering glargine once daily is adequate, usage instructions recommend adapting the number of daily injections for NPH as necessary, as is common in clinical practice. Thus, for studies limiting NPH to a single daily injection, the comparator could not be considered adequate (Eliaschewitz 2006; Fritsche 2003; Home 2015; Hsia 2011; Kawamori 2003; Massi 2003; Pan 2007; Riddle 2003; Yki-Järvinen 2006; Yokoyama 2006).

Target values for fasting blood glucose concentration ranged from 4.0 mmol/L to 7.8 mmol/L (72 mg/dL to 140 mg/dL) (Eliaschewitz 2006; Fritsche 2003; Home 2015; Hsia 2011; Kawamori 2003; Massi 2003; Pan 2007; Betônico 2019; Riddle 2003; Rosenstock 2001; Rosenstock 2009; Yki-Järvinen 2006). Two studies set nocturnal blood glucose targets ranging from 4.4 mmol/L to 6.6 mmol/L (80 mg/dL to 120 mg/dL) (Home 2015; Betônico 2019). One study prespecified an additional target for postprandial blood glucose concentration below 10 mmol/L (180 mg/dL) (Betônico 2019). For four studies target values remained unclear (Berard 2015; Hermanns 2015; NCT00687453; Yokoyama 2006).

The design of the investigation by Yokoyama 2006 required upward titration of insulin glargine with the aim of basal insulin making up 50% of the total daily insulin requirement. In contrast to this, the percentage of NPH in the total daily insulin requirement was left unchanged, thus introducing a difference in the treatments of the two comparison groups. This made the trial unfit to identify substance-specific differences between insulin glargine and NPH insulin. Even though this was the case, we were unable to formally exclude this trial on the basis of our prespecified exclusion criteria. When appropriate, therefore, we conducted a sensitivity analysis that excluded this study.

Detemir versus NPH

All insulins were administered subcutaneously in all included trials. Dosages of investigative drugs and concomitant medications varied among trials and participants. None of the included trials were placebo controlled.

In accordance with usage instructions and common clinical practice, the number of daily injections of NPH should be adjusted as necessary. Thus, the comparator could not be considered adequate in studies limiting NPH to a single daily injection (Fajardo Montañana 2008; Kobayashi 2007 B; NN304-1337; NN304-1808; NN304-3614).

Target values for fasting blood glucose concentration ranged from 4.0 mmol/L to 7.0 mmol/L (72 mg/dL to 126 mg/dL) (Fajardo Montañana 2008; Haak 2005; Hermansen 2006; Kobayashi 2007 A; Kobayashi 2007 B; NN304-1337). A nocturnal blood glucose target was set in one study ranging from 4.0 mmol/L to 7.0 mmol/L (72 mmol/L to 126 mg/dL) (Haak 2005). Four studies prespecified an additional target for postprandial blood glucose concentration ranging between below 6.7 mmol/L (120 mg/dL) to below 10 mmol/L (180 mg/dL) (Fajardo Montañana 2008; Haak 2005; Kobayashi 2007 A; Kobayashi 2007 B). In Hermansen 2006, a predinner blood glucose target of 6.0 mmol/L (108 mg/dL) or below was also set. For two studies, target values remained unclear (NN304-1808; NN304-3614).

In trials comparing glargine or detemir to NPH, reported target blood glucose levels used in the adjustment of blood glucose lowering medications were consistent with the target range recommended by ADA for most non-pregnant adults with diabetes (ADA 2020), but they were generally at the lower end of the recommended target range. Furthermore, they did not take into account ADA's recommendation that the goals be adjusted individually, depending on the duration of diabetes, known CVD and other factors. In the included trials, the participants had diabetes for eight to 19 years at the start of the trial. In current clinical practice, blood glucose targets for many of the trials' participants would probably have been raised. This also casts doubt on the adequacy of the interventions and comparators.

Outcomes

Glargine versus NPH

HbA1c was the defined primary outcome in all but four trials (Berard 2015; Hermanns 2015; Rosenstock 2009; Yokoyama 2006). Further defined primary outcomes were progression of retinopathy in one trial (Rosenstock 2009), and health-related quality of life in another (Hermanns 2015). For two trials, the primary outcome remained unclear (Berard 2015; Yokoyama 2006). For all but two trials (Berard 2015; Yokoyama 2006), information on adverse events was reported. Reports on late diabetes complications were available for eight trials (Home 2015; Hsia 2011; Massi 2003; NCT00687453; Betônico 2019; Rosenstock 2001; Rosenstock 2009; Yki-Järvinen 2006). Fourteen trials either reported mortality directly, or it could be deduced from provided information (Eliaschewitz 2006; Fritsche 2003; Hermanns 2015; Home 2015; Hsia 2011; Kawamori 2003; Massi 2003; NCT00687453; Pan 2007; Betônico 2019; Riddle 2003; Rosenstock 2001; Rosenstock 2009; Yki-Järvinen 2006). Three trials did not report information on health-related quality of life (Hermanns 2015; Massi 2003; Rosenstock 2001). No trial provided information on socioeconomic effects.

Detemir versus NPH

HbA1c was the defined primary outcome in six trials (Haak 2005; Hermansen 2006; Kobayashi 2007 A; Kobayashi 2007 B; NN304-1337; NN304-1808). Further defined primary outcomes were weight loss (Fajardo Montañana 2008) and changes in trunk fat mass (NN304-3614).

All trials reported information on adverse events. All trials either reported on mortality, or it could be deduced from the information provided.

Reports on late diabetes complications were available in five trials (Fajardo Montañana 2008; Haak 2005; Kobayashi 2007 B; NN304-1337; NN304-1808).

Three trials reported information on health-related quality of life (Fajardo Montañana 2008; Haak 2005; Kobayashi 2007 A). No trial provided information on socioeconomic effects.

Excluded studies

Full-text evaluation in the study selection process of this review update resulted in the exclusion of 36 trials (40 articles/records). The main reasons for exclusion were that the study was a systematic review (meta-analysis/HTA report), that the comparison was not adequate, and that the study was not a RCT (see Figure 1). For details see Characteristics of excluded studies table.

Studies awaiting classification

We classified three trials with five references as awaiting classification (see Characteristics of studies awaiting classification table). All three trials with an estimated total of 140 participants were listed in ClinicalTrials.gov as having been completed (NCT00788840; NCT01310452; NCT01500850), but no study results were reported and no publications were available. We contacted the investigators for each trial, but none of them replied.

Ongoing trials

We found two potentially relevant ongoing RCTs. One trial investigated the ultra-long-acting insulin analogue insulin degludec in comparison to insulin detemir, insulin glargine or NPH insulin in adults aged 60 to 75 years with type 2 diabetes mellitus who were at high risk of developing Alzheimer's disease (EUCTR2017-004454-42-ES). The estimated number of participants in this trial is 188. The trial will assess the rate of hypoglycaemic events and blood glucose measures which are primary and secondary outcomes in our review. The estimated completion date for the trial is not stated. The second trial investigates the ultra-long-acting insulin analogue insulin glargine U-300 in comparison to NPH insulin in insulin-naive adults with type 2 diabetes mellitus who were suboptimally controlled on their previous antidiabetic treatment (NCT03389490). The estimated number of participants is 50. Changes in HbA1c and the incidence of hypoglycaemia, which are primary and secondary outcomes in our review, are predefined secondary outcomes in this trial. For further details see Characteristics of ongoing studies table.

Risk of bias in included studies

For details on the risk of bias in the included trials, see Characteristics of included studies table.

For an overview of assessments of 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 (blank cells indicate that the particular outcome was not measured in some trials).

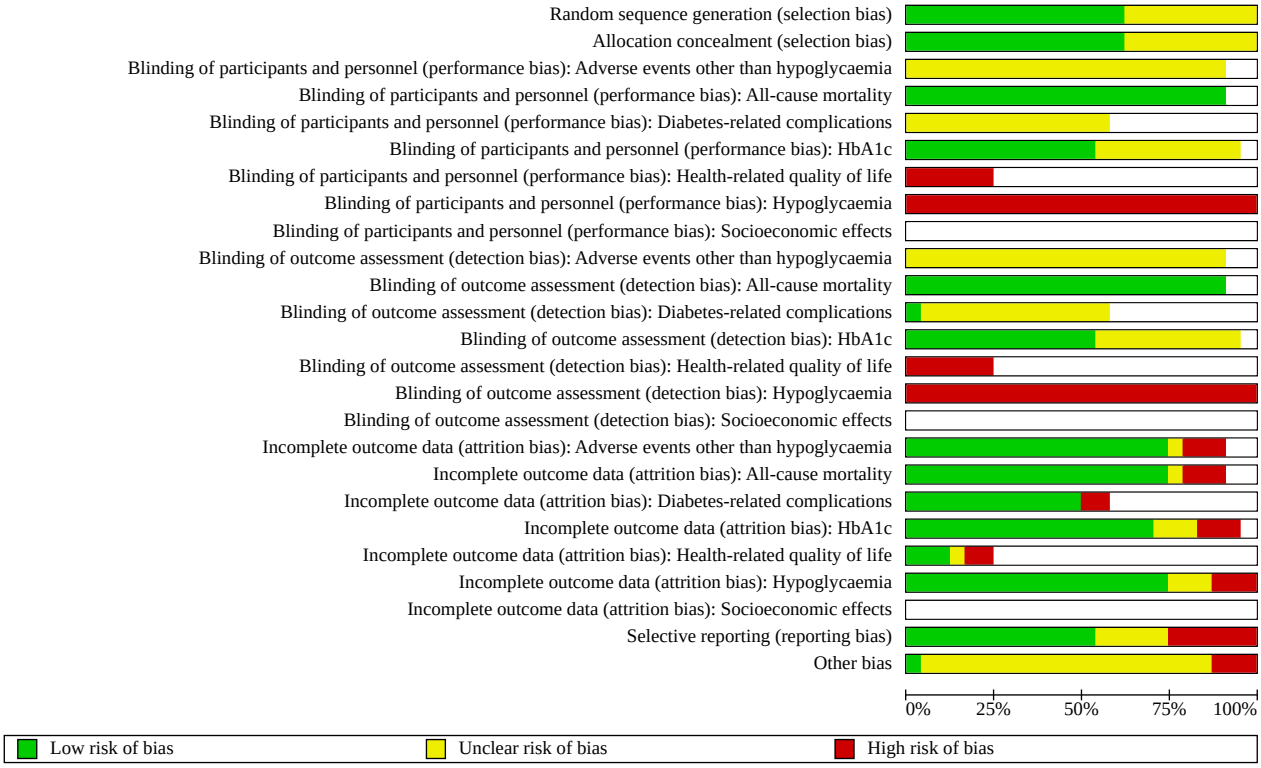


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included trial (blank cells indicate that the particular outcome was not measured in the trial)

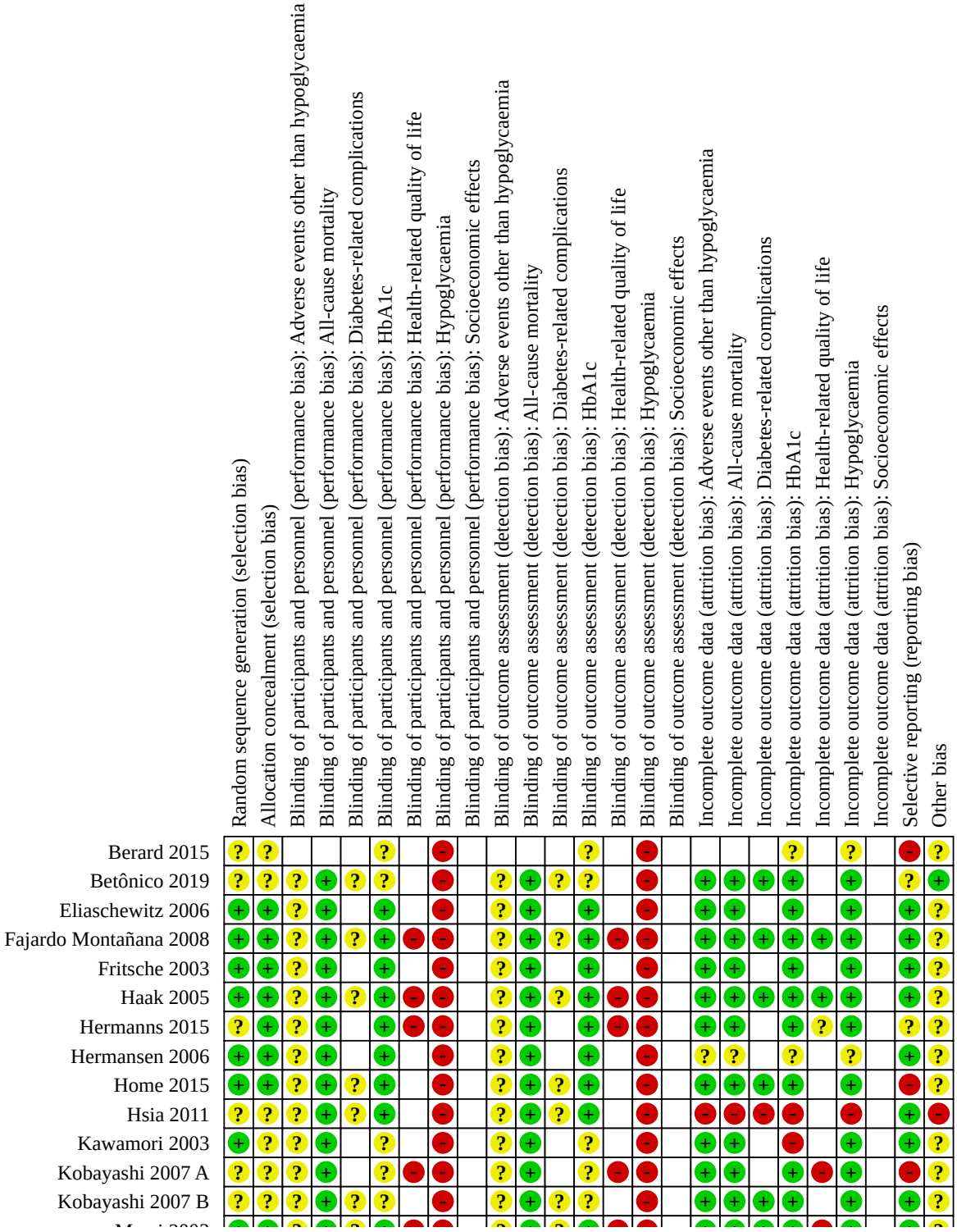
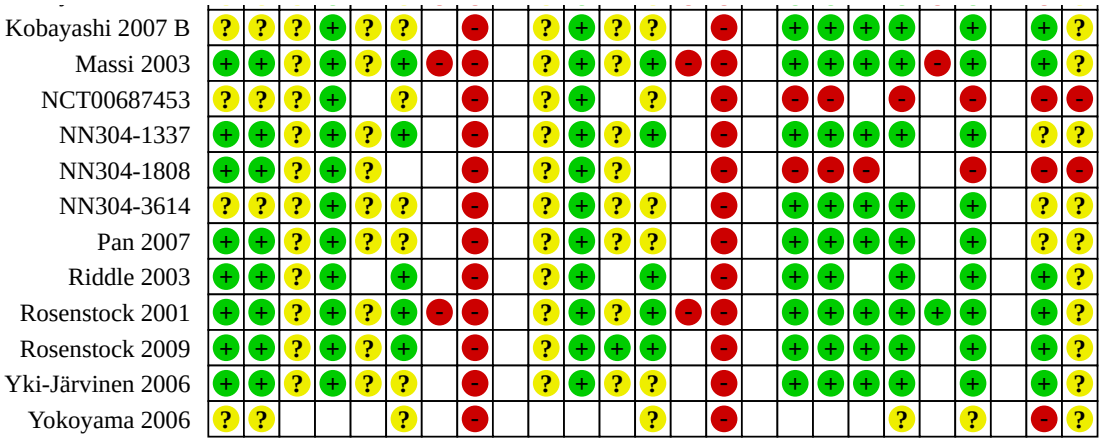


Figure 3. (Continued)



Allocation

All included studies were RCTs. Regarding method of randomisation and allocation concealment, we judged seven trials to have a low risk of bias based on the information from journal publications (Fajardo Montañana 2008; Fritsche 2003; Hermansen 2006; Home 2015; Massi 2003; NN304-1808; Riddle 2003). In six additional trials, randomisation and allocation concealment were considered adequate in the IQWiG report 2009 (Eliaschewitz 2006; Haak 2005; NN304-1337; Pan 2007; Rosenstock 2001; Rosenstock 2009; Yki-Järvinen 2006) (IQWiG 2009), while in one trial randomisation was adequate but allocation concealment unclear (Kawamori 2003). For another trial, detailed information was only available for allocation concealment, while the randomisation method was unclear (Hermanns 2015). The remaining eight trials only reported that participants were randomised without providing any information on the method used (Berard 2015; Hsia 2011; Kobayashi 2007 A; Kobayashi 2007 B; NCT00687453; NN304-3614; Betônico 2019; Yokoyama 2006). Therefore, we considered these trials to have an unclear risk of bias with regard to randomisation and allocation concealment.

Blinding

Participants or carers were not blinded to the interventions in any of the included trials. Even if blinding is difficult in such trials because glargine and detemir are clear solutions while NPH is milky in appearance, the fact remains that an open 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 primary and secondary outcomes in this review, except HbA1c, were participant reported, investigator assessed or both. Thirteen trials conducted assessment of HbA1c in central laboratories (Eliaschewitz 2006; Fajardo Montañana 2008; Fritsche 2003; Haak 2005; Hermanns 2015; Hermansen 2006; Home 2015; Hsia 2011; Massi 2003; NN304-1337; Riddle 2003; Rosenstock 2001; Rosenstock 2009). A blinded outcome assessment can therefore be assumed and we considered these studies to carry a low risk of performance and detection bias for this outcome measure. Non-serious adverse events and diabetes-related complications were participant-reported or investigator assessed in all but one trial and were, therefore, considered unclear risk of performance and detection bias. One trial described an adjudicated outcome measurement for diabetic retinopathy with treatment-group-masked grading of fundus photographs, and, therefore, carried a low risk of detection bias for this outcome (Rosenstock 2009). Health-related quality of life measurements and non-severe or severe hypoglycaemia were exclusively participant-reported in the included trials. As blood glucose was self-measured in all trials, including confirmed hypoglycaemic events, an increased risk of subjective influence existed. Therefore, these outcomes carried a high risk of performance and detection bias. We considered serious hypoglycaemia, fulfilling at least one criterion of a serious adverse event, serious adverse events themselves and mortality, to carry a low risk of performance and detection bias, since the possibility of subjective interference is minimal for these outcome measures.

Incomplete outcome data

Twenty-two trials reported the number of participants who were randomised and who finished the trial (Eliaschewitz 2006; Fajardo Montañana 2008; Fritsche 2003; Haak 2005; Hermanns 2015; Hermansen 2006; Home 2015; Hsia 2011; Kawamori 2003; Kobayashi 2007 A; Kobayashi 2007 B; Massi 2003; NCT00687453; NN304-1337; NN304-1808; NN304-3614; Pan 2007; Betônico 2019; Riddle 2003; Rosenstock 2001; Rosenstock 2009; Yki-Järvinen 2006). The percentage of randomised participants completing their respective trials ranged from 48% to 98%. The remaining two trials only stated the number of randomised participants (Berard 2015; Yokoyama 2006).

Nineteen trials used an ITT approach for efficacy outcomes and 22 trials for safety outcomes. Even though none of the trials included all randomised participants in the analyses (so that they were not, in a strict sense, ITT analyses), the difference between randomised and analysed participants was small in all but three trials (Hsia 2011; NCT00687453; NN304-1808), so we judged this as no substantial problem. One trial reported a per-protocol analysis of efficacy outcomes with an equivalence design (Eliaschewitz 2006), and in another one with a non-inferiority design (Kawamori 2003).

Seventeen trials used LOCF in the analyses for missing data (Eliaschewitz 2006; Fajardo Montañana 2008; Fritsche 2003; Haak 2005; Hermanns 2015; Hermansen 2006; Home 2015; Hsia 2011; Kobayashi 2007 A; Kobayashi 2007 B; NCT00687453; NN304-1337; NN304-1808; NN304-3614; Riddle 2003; Rosenstock 2001; Rosenstock 2009). It was unclear how the remaining seven investigations treated missing data in the analyses (Berard 2015; Kawamori 2003; Massi 2003; Pan 2007; Betônico 2019; Yki-Järvinen 2006; Yokoyama 2006).

Twenty-two trials described discontinuing participants and provided at least some details on the reasons for terminating the trial. Two trials reported neither the number of discontinuing participants nor the reasons for withdrawal (Berard 2015; Yokoyama 2006).

Three trials were at high risk of incomplete outcome data for all outcomes of relevance for this review. The trials with completion rates of only 48% (NN304-1808), 60% (Hsia 2011), and 63% (NCT00687453) were prematurely discontinued. Two trials stated the reasons for discontinuation, which were recruitment problems (NN304-1808) and funding limits (Hsia 2011). We considered two trials to have incomplete outcome data for the primary outcome health-related quality of life (Kobayashi 2007 A; Massi 2003). In one trial, 8% (glargine) and 23% (NPH) of the trial population were not included in health-related quality of life analyses (Kobayashi 2007 A). In the other trial, 12% (glargine) and 15% (NPH) of the trial population were not included in health-related quality of life analyses because validated questionnaires were not available in all languages (Massi 2003). In one trial, only per-protocol analysis was available for HbA1c measurement, with missing data of 16% in the glargine group and 20% in the NPH group (Kawamori 2003). Therefore, this trial was at high risk of reporting incomplete outcome data for this secondary outcome.

Selective reporting

Four trials have not yet been published in peer-review journals (NCT00687453; NN304-1337; NN304-1808; NN304-3614), and information was only obtained from pharmaceutical manufacturers' study reports, ClinicalTrials.gov entries, the IQWiG report or correspondence with the study investigator. Six trials had a high risk of reporting bias on one or more of the outcomes of relevance for this review (Berard 2015; Home 2015; Kobayashi 2007 A; NCT00687453; NN304-1808; Yokoyama 2006). Two trials had an unclear risk of reporting bias (Hermanns 2015; Pan 2007). The risk of reporting bias was low in all other trials. For details, see Appendix 10 and Appendix 11.

Other potential sources of bias

We judged three trials at high risk in the 'other bias' section because of their premature termination (Hsia 2011; NCT00687453; NN304-1808). With the exception of one (Betônico 2019), all other trials had an unclear risk in this section, either because they had received funding from a pharmaceutical company (Berard 2015; Eliaschewitz 2006; Fajardo Montañana 2008; Fritsche 2003; Hermanns 2015; Hermansen 2006; Home 2015; Kawamori 2003; Kobayashi 2007 A; Kobayashi 2007 B; Massi 2003; NN304-1337; NN304-3614; Pan 2007; Riddle 2003; Rosenstock 2001; Rosenstock 2009; Yki-Järvinen 2006), or did not report their funding source (Haak 2005; Yokoyama 2006).

Effects of interventions

See: **Summary of findings 1** Insulin glargine versus NPH insulin for type 2 diabetes mellitus; **Summary of findings 2** Insulin detemir versus NPH insulin for type 2 diabetes mellitus

Baseline characteristics

For details of baseline characteristics, see Appendix 8 and Appendix 9.

Long-acting insulin analogue glargine versus NPH insulin

As it is not possible to include a comparison group twice in the same meta-analysis, we could not consider all treatment arms from two trials in the meta-analyses (Fritsche 2003; Hsia 2011). For reasons of homogeneity, only the comparison of glargine in the evening versus NPH in the evening was included in our analyses.

In case of cross-over studies, we considered only the results from the first period for continuous outcomes, but from both periods for dichotomous outcomes (Hermanns 2015; Betônico 2019).

Primary outcomes

Diabetes-related complications

Two trials reported a total of six non-fatal myocardial infarctions, three in people treated with glargine and three in people treated with NPH (very low-certainty evidence) (Pan 2007; Betônico 2019).

Four trials provided information on fatal myocardial infarctions, three in people treated with glargine, and one in a person treated with NPH (very low-certainty evidence) (Home 2015; Hsia 2011; Betônico 2019; Yki-Järvinen 2006).

One trial with 32 participants reported no strokes in either group (very low-certainty evidence) (Betônico 2019). There were no fatal strokes in four trials with 934 participants (very low-certainty evidence) (Home 2015; Hsia 2011; Betônico 2019; Yki-Järvinen 2006).

For end-stage renal disease for glargine versus NPH, there were no events in either group (1 trial, 34 participants; very low-certainty evidence; Betônico 2019).

There was no evidence of a difference in progression of retinopathy (three steps) (RR 1.03, 95% CI 0.60 to 1.77; P = 0.90; 5 trials, 1974 participants; very low-certainty evidence; Analysis 1.1). The 95% prediction interval ranged between 0.22 and 4.83.

Amputations: there were no events in either group (1 trial, 34 participants; very low-certainty evidence; Betônico 2019).

None of the trials provided further information on late diabetic complications.

Hypoglycaemic episodes

The RR for severe hypoglycaemia was 0.68 (95% CI 0.46 to 1.01 in random-effects meta-analysis; P = 0.06; 14 trials, 6164 participants; very low-certainty evidence; Analysis 1.2). The 95% prediction interval ranged between 0.33 and 1.40. Fixed-effect meta-analysis showed a RR of 0.67 (95% CI 0.50 to 0.90; P = 0.007).

The RR for serious hypoglycaemia was 0.75 (95% CI 0.52 to 1.09; P = 0.54; 10 trials, 4685 participants; low-certainty evidence; Analysis 1.3). The 95% prediction interval ranged between 0.48 and 1.16.

The RR for confirmed hypoglycaemia less than 75 mg/dL was 0.92 (95% CI 0.85 to 1.01; P = 0.08; 7 trials, 4115 participants; low-certainty evidence; Analysis 1.4). The 95% prediction interval ranged between 0.69 and 1.22.

The RR for confirmed hypoglycaemia less than 55 mg/dL was 0.88 in favour of glargine (95% CI 0.81 to 0.96; P = 0.005; 8 trials, 4388 participants; moderate-certainty evidence; Analysis 1.5). The 95% prediction interval ranged between 0.79 and 0.98.

The RR for nocturnal confirmed hypoglycaemia less than 75 mg/dL was 0.78 (95% CI 0.68 to 0.89; P < 0.001; 8 trials, 4225 participants; very low-certainty evidence; Analysis 1.6). The 95% prediction interval ranged between 0.53 and 1.14.

The RR for nocturnal confirmed hypoglycaemia less than 55 mg/dL was 0.74 in favour of glargine (95% CI 0.64 to 0.85; P < 0.001; 8 trials, 4759 participants; moderate-certainty evidence; Analysis 1.7). The 95% prediction interval ranged between 0.62 and 0.88.

Health-related quality of life

Three trials reported health-related quality of life (1228 participants; very low-certainty evidence).

Massi 2003 used the Well-being Questionnaire (W-BQ22). The difference between trial start and trial end for total score was 1.0 (95% CI −45.0 to 32.0) for glargine and 0.0 (95% CI −25.2 to 46.2) for NPH (P = 0.40).

Rosenstock 2001 used the W-BQ22. The difference between trial start and trial end for total score was 0.5 (95% CI −22.0 to 36.0) for glargine and 0.0 (95% CI −37.0 to 39.0) for NPH (P = 0.25).

Hermanns 2015 used the EuroQol 5 (EQ-5) instrument. The difference between trial start and trial end for EQ-5 descriptive was −0.009 (SD 0.1727) for glargine and 0.001 (SD 0.1606) for NPH (P = 0.62). The difference between trial start and trial end for EQ-5 Visual Analogue Scale (VAS) was −0.0 (SD 0.1646) for glargine and 0.009 (SD 0.1655) for NPH (P = 0.64).

Secondary outcomes

All-cause mortality

The Peto OR for death from any cause was 1.06 (95% CI 0.62 to 1.82; P = 0.83; 14 trials, 6173 participants; low-certainty evidence; Analysis 1.8).

Adverse events other than hypoglycaemia

The RR for serious adverse events was 0.98 (95% CI 0.87 to 1.10; P = 0.74; 13 trials, 5499 participants; moderate-certainty evidence; Analysis 1.9). The 95% prediction interval ranged between 0.86 and 1.12.

The RR for all adverse events was 1.01 (95% CI 0.98 to 1.03; P = 0.62; 14 trials, 6170 participants; moderate-certainty evidence; Analysis 1.10). The 95% prediction interval ranged between 0.99 and 1.03.

The RR for adverse events leading to discontinuation of the trial was 1.21 (95% CI 0.84 to 1.76; P = 0.30; 13 trials, 6149 participants; moderate-certainty evidence; Analysis 1.11). The 95% prediction interval ranged between 0.79 and 1.84.

There was an increase in weight gain (BMI) in favour of NPH insulin (MD 0.12 kg/m^2, 95% CI 0.02 to 0.22; P = 0.02; 8 trials, 2405 participants; Analysis 1.12). The 95% prediction interval ranged between 0.06 kg/m^2 and 0.26 kg/m^2.

The RR for adverse skin reactions was 1.06 (95% CI 0.83 to 1.35; P = 0.63; 10 trials, 4735 participants; Analysis 1.13). The 95% prediction interval ranged between 0.80 and 1.41.

The RR for eye-related adverse events was 1.08 (95% CI 0.86 to 1.35; P = 0.52; 9 trials, 4204 participants; Analysis 1.14). The 95% prediction interval ranged between 0.83 and 1.41.

Socioeconomic effects

No study investigated socioeconomic effects.

HbA1c

The MD in HbA1c was −0.07% (95% CI −0.18 to 0.03; P = 0.17; 16 trials, 5809 participants; low-certainty evidence; Analysis 1.15). The 95% prediction interval ranged between −46% and 0.32%.

Subgroup analyses

We performed subgroup analyses for trials with OADs as concomitant blood glucose lowering medications versus trials with short-acting insulin as a concomitant blood glucose lowering medication for hypoglycaemic events (severe, serious, confirmed, nocturnal confirmed) and progression of diabetic retinopathy. Interaction was only found for the outcome progression of retinopathy. Retinopathy progression (three steps) for OADs showed a RR of 0.73 (95% CI 0.38 to 1.38, P = 0.33). Retinopathy progression (three steps) for short-acting insulin showed a RR of 2.75 (95% CI 1.10 to 6.91, P = 0.03) (test for subgroup difference: I^2 = 81.6%; P = 0.02).

We performed subgroup analyses for trials with NPH administration once daily versus NPH administration more than once daily for hypoglycaemic events (severe, serious, confirmed, nocturnal confirmed) and progression of diabetic retinopathy. Interaction was only found for the outcome nocturnal confirmed hypoglycaemia less than 75 mg/dL. Nocturnal confirmed hypoglycaemia less than 75 mg/dL for NPH once daily showed a RR of 0.74 (95% CI 0.62 to 0.89; P = 0.001). Nocturnal confirmed hypoglycaemia less than 75 mg/dL for NPH more than once daily showed a RR of 0.91 (95% CI 0.82 to 1.01; P = 0.11) (test for subgroup difference: I^2 = 74.7%; P = 0.05).

We did not conduct any further subgroup analyses because there were not enough trials or events to evaluate effects.

Sensitivity analyses

We performed sensitivity analyses for the following factors: very long (follow-up more than 12 months) and very large trials (more than 1000 participants). Trials did not differ enough in terms of other variables to allow meaningful sensitivity analyses. Analyses including and excluding the results from Yokoyama 2006 were also not feasible. We investigated the robustness of the pooled results by repeating the analyses using different statistical models (fixed- and random-effects).

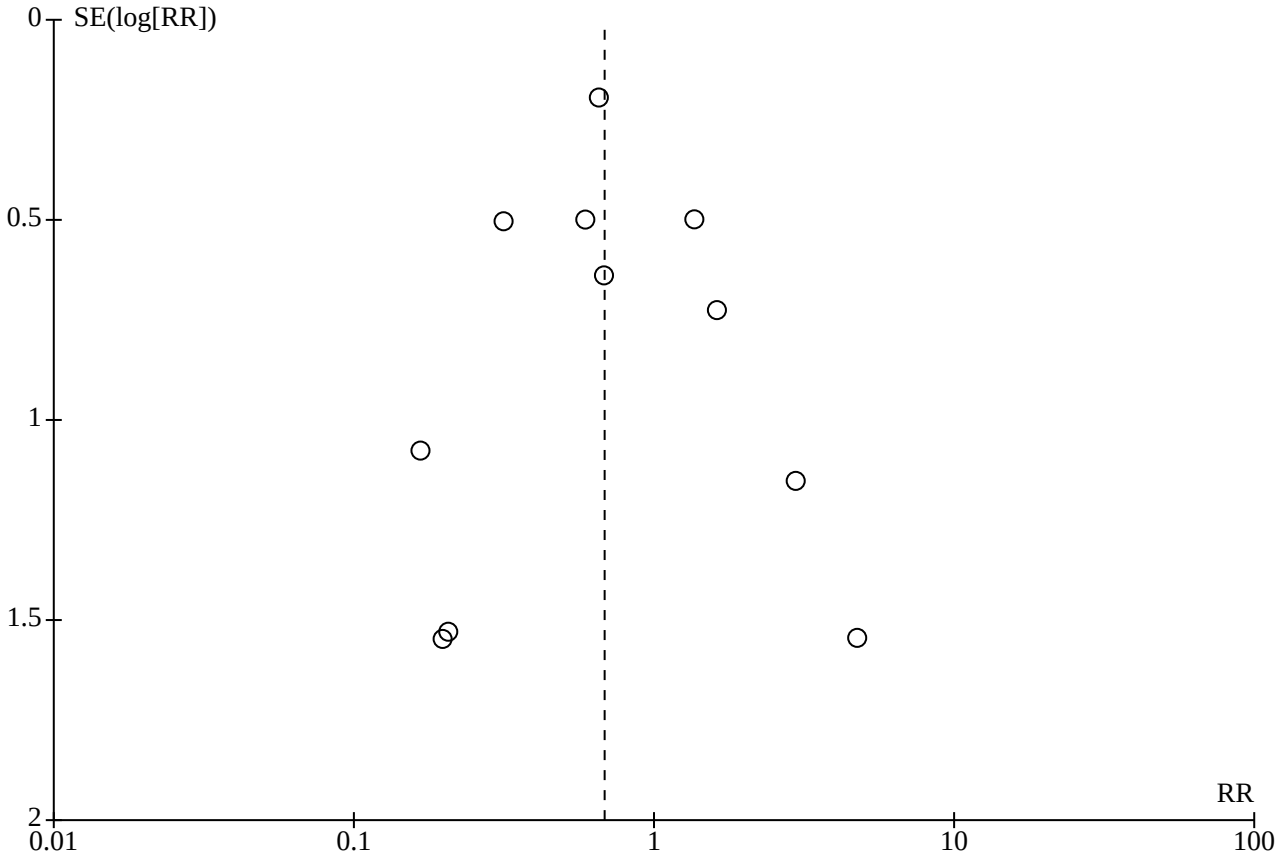
Nocturnal confirmed hypoglycaemia less than 75 mg/dL all studies showed a RR of 0.78 (95% CI 0.68 to 0.89; P = 0.003). Nocturnal confirmed hypoglycaemia less than 75 mg/dL for very large and very long studies only showed a RR (0.92, 95% CI 0.82 to 1.02; P = 0.11). The meta-analyses' results remained robust for all other outcomes.

Results also remained robust when we repeated the analyses using different statistical models.

Assessment of reporting bias

We drew a funnel plot for the primary endpoint severe hypoglycaemia (14 trials; Figure 4). The funnel plot did not indicate any increased risk of publication bias.

Figure 4. Funnel plot of comparison: 1 Insulin glargine versus NPH insulin, outcome: 1.2 Severe hypoglycaemia.



Long-acting insulin analogue detemir versus NPH insulin

Primary outcomes

Diabetes-related complications

Three trials reported a total of three non-fatal myocardial infarctions, two in participants treated with detemir and one in a participant treated with NPH (very low-certainty evidence) (Fajardo Montañana 2008; Haak 2005; NN304-3614).

Fajardo Montañana 2008 reported no fatal myocardial infarctions in either group. No other trial reported on this endpoint.

Three trials reported stroke (Fajardo Montañana 2008; Haak 2005; NN304-1337). One trial reported no fatal strokes in any group (NN304-1337). The other two reported two non-fatal events in the detemir groups and one non-fatal event in the NPH groups. The certainty of evidence was very low.

Fajardo Montañana 2008 reported that no end-stage renal disease occurred in any of the participants. No further information was available in the other trials.

Three-step progression of retinopathy for detemir versus NPH showed a RR of 1.50 (95% CI 0.68 to 3.32; P = 0.32; 2 trials; 972 participants; very low-certainty evidence; Analysis 2.1).

Fajardo Montañana 2008 reported that no participants underwent amputations.

No further information on diabetic late complications were available in any of the trials.

Hypoglycaemic episodes

The RR for severe hypoglycaemia was 0.45 (95% CI 0.17 to 1.20, P = 0.63; 5 trials, 1804 participants; very low-certainty evidence; Analysis 2.2). The 95% prediction interval ranged between 0.09 and 2.21.

The Peto OR for serious hypoglycaemia was 0.16 (95% CI 0.04 to 0.61; P = 0.007; 5 trials, 1777 participants; low-certainty evidence; Analysis 2.3).

The RR for confirmed hypoglycaemia less than 75 mg/dL was 0.73 in favour of detemir (95% CI 0.61 to 0.86; P < 0.001; 4 trials, 1718 participants; very low-certainty evidence; Analysis 2.4). The 95% prediction interval ranged between 0.36 and 1.48.

The RR for confirmed hypoglycaemia less than 55 mg/dL was 0.48 in favour of detemir (95% CI 0.32 to 0.71; P < 0.001; 4 trials, 1718 participants; low-certainty evidence; Analysis 2.5). The 95% prediction interval ranged between 0.20 and 1.13.

The RR for nocturnal confirmed hypoglycaemia less than 75 mg/dL was 0.57, 95% CI 0.47 to 0.68; P < 0.001; 4 trials; 1718 participants; low-certainty evidence; Analysis 2.6 in favour of detemir. The 95% prediction interval ranged between 0.39 and 0.84.

The RR for nocturnal confirmed hypoglycaemia less than 55 mg/dL was 0.32 in favour of detemir (95% CI 0.16 to 0.63; P = 0.001; 4 trials; 1718 participants; low-certainty evidence; Analysis 2.7). The 95% prediction interval ranged between 0.07 and 1.42.

Health-related quality of life

Three trials reported information on health-related quality of life (Fajardo Montañana 2008; Haak 2005; Kobayashi 2007 B). As the trials used different instruments for measuring health-related quality of life, a meta-analysis was not feasible.

Haak 2005 used the Diabetes Health Profile 2 (DHP-2) questionnaire. The MD in barriers to activity for detemir compared with NPH was −0.16 (95% CI −2.45 to 2.13; P = 0.89). The MD in disinhibited eating for detemir compared with NPH was 1.34 (95% CI −1.52 to 4.20; P = 0.36). The MD in psychological distress for detemir compared with NPH was −0.19 (95% CI −2.46 to 2.09; P = 0.87).

Fajardo Montañana 2008 used the SF-36 questionnaire. The MD in total score physical health for detemir compared with NPH was 2.83 (95% CI −1.56 to 7.23; P = 0.21). The MD in total score mental health for detemir compared with NPH was 4.19 (95% CI −0.22 to 8.61; P = 0.06).

Kobayashi 2007 A used the Insulin Therapy Related Quality Of Life At Night (ITR-QOLN) instrument. The MD in total score for detemir compared with NPH was 1.7 (95% CI −4.4 to 7.8; P = 0.58).

Secondary outcomes

All-cause mortality

The Peto OR for death from any cause was 0.74 (95% CI 0.20 to 2.65; P = 0.64; 8 trials, 2328 participants; low-certainty evidence; Analysis 2.8).

Adverse events other than hypoglycaemia

The RR for serious adverse events was 0.88 (95% CI 0.64 to 1.20; P = 0.40; 8 trials, 2328 participants; moderate-certainty evidence; Analysis 2.9). The 95% prediction interval ranged between 0.60 and 1.30.

The RR for all adverse events was 1.03 (95% CI 0.96 to 1.11; P = 0.35; 8 trials, 2328 participants; moderate-certainty evidence; Analysis 2.10). The 95% prediction interval ranged between 0.94 and 1.13.

The RR for adverse events leading to discontinuation of the trial was 1.22 (95% CI 0.67 to 2.25; P = 0.52; 8 trials, 2328 participants; moderate-certainty evidence; Analysis 2.11). The 95% prediction interval ranged between 0.57 and 2.62.

The MD for weight gain (BMI) was −0.60 kg/m^2 (95% CI −0.88 to −0.32; P < 0.001; 1 trial; 278 participants) (Fajardo Montañana 2008).

The RR for adverse skin reactions was 1.28 (95% CI 0.63 to 2.59; P = 0.50; 5 trials; 1777 participants; Analysis 2.12).

The RR for eye-related adverse events was 0.75 (95% CI 0.41 to 1.37; P = 0.34; 6 trials; 1386 participants; Analysis 2.13).

Socioeconomic effects

No study investigated socioeconomic effects.

HbA1c

The MD for HbA1c was 0.13% (95% CI −0.02 to 0.28; P = 0.08; 7 trials, 2233 participants; very low-certainty evidence; Analysis 2.14). The 95% prediction interval ranged between −0.28% and 0.54%.

Subgroup analyses

Subgroup analyses in trials with OADs versus short-acting insulin as concomitant blood glucose-lowering medications either showed no substantial differences (severe, serious, confirmed and confirmed nocturnal hypoglycaemia), or were not feasible because of the low number of trials and events. This was also true for subgroup analyses involving trials administering NPH once daily versus trials administering NPH at least twice daily.

Sensitivity analyses

We performed sensitivity analyses for the following factors: published or unpublished trials, and commercially or non-commercially funded trials. Trials did not differ enough in terms of other variables to allow for meaningful additional sensitivity analyses. We also investigated the robustness of the pooled results by repeating the analyses using different statistical models (fixed- and random-effects).

Severe hypoglycaemia including all trials found an OR of 0.37 (95% CI 0.15 to 0.92; P = 0.03). Severe hypoglycaemia including published trials only found an OR of 0.43 (95% CI 0.17 to 1.13; P = 0.09). The results of the meta-analyses remained robust for all other outcomes.

The results of the meta-analyses remained robust for all outcomes after exclusion of non-commercially funded studies and following comparisons using different statistical models.

Assessment of reporting bias

We did not draw funnel plots due to the limited number of trials (eight).

DISCUSSION

Summary of main results

With regard to diabetes complications information on myocardial infarction, stroke, amputations and end-stage renal disease was available from few trials only with a small number of events. No trustworthy inferences could be drawn from these results. There were more data on retinopathy; however, meta-analyses did not result in statistically or clinically relevant differences between treatment with glargine or detemir and NPH.

There were no clear differences for all-cause mortality when comparing treatment with long-acting insulin-analogues to NPH treatment. Information was available from almost all included trials and the number of people dying during a trial was low.

Three trials comparing glargine to NPH and three further trials comparing detemir to NPH reported outcomes on health-related quality of life utilising mostly different instruments. None of them found substantial differences between treatment with glargine or detemir and NPH.

We found no substantial differences between interventions and comparators in the frequency of adverse events.

No trial reported on socioeconomic effects.

Treatment of people with type 2 diabetes mellitus with insulin glargine and insulin detemir compared to NPH insulin resulted in no substantial differences in hypoglycaemic episodes, HbA1c lowering was comparable between treatments. Serious hypoglycaemia was somewhat lower following insulin detemir treatment compared to NPH insulin. Both insulin glargine and insulin detemir showed lower confirmed (nocturnal) hypoglycaemia rates in comparison to NPH insulin.

We considered no evidence to be of high certainty and all trials to have an unclear or high risk of bias in one or more risk of bias domains.

Overall completeness and applicability of evidence

This Cochrane Review is the most current and comprehensive systematic review to compare the effects of (ultra-)long-acting insulin analogues with those of NPH insulin. We have included 16 trials (6330 participants) comparing glargine to NPH and eight trials(2342 participants) comparing detemir to NPH.

We conducted an extensive search for trials, included publications in all languages, and tried to obtain additional data on all trials. However, the provision of additional data was limited. We also took into consideration additional information published in a report by the German Institute for Quality and Efficiency in Health Care that was based on the original trial reports (IQWiG 2009).

The diagnostic criteria for type 2 diabetes mellitus were not specified in most of the included trials. Participants had diabetes for eight years or longer at the beginning of all trials.

In the included trials, blood glucose targets set for insulin dose titration were comparable to those set in studies comparing the effects of a near-normal blood glucose reduction with a less intense reduction. In some cases, they were even lower. In other words, the trials aimed to achieve a near-normal reduction in blood glucose levels for the participants. This contrasts with the recommendations of professional associations for the individual setting of target values (ADA 2020). For example, a more moderate therapy target is recommended for people with a long duration of illness, significant comorbidity or diabetes-associated complications, and for people with limited life expectancy and resources (ADA 2020). In fact, since all trial participants had the disease for a relatively long time, higher target levels may well have been more appropriate. Incidence of serious or severe hypoglycaemia is directly associated with the intensity of blood glucose lowering. From this follows that less stringent blood glucose or HbA1c target values will result in less frequent major hypoglycaemic events and absolute risk reducing effect will be lower. Therefore, results from the studies at hand are only applicable to people in whom very low blood glucose concentrations are targeted.

However, even for those people for whom a blood glucose reduction to near normal concentrations can be considered an adequate treatment goal, the trial results provided only limited information about the different effects of insulin analogues and NPH insulin. In most studies (10/16 glargine trials and 5/8 detemir trials) limited NPH to a single injection per day. Also, an adjustment of the blood glucose-lowering comedications (short-acting insulin or oral glucose-lowering agents) was not possible – both of which do not correspond to current good clinical practice.

Because of the limited applicability of the results it remains unclear if the same effects will be observed in daily clinical practice. An indication that this is not the case is provided by the study of Lipska and colleagues, a retrospective observational study using data from a large US health management organisation (Lipska 2018). The authors found that initiating therapy with a long-acting insulin analogue was not associated with a reduced risk of hypoglycaemic emergency department visits, hospital admissions or improved glycaemic control compared to NPH insulin.

We identified no trials investigating NPH insulin therapy with ultra-long-acting insulin analogues treatment. Data can only be derived from indirect comparisons based on the results from trials comparing long-acting and ultra-long-acting insulin analogues. The results of a network meta-analysis suggested that compared to NPH insulin ultra-long-acting insulin analogues reduce the risk of hypoglycaemic events s (Madenidou 2018). However, regarding the applicability of the results, in addition to the uncertainty of indirect comparisons, restrictions apply as again the set target titration values corresponded to a near-normal blood glucose reduction (Gerstein 2012; Rosenstock 2018).

Quality of the evidence

For most patient-important outcomes, no or very limited information was available and only in a small number of trials. Furthermore, the reported frequency of such outcomes was low. Duration of follow-up was 12 months or less for all studies but one, which lasted for 60 months (Rosenstock 2009).

None of the included 24 studies could be classified as having low risk of bias for all risk of bias domains. The major shortcoming in all included trials was that neither participants nor study personnel were blinded to the respective interventions. Although blinding of participants and personnel would have been complicated, no effort was made to at least provide for a blinded outcome

assessment. While this is of lesser concern for objective outcomes such as centrally measured HbA1c or death from any cause, it means that more subjective and self-reported outcomes such as hypoglycaemia are at high risk of bias.

This is even more important when the bias-prone definitions of hypoglycaemia in the included trials are taken into consideration. Patients may inappropriately deny having had severe hypoglycaemia and in this context 'third party help' is a soft and variable description of severity. More robust definitions such as 'injection of glucose or glucagon by a third person' may result in more reliable data (Mühlhauser 1998). Since classification of hypoglycaemia as a serious adverse event requires the presence of specific additional criteria (ICH 2016), severe hypoglycaemic events, which simultaneously fulfil at least one of these criteria, are less vulnerable to bias. To minimise the risk of bias, apart from severe or serious hypoglycaemia, we only considered events for which a confirmed blood glucose measurement was available (ADA 2005). But even for confirmed hypoglycaemia, the risk of bias was high as participants may have chosen not to report events or may have made mistakes when transcribing blood glucose readings.

In addition, randomisation and allocation of concealment remained unclear in many trials.

Pharmaceutical companies producing long-acting insulin analogues funded most trials. Some argue that systematic bias favours products that are made by the company funding the research. Explanations include the selection of an inappropriate comparator to the product under investigation, and publication bias (Lexchin 2003).

Major reasons for downgrading the certainty of the evidence (GRADE) were lack of blinding of participants, study personnel and outcome-assessment, inconsistency (95% prediction intervals) and imprecision (small numbers of studies reporting on outcomes and low frequency of events).

Potential biases in the review process

As part of the original review, we contacted all authors of the available trials and producers of insulin-analogues and requested missing data and clarification of risk when bias domains could not be adequately assessed. For this update, we contacted all authors of the additionally identified trials, unless they had been included in the IQWiG report. This was because additional data had already been provided for the IQWiG report. We again contacted the two pharmaceutical companies manufacturing insulin glargine and insulin detemir. We also sought additional data from documents available from the USA and European medical agencies and trial registries. The IQWiG report was an important source of data because it included data provided by Sanofi and Novo Nordisk. But despite these efforts, a large quantity of data were still missing, which limited our investigations of the effects of the different insulins on a large number of outcomes and influenced our assessments of risk of bias and certainty of the evidence.

We excluded trials that lasted less than 24 weeks. While this is consistent with our effort to investigate the long-term effects of long-acting insulin analogues compared to NPH, especially on diabetes-related complications, it also resulted in fewer data on outcomes such as HbA1c and hypoglycaemia.

We were unable to draw funnel plots because of the small number of trials comparing detemir to NPH.

It was only possible to investigate heterogeneity by conducting subgroup and sensitivity analyses for a limited number of outcomes and variables.

Two review authors extracted the data. However, the review authors extracting the data were not blinded to the trial they were extracting data from.

Agreements and disagreements with other studies or reviews

Several other systematic reviews and meta-analyses have investigated the effects of treatment with (ultra-)long-acting insulin analogues compared to treatment with NPH (Bi 2012; Freemantle 2016; Frier 2013; Owens 2017; Rys 2015). However, they all differ from this Cochrane Review in several aspects: only Bi 2012 compared insulin glargine and insulin detemir to NPH insulin, but did not provide separate analyses and results for the two insulin-analogues. Owens 2017 only included trials comparing glargine U100 once daily in combination with OAD with treatment with NPH once daily combined with OADs. Freemantle 2016 compared glargine U300 to other basal insulins in a network meta-analysis. Rys 2015 included trials comparing NPH with glargine and Frier 2013 included trials comparing NPH with detemir. With the exception of Owens 2017, trials of less than 24 weeks' duration were also considered. Frier 2013 did not conduct any meta-analyses.

Despite these differences, the reported results were similar. All authors reported comparable effects of (ultra-)long-acting insulin analogues and NPH on HbA1c and weight gain, and they all found a lower rate of nocturnal hypoglycaemia when using long-acting insulin-analogues compared to NPH. Owens 2017 and Bi 2012 also found lower rates of overall hypoglycaemia and Rys 2015 found less symptomatic hypoglycaemia when treating with insulin analogues. In Owens 2017 and Rys 2015, there were no beneficial effects of insulin analogues on severe hypoglycaemia.

AUTHORS' CONCLUSIONS

Implications for practice

In people with type 2 diabetes mellitus, treatment with insulin detemir reduced the incidence of serious hypoglycaemia, and treatment with insulin glargine or detemir reduced the incidence of confirmed hypoglycaemic and confirmed nocturnal hypoglycaemic events, as compared with NPH insulin, with no substantial difference in glycosylated haemoglobin A1c (HbA1c) lowering. However, serious hypoglycaemic events were rare and the absolute risk reducing effect was low. Approximately one in 100 people treated with insulin detemir instead of NPH insulin benefited.

In all studies, low blood glucose and HbA1c targets, corresponding to near normal or even non-diabetic blood glucose levels, were set. Therefore, results from the studies at hand are only applicable to people in whom such low blood glucose concentrations are targeted. However, current guidelines recommend less intensive blood glucose lowering for the majority of people with type 2 diabetes in daily practice (e.g. people with cardiovascular diseases, with a long history of type 2 diabetes, who are susceptible to hypoglycaemia or elderly people). Additionally, low-certainty evidence and trial designs that did not conform with current

clinical practice meant it remains unclear if the same effects will be observed in daily clinical practice.

We found no clear effects of glargine or detemir compared with NPH on diabetes-related complications.

Data on health-related quality of life and socioeconomic effects were limited or not available.

Implications for research

For most patient-important outcomes it remains to be clarified if there is a clinically relevant difference between treatment with insulin glargine or detemir and NPH insulin in people with type 2 diabetes mellitus. Furthermore, data are required on socioeconomic effects, as well as from low- and middle-income countries as they were under-represented in the available trials.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Berard 2015

Study characteristics	
Methods	**Study design:** parallel RCT **Number of study centres:** 1
Participants	**Inclusion criteria:** participant in the ACCORD trial from the Winnipeg ACCORD trial centre, receiving basal insulin therapy with a long-acting insulin analogue, ineligible for financial reimbursement for the drug (provincial or private) or unable to afford to pay for insulin glargine **Exclusion criteria:** people who required any medical treatment that would preclude their safe participation in the study (as determined in the description by their physician), participation in any clinical trial other than the ACCORD extension trial **Diagnostic criteria:** —
Interventions	**Intervention:** insulin glargine **Comparator:** NPH insulin **Run-in period:** — **Extension period:** no
Outcomes	Hypoglycaemia symptomatic, severe and nocturnal; HbA1c; FPG; insulin dosages; bodyweight; DTSQs and DTSQc

Berard 2015 *(Continued)*

	Composite outcome measures reported: no
Study details	**Trial terminated early (for benefit/because of AEs):** no **Trial ID:** —
Publication details	**Language of publication:** English **Funding:** commercial funding (Sanofi Canada) **Publication status:** peer-reviewed journal/full article
Stated aim of study	**Quote:** "…to ensure patient safety when insulin glargine was replaced by NPH insulin. The study also sought to determine differences in blood glucose control, frequency of hypoglycaemia, insulin dosing, health resource utilization and quality of life in the groups."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "Randomization was completed at site levels after screening visits occurred. An independent source randomly prepared envelopes containing assignments of either insulin glargine or NPH insulin. These envelopes were then distributed to the participants in a consecutive fashion." **Comment:** unclear generation of randomisation sequence
Allocation concealment (selection bias)	Unclear risk	**Quote:** "Randomization was completed at site levels after screening visits occurred. An independent source randomly prepared envelopes containing assignments of either insulin glargine or NPH insulin. These envelopes were then distributed to the participants in a consecutive fashion." **Comment:** unclear if envelops were opaque
Blinding of participants and personnel (performance bias) HbA1c	Unclear risk	**Quote:** "open-label." **Comment:** investigator-assessed outcome measurement
Blinding of participants and personnel (performance bias) Hypoglycaemia	High risk	**Quote:** "open-label." **Comment:** self-reported outcome measurement
Blinding of outcome assessment (detection bias) HbA1c	Unclear risk	**Quote:** "open-label." **Comment:** investigator-assessed outcome measurement
Blinding of outcome assessment (detection bias) Hypoglycaemia	High risk	**Quote:** "open-label." **Comment:** self-reported outcome measurement
Incomplete outcome data (attrition bias) HbA1c	Unclear risk	**Comment:** no information on participants included in analyses
Incomplete outcome data (attrition bias)	Unclear risk	**Comment:** no information on participants included in analyses

Berard 2015 *(Continued)*

Hypoglycaemia

Selective reporting (reporting bias)	High risk	**Comment:** deaths, AEs and SAEs are not reported but were probably assessed
Other bias	Unclear risk	**Comment:** funding received by a pharmaceutical company

Betônico 2019

Study characteristics	
Methods	**Study design:** cross-over RCT; non-inferiority design **Number of study centres:** 1
Participants	**Inclusion criteria:** type 2 diabetes mellitus; chronic kidney disease, stages 3 and 4 (glomerular filtration rate 15–59 mL/minute/1.73 m^2) secondary to diabetic nephropathy, aged 40–80 years; use of basal bolus insulin ≥ 3 months before the study (NPH as basal insulin and regular insulin at meals) **Exclusion criteria:** chronic kidney disease or nephropathy from other aetiologies; use of concomitant OADs or OADs with insulin therapy; severe psychiatric disorders HIV systemic neoplasia; pregnant women **Diagnostic criteria:** ADA 2015
Interventions	**Intervention:** insulin glargine **Comparator:** NPH insulin **Run-in period:** no **Extension period:** no
Outcomes	HbA1c, number of hypoglycaemic events, SMBG, continuous glucose monitoring, glycaemic variability, total daily insulin dose, weight and BMI, end-stage renal disease, hospitalisation, death, creatinine, glomerular filtration rate **Composite outcome measures reported:** no
Study details	**Trial terminated early (for benefit/because of AEs):** no **Trial ID:** NCT02451917
Publication details	**Language of publication:** English **Funding:** non-commercially (University of Sao Paulo General Hospital) **Publication status:** peer-reviewed journal/full article; report at ClinicalTrials.gov
Stated aim of study	**Quote:** "…the purpose of this randomized open-label crossover study was to compare the efficacy and safety profile of a long-acting insulin analogue (glargine U100) and NPH insulin in patients with type 2 diabetes mellitus and CKD stages 3 and 4."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Betônico 2019 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	**Quote:** "Randomization was stratified by the HbA1 value at baseline: <9.0% or >9.0%" (75 mmol/mol), in a 1:1 ratio, and the individuals who met all inclusion criteria were allocated alternately to either an IGlar or an NPH I treatment. After 24 weeks, basal insulins were switched, patients taking IGlar were transferred to receive INPH (IGlar/INPH sequence), whereas patients using INPH in the first phase switched to IGlar (INPH/IGlar sequence)." **Comment:** insufficient information available.
Allocation concealment (selection bias)	Unclear risk	**Comment:** insufficient information available
Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "open label." **Comment:** investigator-assessed and self-reported outcome measurement
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Quote:** "open label." **Comment:** investigator-assessed outcome measurement
Blinding of participants and personnel (performance bias) Diabetes-related complications	Unclear risk	**Quote:** "open label." **Comment:** investigator-assessed and self-reported outcome measurement
Blinding of participants and personnel (performance bias) HbA1c	Unclear risk	**Quote:** "open label." **Comment:** investigator-assessed outcome measurement
Blinding of participants and personnel (performance bias) Hypoglycaemia	High risk	**Quote:** "open label." **Comment:** investigator-assessed and self-reported outcome measurement
Blinding of outcome assessment (detection bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "open label." **Comment:** investigator-assessed and self-reported outcome measurement
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Quote:** "open label."
Blinding of outcome assessment (detection bias) Diabetes-related complications	Unclear risk	**Quote:** "open label." **Comment:** investigator-assessed and self-reported outcome measurement
Blinding of outcome assessment (detection bias) HbA1c	Unclear risk	**Quote:** "open label." **Comment:** investigator-assessed outcome measurement
Blinding of outcome assessment (detection bias)	High risk	**Quote:** "open label."

Betônico 2019 *(Continued)*

Hypoglycaemia		**Comment:** investigator-assessed outcome measurement
Incomplete outcome data (attrition bias) Adverse events other than hypoglycaemia	Low risk	**Comment:** no missing data; ITT analyses
Incomplete outcome data (attrition bias) All-cause mortality	Low risk	**Comment:** no missing data; ITT analyses
Incomplete outcome data (attrition bias) Diabetes-related complications	Low risk	**Comment:** no missing data; ITT analyses
Incomplete outcome data (attrition bias) HbA1c	Low risk	**Comment:** no missing data; ITT analyses
Incomplete outcome data (attrition bias) Hypoglycaemia	Low risk	**Comment:** no missing data; ITT analyses
Selective reporting (reporting bias)	Unclear risk	**Comment:** none detected
Other bias	Low risk	**Comment:** none detected

Eliaschewitz 2006

Study characteristics	
Methods	**Study design:** parallel RCT; equivalence design **Number of study centres:** 56
Participants	**Inclusion criteria:** men or women; aged ≤ 75 years; BMI ≤ 35 kg/m^2; type 2 diabetes mellitus and failed to achieve good metabolic control on OADs (HbA1c levels ≥ 7.5% and ≤ 10.5%; FBG ≥ 100 mg/dL; required to have been receiving OADs (any SUs, including glimepiride, or a combination of SUs with other OADs such as metformin or acarbose) for ≥ 6 months; previous doses of SUs were required to have been at least equivalent to glimepiride 3 mg; needed to be willing to follow a tight antidiabetic therapy; women of childbearing age needed to use an acceptable form of contraception **Exclusion criteria:** previous treatment with any insulin in the 3 months before the study; pregnancy or breastfeeding; likely to require treatment with drugs not permitted by the study protocol (non-cardioselective β-blockers and systemic corticosteroids); enrolment in a previous study of insulin glargine; received an investigative drug within 3 months of the study; history of alcohol abuse **Diagnostic criteria:** —
Interventions	**Intervention:** insulin glargine **Comparator:** NPH insulin **Run-in period:** no (4 weeks' screening period) **Titration period:** 6 weeks

Eliaschewitz 2006 *(Continued)*

	Treatment before study: OADs (any SUs, including glimepiride, or a combination of SUs with other OADs such as metformin or acarbose) equivalent to glimepiride 3 mg per day for ≥ 6 months **Extension period:** no
Outcomes	**Primary outcome:** change in HbA1c from baseline to end of study (week 24) **Secondary outcomes:** percentage of participants who achieved a target HbA1c value ≤ 7.5% by the end of the study; change in FBG; percentage of participants who achieved an FBG ≤ 100 mg/dL by end of study **Additional published outcomes:** treatment satisfaction (DTSQc); pharmacoeconomics; symptomatic hypoglycaemic events; symptomatic nocturnal hypoglycaemia; treatment-emergent AEs **Composite outcome measures reported:** no
Study details	**Trial terminated early (for benefit/because of AEs):** no **Trial ID:** —
Publication details	**Language of publication:** English **Funding:** commercial funding (Sanofi) **Publication status:** peer-reviewed journal/full article
Stated aim of study	**Quote:** "…to compare the efficacy and safety of basal insulin therapy with insulin glargine with those of NPH insulin, both in combination with glimepiride in a predominantly non-white (> 53%) population of patients with type 2 diabetes living in Central and South America."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** no information from publication, but according to IQWiG report adequate
Allocation concealment (selection bias)	Low risk	**Comment:** no information from publication, but according to IQWiG report adequate
Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "open labeled." **Comment:** investigator-assessed and self-reported outcome measurement
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Quote:** "open labeled." **Comment:** investigator-assessed outcome measurement
Blinding of participants and personnel (performance bias) HbA1c	Low risk	**Quote:** "open-labeled;" "Blood samples were collected at the study centre and sent to a central laboratory for determination of HbA1c levels." **Comment:** adjudicated outcome measurement
Blinding of participants and personnel (performance bias)	High risk	**Quote:** "open-labeled." **Comment:** self-reported outcome measurement

Eliaschewitz 2006 *(Continued)*

Hypoglycaemia		
Blinding of outcome assessment (detection bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "open-labeled." **Comment:** there is no indication that the endpoint assessment was blinded
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Quote:** "open-labeled." **Comment:** there is no indication that the endpoint assessment was blinded
Blinding of outcome assessment (detection bias) HbA1c	Low risk	**Quote:** "open labeled;" "Blood samples were collected at the study centre and sent to a central laboratory for determination of HbA1c levels." **Comment:** determined in a central laboratory
Blinding of outcome assessment (detection bias) Hypoglycaemia	High risk	**Quote:** "open labeled." **Comment:** there is no indication that the endpoint assessment was blinded.
Incomplete outcome data (attrition bias) Adverse events other than hypoglycaemia	Low risk	**Quote:** "…the safety-evaluable analysis population included all randomized patients who received at least one dose of the study medication and formed the population for all safety analyses…" **Comment:** no missing data; ITT/LOCF according to IQWiG-report
Incomplete outcome data (attrition bias) All-cause mortality	Low risk	**Quote:** "…the safety-evaluable analysis population included all randomized patients who received at least one dose of the study medication and formed the population for all safety analyses…" **Comment:** no missing data; ITT/LOCF according to IQWiG-report
Incomplete outcome data (attrition bias) HbA1c	Low risk	**Quote:** "The primary efficacy variable was the change in HbA1c from baseline to the end of the study in the per-protocol population." "…per-protocol population included all patients from the full analysis set, except those with major protocol deviations." **Comment:** primary efficacy variable was HbA1c in per-protocol population; in addition, ITT/LOCF analysis available from IQWiG-report
Incomplete outcome data (attrition bias) Hypoglycaemia	Low risk	**Quote:** "…the safety-evaluable analysis population included all randomized patients who received at least one dose of the study medication and formed the population for all safety analyses…" **Comment:** no missing data; ITT according to IQWiG report
Selective reporting (reporting bias)	Low risk	**Comment:** none detected
Other bias	Unclear risk	**Comment:** funding received by a pharmaceutical company

Fajardo Montañana 2008

Study characteristics	
Methods	**Study design:** parallel RCT

Fajardo Montañana 2008 *(Continued)*

	Number of study centres: 41
Participants	**Inclusion criteria:** men or women aged ≥ 18 years type 2 diabetes mellitus; overweight or obese – BMI 25.0–40 kg/m^2; HbA1c 7.5–11.0%; treated with 2 daily doses of insulin (≥ 1 of them a premix) for ≥ 3 months ± metformin 1000–2550 mg daily **Exclusion criteria:** oral glucose-lowering drugs other than metformin; total daily insulin dose ≥ 2 IU/kg; any condition rendering the participant unsuitable to participate; anticipated changes in concomitant medications known to interfere with glucose metabolism; proliferative retinopathy or maculopathy requiring acute treatment in the preceding 6 months; uncontrolled hypertension; pregnancy and breast-feeding **Diagnostic criteria:** —
Interventions	**Intervention:** insulin detemir **Comparator:** NPH insulin **Run-in period:** — **Extension period:** no
Outcomes	Weight change; HbA1c; FPG; 7-point glucose profiles; proportions of participants achieving HbA1c ≤ 7.0%; proportion of participants reaching pre- and postprandial BG targets; lipid profile; homeostatic model assessment for insulin resistance (HOMA-IR); insulin doses; hypoglycaemia (major, minor, other, nocturnal); AEs; standard laboratory analyses; physical examinations; treatment satisfaction and QoL **Composite outcome measures reported:** no
Study details	**Trial terminated early (for benefit/because of AEs):** no **Trial ID:** NN304-1659; NCT00504673; EUCTR2005-000976-42
Publication details	**Language of publication:** English **Funding:** commercial funding (Novo Nordisk) **Publication status:** peer-reviewed journal, full article
Stated aim of study	**Quote:** "To assess weight change when once-daily insulin detemir (detemir) or neutral protamine Hagedorn insulin (NPH) are used in already overweight type 2 diabetes patients requiring intensified insulin therapy."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "Clinical Supplies Operations at Novo Nordisk A/S generated the randomization list and supplied the sealed codes. Local investigators enrolled patients and assigned them to groups by choosing the lowest available randomization number at their site; treatment was then revealed by scratching off the protective surface of the sealed code." **Comment:** satisfactory generation of randomization sequence
Allocation concealment (selection bias)	Low risk	**Quote:** "Clinical Supplies Operations at Novo Nordisk A/S generated the randomization list and supplied the sealed codes. Local investigators enrolled patients and assigned them to groups by choosing the lowest available random-

Fajardo Montañana 2008 *(Continued)*

		ization number at their site; treatment was then revealed by scratching off the protective surface of the sealed code." **Comment:** satisfactory allocation concealment
Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "open label." **Comment:** investigator-assessed and self-reported outcome measurement
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Quote:** "open label." **Comment:** investigator-assessed outcome measurement
Blinding of participants and personnel (performance bias) Diabetes-related complications	Unclear risk	**Quote:** "open label." **Comment:** investigator-assessed and self-reported outcome measurement
Blinding of participants and personnel (performance bias) HbA1c	Low risk	**Quote:** "open label." **Comment:** investigator-assessed, centrally measured outcome measurement
Blinding of participants and personnel (performance bias) Health-related quality of life	High risk	**Quote:** "open label." **Comment:** self-reported outcome measurement
Blinding of participants and personnel (performance bias) Hypoglycaemia	High risk	**Quote:** "open label." **Comment:** investigator-assessed and self-reported outcome measurement
Blinding of outcome assessment (detection bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "open label." **Comment:** investigator-assessed and self-reported outcome measurement.
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Quote:** "open label." **Comment:** investigator-assessed outcome measurement
Blinding of outcome assessment (detection bias) Diabetes-related complications	Unclear risk	**Quote:** "open label." **Comment:** investigator-assessed and self-reported outcome measurement
Blinding of outcome assessment (detection bias) HbA1c	Low risk	**Quote:** "open label." **Comment:** centrally measured outcome measurement
Blinding of outcome assessment (detection bias)	High risk	**Quote:** "open label." **Comment:** self-reported outcome measurement

Fajardo Montañana 2008 *(Continued)*

Health-related quality of life		
Blinding of outcome assessment (detection bias) Hypoglycaemia	High risk	**Quote:** "open label." **Comment:** investigator-assessed and self-reported outcome measurement
Incomplete outcome data (attrition bias) Adverse events other than hypoglycaemia	Low risk	**Quote:** "Last Observation Carried Forward (LOCF) from the closer data of missing after basal visit." **Comment:** time point of participants lost to follow-up unknown, completer rates were 94% and 92% in the respective treatment groups
Incomplete outcome data (attrition bias) All-cause mortality	Low risk	**Quote:** "Last Observation Carried Forward (LOCF) from the closer data of missing after basal visit." **Comment:** time point of participants lost to follow-up unknown, completer rates were 94% and 92% in the respective treatment groups
Incomplete outcome data (attrition bias) Diabetes-related complications	Low risk	**Quote:** "Last Observation Carried Forward (LOCF) from the closer data of missing after basal visit." **Comment:** time point of participants lost to follow-up unknown, completer rates were 94% and 92% in the respective treatment groups
Incomplete outcome data (attrition bias) HbA1c	Low risk	**Quote:** "Last Observation Carried Forward (LOCF) from the closer data of missing after basal visit." **Comment:** time point of participants lost to follow-up unknown, completer rates were 94% and 92% in the respective treatment groups
Incomplete outcome data (attrition bias) Health-related quality of life	Low risk	**Quote:** "Last Observation Carried Forward (LOCF) from the closer data of missing after basal visit." **Comment:** time point of participants lost to follow-up unknown, completer rates were 94% and 92% in the respective treatment groups
Incomplete outcome data (attrition bias) Hypoglycaemia	Low risk	**Quote:** "Last Observation Carried Forward (LOCF) from the closer data of missing after basal visit." **Comment:** time point of participants lost to follow-up unknown, completer rates were 94% and 92% in the respective treatment groups
Selective reporting (reporting bias)	Low risk	**Comment:** none detected
Other bias	Unclear risk	**Comment:** funding received by a pharmaceutical company

Fritsche 2003

Study characteristics	
Methods	**Study design:** parallel RCT; non-inferiority design **Number of study centres:** 111
Participants	**Inclusion criteria:** type 2 diabetes mellitus, aged < 75 years; previous therapy with SU as monotherapy or in combination with metformin or acarbose; BMI < 35 kg/m^2; HbA1c 7.5–10.5%; FPG ≥ 6.7 mmol/L

Fritsche 2003 *(Continued)*

	Exclusion criteria: pregnancy or breastfeeding; pretreatment with insulin or any investigational drugs within the previous 3 months; clinically relevant somatic or mental diseases **Diagnostic criteria:** —
Interventions	**Intervention 1:** insulin glargine in the morning **Intervention 2:** insulin glargine at bedtime **Comparator:** NPH insulin at bedtime **Run-in period:** 4 weeks **Titration period:** complete treatment phase; prespecified algorithm **Treatment before study:** SU as monotherapy or in combination with metformin or acarbose **Extension period:** no
Outcomes	**Primary outcomes:** change of HbA1c from baseline to endpoint; frequency of participants who experienced hypoglycaemic events **Secondary outcomes:** HbA1c ≤ 7.5%; FPG ≤ 5.6 mmol/L; response rates; mean 24-hour BG values **Additional published outcomes:** insulin doses; AEs; bodyweight **Composite outcome measures reported:** no
Study details	**Trial terminated early (for benefit/because of AEs):** no **Trial ID:** —
Publication details	**Language of publication:** English **Funding:** commercial funding (Sanofi) **Publication status:** peer-reviewed journal/full article
Stated aim of study	**Quote:** "…we investigate the efficacy and safety of a combination therapy of sulphonylurea with either morning or bedtime insulin glargine or bed-time NPH insulin in patients with diabetes mellitus type 2 whose diabetes was poorly controlled with oral antidiabetic drugs alone."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "All patients who had entered the screening phase received a patient number. With a randomization schedule generated by the sponsor, eligible patients were linked sequentially to treatment codes allocated at random. This schedule was stratified by centre on a 1:1:1 basis." **Comment:** adequate
Allocation concealment (selection bias)	Low risk	**Quote:** "All patients who had entered the screening phase received a patient number. With a randomization schedule generated by the sponsor, eligible patients were linked sequentially to treatment codes allocated at random. This schedule was stratified by centre on a 1:1:1 basis." **Comment:** adequate

Fritsche 2003 *(Continued)*

Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "…open-label…" **Comment:** investigator-assessed and self-reported outcome measurement
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Quote:** "…open-label…" **Comment:** investigator-assessed outcome measurement
Blinding of participants and personnel (performance bias) HbA1c	Low risk	**Quote:** "…open-label…" **Comment:** centrally measured outcome measurement
Blinding of participants and personnel (performance bias) Hypoglycaemia	High risk	**Quote:** "…open-label…" **Comment:** self-reported outcome measurement
Blinding of outcome assessment (detection bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "…open-label…" **Comment:** investigator-assessed and self-reported outcome measurement; there is no indication that the endpoint assessment was blinded
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Quote:** "…open-label…" **Comment:** investigator-assessed outcome measurement; there is no indication that the endpoint assessment was blinded
Blinding of outcome assessment (detection bias) HbA1c	Low risk	**Quote:** "…open-label…" **Comment:** determined in a central laboratory
Blinding of outcome assessment (detection bias) Hypoglycaemia	High risk	**Quote:** "…open-label…" **Comment:** self-reported outcome measurement; there is no indication that the endpoint assessment was blinded
Incomplete outcome data (attrition bias) Adverse events other than hypoglycaemia	Low risk	**Quote:** "…these 695 patients represent the intention-to-treat sample (full-analysis set)." **Comment:** ITT/LOCF according to IQWiG-report
Incomplete outcome data (attrition bias) All-cause mortality	Low risk	**Quote:** "…these 695 patients represent the intention-to-treat sample (full-analysis set)." **Comment:** ITT/LOCF according to IQWiG-report
Incomplete outcome data (attrition bias) HbA1c	Low risk	**Quote:** "…these 695 patients represent the intention-to-treat sample (full-analysis set)." **Comment:** primary efficacy variable was HbA1c in per-protocol population; in addition, ITT/LOCF analysis available from IQWiG report
Incomplete outcome data (attrition bias) Hypoglycaemia	Low risk	**Quote:** "…these 695 patients represent the intention-to-treat sample (full-analysis set)."

Fritsche 2003 *(Continued)*

		Comment: ITT/LOCF according to IQWiG-report
Selective reporting (reporting bias)	Low risk	**Comment:** none detected
Other bias	Unclear risk	**Comment:** funding received by a pharmaceutical company

Haak 2005

Study characteristics	
Methods	**Study design:** parallel RCT; non-inferiority design **Number of study centres:** 63
Participants	**Inclusion criteria:** type 2 diabetes mellitus ≥ 12 months, aged ≥ 35 years; insulin treatment for ≥ 2 months (basal insulin dose ≥ 30% of the total daily insulin dose); HbA1c ≤ 12% **Exclusion criteria:** pregnancy or breastfeeding; OADs within the previous 2 months; proliferative retinopathy; uncontrolled hypertension; recurrent major hypoglycaemia; impaired renal or hepatic function; cardiac problems; daily basal insulin dose > 100 IU/day **Diagnostic criteria:** ADA
Interventions	**Intervention:** insulin detemir **Comparator:** NPH insulin **Run-in period:** no (3 weeks screening period) **Extension period:** no
Outcomes	HbA1c; FPG; self-measured BG profiles; within subject variation of FBG; insulin doses; percentage of participants experiencing a hypoglycaemic episode (overall, severe and nocturnal); bodyweight; AEs; safety **Composite outcome measures reported:** no
Study details	**Trial terminated early (for benefit/because of AEs):** no **Trial ID:** NN304-1336
Publication details	**Language of publication:** English **Funding:** unclear **Publication status:** peer-reviewed journal/full article
Stated aim of study	**Quote:** "efficacy and safety comparison of insulin detemir and NPH insulin in patients with type 2 diabetes on a basal-bolus regimen."
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Haak 2005 *(Continued)*

Random sequence generation (selection bias)	Low risk	**Comment:** no information from publication, but according to IQWiG report adequate
Allocation concealment (selection bias)	Low risk	**Comment:** no information from publication, but according to IQWiG report adequate
Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "open-label." **Comment:** investigator-assessed and self-reported outcome measurement
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Quote from publication:** "open-label." **Comment:** investigator-assessed outcome measurement
Blinding of participants and personnel (performance bias) Diabetes-related complications	Unclear risk	**Quote:** "open-label." **Comment:** investigator-assessed outcome measurement
Blinding of participants and personnel (performance bias) HbA1c	Low risk	**Quote:** "open-label." **Comment:** centrally measured outcome measurement
Blinding of participants and personnel (performance bias) Health-related quality of life	High risk	**Quote:** "open-label." **Comment:** self-reported outcome measurement
Blinding of participants and personnel (performance bias) Hypoglycaemia	High risk	**Quote:** "open-label." **Comment:** self-reported outcome measurement
Blinding of outcome assessment (detection bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "open-label." **Comment:** investigator-assessed and self-reported outcome measurement
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Quote:** "open-label." **Comment:** investigator-assessed outcome measurement
Blinding of outcome assessment (detection bias) Diabetes-related complications	Unclear risk	**Quote:** "open-label." **Comment:** investigator-assessed outcome measurement
Blinding of outcome assessment (detection bias) HbA1c	Low risk	**Quote:** "open-label." **Comment:** centrally measured outcome measurement
Blinding of outcome assessment (detection bias)	High risk	**Quote:** "open-label."

Haak 2005 *(Continued)*

Health-related quality of life		**Comment:** self-reported outcome measurement
Blinding of outcome assessment (detection bias) Hypoglycaemia	High risk	**Quote:** "open-label." **Comment:** self-reported outcome measurement
Incomplete outcome data (attrition bias) Adverse events other than hypoglycaemia	Low risk	**Comment:** ITT/LOCF according to IQWiG report; 92.4% of randomised and 95.1% of treated participants finished the trial; reasons for withdrawals given but without numbers
Incomplete outcome data (attrition bias) All-cause mortality	Low risk	**Comment:** ITT/LOCF according to IQWiG report; 92.4% of randomised and 95.1% of treated participants finished the trial; reasons for withdrawals given but without numbers
Incomplete outcome data (attrition bias) Diabetes-related complications	Low risk	**Comment:** ITT/LOCF according to IQWiG report; 92.4% of randomised and 95.1% of treated participants finished the trial; reasons for withdrawals given but without numbers
Incomplete outcome data (attrition bias) HbA1c	Low risk	**Comment:** ITT/LOCF according to IQWiG report; 92.4% of randomised and 95.1% of treated participants finished the trial; reasons for withdrawals given but without numbers
Incomplete outcome data (attrition bias) Health-related quality of life	Low risk	**Comment:** ITT/LOCF according to IQWiG report; 92.4% of randomised and 95.1% of treated participants finished the trial; reasons for withdrawals given but without numbers
Incomplete outcome data (attrition bias) Hypoglycaemia	Low risk	**Comment:** ITT/LOCF according to IQWiG report; 92.4% of randomised and 95.1% of treated participants finished the trial; reasons for withdrawals given but without numbers
Selective reporting (reporting bias)	Low risk	**Comment:** none detected
Other bias	Unclear risk	**Comment:** funding source not reported

Hermanns 2015

Study characteristics	
Methods	**Study design:** cross-over RCT **Number of study centres:** 39
Participants	**Inclusion criteria:** aged 18–80 years; type 2 diabetes mellitus; BMI > 22 kg/2² to < 40 kg/m²; HbA1c 7.0–10.0%; FBG ≥ 6.7 mmol/L (120 mg/dL) **Exclusion criteria:** treatment with any insulin in the 3 months prior to inclusion; treatment with > 2 OADs in the 4 weeks prior to inclusion; continuous treatment with thiazolidinediones or GLP-1 receptor agonists; history of ketoacidosis; history of drug or alcohol abuse; diabetic retinopathy with surgical treatment (laser photocoagulation or vitrectomy) in the 3 months prior to study entry or which may require surgical treatment within 3 months; prior pancreatectomy; impaired hepatic function; impaired renal function; current treatment for a mental disorder according to the International Classification of Diseases – 10th Revision F 5 diagnoses; systemic corticoid treatment for > 2 months; prior bariatric

Hermanns 2015 *(Continued)*

	surgery, or major dietary changes for weight management during the last 3 months resulting in weight reduction > 5 kg **Diagnostic criteria:** according to ADA criteria (2008)
Interventions	**Intervention:** insulin glargine **Comparator:** NPH insulin **Run-in period:** — **Extension period:** no
Outcomes	ITEQ score; PAID questionnaire; SF-12 Health Survey; EQ-5D; DTSQs; HbA1c; FPG; 7-point BG profiles; bodyweight; waist circumference; blood pressure; lipids; hypoglycaemic events (symptomatic or severe, or both); total daily insulin doses; patients' treatment preferences; SAEs; AEs; pain, redness or inflammation at the injection site **Composite outcome measures reported:** yes: (primary endpoint) DRQoL score consisting of ITEQ score, PAID questionnaire and the mental health score of the SF-12
Study details	**Trial terminated early (for benefit/because of AEs):** no **Trial ID:** NCT00941369; EUCTR2009-010913-59
Publication details	**Language of publication:** English **Funding:** commercial funding (Sanofi) **Publication status:** peer-reviewed journal/full article
Stated aim of study	**Quote:** "…the primary objective of this study was to investigate the impact of insulin glargine versus NPH insulin on a composite Diabetes Related Quality of Life score (DRQoL), consisting of a standardized and unweighted Insulin Treatment Experience Questionnaire Score (ITEQ), a Problem Areas in Diabetes (PAID) questionnaire score, and the mental health score in the Short Form (SF)-12® Health Survey, in a randomized controlled study."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "in each study centre, patients were block randomized on a 1:1 basis…" **Comment:** no information on randomisation method.
Allocation concealment (selection bias)	Low risk	**Comment:** according to the information from the study author, sealed envelops were used
Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "…open-label, randomized, multi-center, crossover phase IV trial…" **Comment:** investigator-assessed and self-reported outcome measurement; neither the investigators nor the participants were blinded to the interventions
Blinding of participants and personnel (performance bias)	Low risk	**Quote:** "…open-label, randomized, multi-center, crossover phase IV trial…" **Comment:** investigator-assessed outcome measurement; neither the investigators nor the participants were blinded to the interventions

Hermanns 2015 *(Continued)*
All-cause mortality

Blinding of participants and personnel (performance bias) HbA1c	Low risk	**Quote:** "…open-label, randomized, multi-center, crossover phase IV trial…" **Comment:** probably centrally measured outcome measurement; neither the investigators nor the participants were blinded to the interventions
Blinding of participants and personnel (performance bias) Health-related quality of life	High risk	**Quote:** "…open-label, randomized, multi-center, crossover phase IV trial…" **Comment:** self-reported outcome measurement; neither the investigators nor the participants were blinded to the interventions
Blinding of participants and personnel (performance bias) Hypoglycaemia	High risk	**Quote:** "…open-label, randomized, multi-center, crossover phase IV trial…" **Comment:** investigator-assessed and self-reported outcome measurement; neither the investigators nor the participants were blinded to the interventions
Blinding of outcome assessment (detection bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "…open-label, randomized, multi-center, crossover phase IV trial…" **Comment:** investigator-assessed and self-reported outcome measurement; no information on possible blinding of outcome assessment
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Quote:** "…open-label, randomized, multi-center, crossover phase IV trial…" **Comment:** investigator-assessed outcome measurement; no information on possible blinding of outcome assessment.
Blinding of outcome assessment (detection bias) HbA1c	Low risk	**Quote:** "…open-label, randomized, multi-center, crossover phase IV trial…" **Comment:** probably centrally measured outcome measurement; no information on possible blinding of outcome assessment
Blinding of outcome assessment (detection bias) Health-related quality of life	High risk	**Quote:** "…open-label, randomized, multi-center, crossover phase IV trial…" **Comment:** self-reported outcome measurement; no information on possible blinding of outcome assessment
Blinding of outcome assessment (detection bias) Hypoglycaemia	High risk	**Quote:** "…open-label, randomized, multi-center, crossover phase IV trial…" **Comment:** investigator-assessed and self-reported outcome measurement; no information on possible blinding of outcome assessment
Incomplete outcome data (attrition bias) Adverse events other than hypoglycaemia	Low risk	**Comment:** no missing data
Incomplete outcome data (attrition bias) All-cause mortality	Low risk	**Comment:** no missing data
Incomplete outcome data (attrition bias) HbA1c	Low risk	**Quote:** "secondary endpoints were analyzed for the intent-to-treat population…, ITT set n=339." **Comment:** ITT/LOCF
Incomplete outcome data (attrition bias)	Unclear risk	**Quote:** "the primary endpoint (DRQoL) was analyzed for the modified intent-to-treat population including randomized patients with valid values

Hermanns 2015 *(Continued)*

Health-related quality of life		for DRQoL for both treatment periods (modified ITT set n=229); randomized n=343, safety set n=340, ITT set n=339, study withdrawal n=47." **Comment:** it remains unclear how many participants were included in the analyses of secondary health-related quality of life (HRQoL) outcomes
Incomplete outcome data (attrition bias) Hypoglycaemia	Low risk	**Quote:** "table 7: Hypoglycemia Outcomes by treatment phase (ITT population); ITT set n=339." **Comment:** ITT/LOCF
Selective reporting (reporting bias)	Unclear risk	**Comment:** results on the HbA1c- and the FPG-response rates, i.e. the proportion of participants who achieved the targets of ≤ 5.6 mmol/L and ≤ 7.0%, are reported but not mentioned in the methods section or the trial report; skin reactions stated in the method section as safety parameter, but no results reported
Other bias	Unclear risk	**Comment:** funding received by a pharmaceutical company

Hermansen 2006

Study characteristics	
Methods	**Study design:** parallel RCT; non-inferiority design **Number of study centres:** 58
Participants	**Inclusion criteria:** insulin-naive people; aged ≥ 18 years; BMI ≤ 35 kg/m^2; HbA1c 7.5–10.0%; type 2 diabetes mellitus for ≥ 12 months; inadequate control required ≥ 4 months treatment with 1 or 2 OADs at doses at least half the recommended maximum or highest tolerated **Exclusion criteria:** use of thiazolidinediones; secondary diabetes, maturity-onset diabetes of the young; proliferate retinopathy/maculopathy requiring treatment, hypoglycaemia unawareness or recurrent major hypoglycaemia, use of drugs affecting glycaemia, impaired hepatic or renal function; significant cardiovascular disease. pregnancy, breastfeeding **Diagnostic criteria:** —
Interventions	**Intervention:** insulin detemir **Comparator:** NPH insulin **Run-in period:** no **Extension period:** no
Outcomes	HbA1c; FPG; within-participant variation in self-measured prebreakfast and predinner plasma glucose; self-measured 10-point plasma glucose profile; hypoglycaemia; weight; AEs **Composite outcome measures reported:** proportion of participants achieving HbA1c ≤ 7.0%; proportion of participants achieving target HbA1c value without hypoglycaemia
Study details	**Trial terminated early (for benefit/because of AEs):** no **Trial ID:** NCT00604396; NN304-1530
Publication details	**Language of publication:** English **Funding:** commercial funding (Novo Nordisk)

Hermansen 2006 *(Continued)*

	Publication status: peer-reviewed/full article
Stated aim of study	**Quote:** "…to assess efficacy and tolerability of insulin detemir or NPH insulin added to oral therapy for type 2 diabetes in a treat-to-target titration protocol."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "randomization carried out via a telephone system." **Comment:** adequate sequence generation method.
Allocation concealment (selection bias)	Low risk	**Quote:** "randomization carried out via a telephone system." **Comment:** appropriate allocation concealment
Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "open-label." **Comment:** investigator-assessed and self-reported outcome measurement
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Quote:** "open-label." **Comment:** investigator-assessed outcome measurement
Blinding of participants and personnel (performance bias) HbA1c	Low risk	**Quote:** "open-label;" "A1C [HbA1c] was measured in a central laboratory." **Comment:** adjudicated outcome measurement
Blinding of participants and personnel (performance bias) Hypoglycaemia	High risk	**Quote:** "open-label;" "Participants measured capillary blood glucose (plasma calibrated) with a Precision Xtra meter (Medisense; Abbott Laboratories, Abbott Park, IL) and were advised to make additional measurements whenever hypoglycaemia was suspected." **Comment:** self-reported outcome measurement
Blinding of outcome assessment (detection bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "open-label." **Comment:** investigator-assessed and self-reported outcome measurement
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Quote:** "open-label." **Comment:** investigator-assessed outcome measurement
Blinding of outcome assessment (detection bias) HbA1c	Low risk	**Quote:** "open-label;" "A1C was measured in a central laboratory." **Comment** adjudicated outcome measurement
Blinding of outcome assessment (detection bias) Hypoglycaemia	High risk	**Quote:** "open-label;" "Participants measured capillary blood glucose (plasma calibrated) with a Precision Xtra meter (Medisense; Abbott Laboratories, Abbott Park, IL) and were advised to make additional measurements whenever hypoglycaemia was suspected."

Hermansen 2006 *(Continued)*

		Comment: self-reported outcome measurement
Incomplete outcome data (attrition bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "Statistical analyses of efficacy and safety presented were based on the intention-to-treat (ITT) population (all randomized and treated participants)." **Comment:** 95.8% (insulin detemir) and 94.1% (NPH insulin) of participants finished trial; reasons for dropouts partly given; modified ITT; according to IQWiG report, LOCF, but only for participants who were treated for ≥ 12 weeks
Incomplete outcome data (attrition bias) All-cause mortality	Unclear risk	**Quote:** "Statistical analyses of efficacy and safety presented were based on the intention-to-treat (ITT) population (all randomized and treated participants)." **Comment:** 95.8% (insulin detemir) and 94.1% (NPH insulin) of participants finished trial; reasons for dropouts partly given; modified ITT; according to IQWiG report, LOCF, but only for participants who were treated for ≥ 12 weeks
Incomplete outcome data (attrition bias) HbA1c	Unclear risk	**Quote:** "Statistical analyses of efficacy and safety presented were based on the intention-to-treat (ITT) population (all randomized and treated participants);" "analyses of A1C and FPG were based on the last observation carried forward for patients completing at least 12 weeks." **Comment:** 95.8% (insulin detemir) and 94.1% (NPH insulin) of the participants finished trial; reasons for dropouts partly given, modified ITT; LOCF, but only for participants who were treated for ≥ 12 weeks
Incomplete outcome data (attrition bias) Hypoglycaemia	Unclear risk	**Quote:** "Statistical analyses of efficacy and safety presented were based on the intention-to-treat (ITT) population (all randomized and treated participants)" **Comment:** 95.8% (insulin detemir) and 94.1% (NPH insulin) of the participants finished trial; reasons for dropouts partly given; modified ITT; according to IQWiG report LOCF, but only for patients who were treated for at least 12 weeks
Selective reporting (reporting bias)	Low risk	**Comment:** no protocol available, but all outcomes that were mentioned in the abstract and methods section of the paper were reported
Other bias	Unclear risk	**Comment:** funding received by a pharmaceutical company

Home 2015

Study characteristics	
Methods	**Study design:** parallel RCT **Number of study centres:** 74
Participants	**Inclusion criteria:** insulin-naive; aged 30–70 years; type 2 diabetes mellitus diagnosed for > 1 year; HbA1c ≥ 7.0% and ≤ 10.5%; BMI < 40 kg/m^2; treated with ≥ 1 OAD (metformin (daily dose ≥ 1000 mg), SU, glinides or alpha-glucosidase inhibitor) at stable dose for ≥ 3 months **Exclusion criteria:** treatment with GLP-1 agonists or with dipeptidyl peptidase-IV inhibitors in the 3 months prior to study entry; treatment with thiazolidinedione as monotherapy; clinically active cardiovascular, neurological, endocrine or other major diseases; active proliferative retinopathy or any other unstable (rapidly progressing) retinopathy that may require photocoagulation or surgical treatment during the study; impaired renal function; impaired hepatic function; history of sensitivity to the study drugs or to drugs with a similar chemical structure; treatment with systemic corticosteroids within the

Home 2015 *(Continued)*

	3 months prior to study entry or likelihood of requiring treatments during the study which are not permitted; alcohol or drug abuse in the last year **Diagnostic criteria:** active proliferative retinopathy: defined by a photocoagulation or vitrectomy occurrence in the 6 months prior to visit 1; any other unstable (rapidly progressing) retinopathy that may require photocoagulation or surgical treatment during the study: assessed by an optic fundus examination that should have been performed in the 2 years prior to study entry; impaired renal function: serum creatinine ≥ 1.5 mg/dL (≥ 133 µmol/L) or ≥ 1.4 mg/dL (≥ 124 µmol/L); impaired hepatic function: ALT or AST (or both) > 3 × upper limit of normal range)
Interventions	**Intervention:** insulin glargine **Comparator:** NPH insulin **Run-in period:** 2 weeks **Extension period:** no
Outcomes	Change in HbA1c from baseline; time profile of HbA1c; FPG; nocturnal SMPG; 8-point SMPG profiles; percentage of participants achieving HbA1c < 7.0% or < 6.5%; daily dose of insulin; prandial insulin use at 6 months as rescue medication; change in bodyweight from baseline; incidence and rate of hypoglycaemia (symptomatic diurnal and nocturnal, asymptomatic and severe); overall safety; treatment satisfaction (DTSQ) **Composite outcome measures reported:** no
Study details	**Trial terminated early:** no **Trial ID:** NCT00949442; EUCTR2007-006640-22
Publication details	**Language of publication:** English **Funding:** commercial funding (Sanofi) **Publication status:** peer-reviewed journal/full article
Stated aim of study	**Quote:** "…to examine whether insulin glargine can lead to better control of glycated haemoglobin (HbA1c) than that achieved by neutral protamine Hagedorn (NPH) insulin, using a protocol designed to limit nocturnal hypoglycaemia."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "…interactive voice-response/interactive web response system." **Comment:** adequate.
Allocation concealment (selection bias)	Low risk	**Quote:** "…interactive voice-response/interactive web response system." **Comment:** adequate
Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "open-label."

Home 2015 *(Continued)*

Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Quote:** "open-label."
Blinding of participants and personnel (performance bias) Diabetes-related complications	Unclear risk	**Quote:** "open-label."
Blinding of participants and personnel (performance bias) HbA1c	Low risk	**Quote:** "open-label." **Comment:** central laboratory
Blinding of participants and personnel (performance bias) Hypoglycaemia	High risk	**Quote:** "open-label."
Blinding of outcome assessment (detection bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "open-label." **Comment:** investigator-assessed and self-reported outcome measurement
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Quote:** "open-label." **Comment:** investigator-assessed outcome measurement
Blinding of outcome assessment (detection bias) Diabetes-related complications	Unclear risk	**Quote:** "open-label." **Comment:** investigator-assessed outcome measurement
Blinding of outcome assessment (detection bias) HbA1c	Low risk	**Quote:** "open label;" "measured in a central laboratory." **Comment:** adjudicated outcome measurement; no information on possible blinding of outcome assessment
Blinding of outcome assessment (detection bias) Hypoglycaemia	High risk	**Quote:** "open-label;" "…confirmed by Self-monitored plasma glucose (SMPG) …" **Comment:** self-reported outcome measurement
Incomplete outcome data (attrition bias) Adverse events other than hypoglycaemia	Low risk	**Quote:** "…other analyses, including hypoglycaemia, were performed for the safety population, comprising all randomized and treated individuals. Missing efficacy and safety values were imputed with the last observation carried forward method for the end of treatment value, defined as the last post-baseline value available during the on-treatment period." **Comment:** 94.5% of intervention and 92.9% of control group participants finished trial, reasons for dropouts and missing data provided per group; ITT/LOCF
Incomplete outcome data (attrition bias) All-cause mortality	Low risk	**Quote:** "…other analyses, including hypoglycaemia, were performed for the safety population, comprising all randomized and treated individuals. Missing efficacy and safety values were imputed with the last observation carried forward method for the end of treatment value, defined as the last post-baseline value available during the on-treatment period."

Home 2015 *(Continued)*

		Comment: 94.5% of intervention and 92.9% of control group participants finished trial, reasons for dropouts and missing data provided per group; ITT/LOCF
Incomplete outcome data (attrition bias) Diabetes-related complications	Low risk	**Quote:** "…other analyses, including hypoglycaemia, were performed for the safety population, comprising all randomized and treated individuals. Missing efficacy and safety values were imputed with the last observation carried forward method for the end of treatment value, defined as the last post-baseline value available during the on-treatment period." **Comment:** 94.5% of intervention and 92.9% of control group participants finished trial, reasons for dropouts and missing data provided per group; ITT/LOCF
Incomplete outcome data (attrition bias) HbA1c	Low risk	**Quote:** "Efficacy analyses (which did not include hypoglycaemia) were assessed in the modified intent-to-treat (ITT) population; namely, all randomized participants who received study medication and had at least one post-baseline assessment of any primary or secondary efficacy variable….Missing efficacy and safety values were imputed with the last observation carried forward method for the end of treatment value, defined as the last post-baseline value available during the on-treatment period." **Comment:** 94.5% of intervention and 92.9% of control group participants finished trial, reasons for dropouts and missing data provided per group; LOCF; modified ITT
Incomplete outcome data (attrition bias) Hypoglycaemia	Low risk	**Quote:** "…other analyses, including hypoglycaemia, were performed for the safety population, comprising all randomized and treated individuals. Missing efficacy and safety values were imputed with the last observation carried forward method for the end of treatment value, defined as the last post-baseline value available during the on-treatment period." **Comment:** 94.5% of intervention and 92.9% of control group participants finished trial, reasons for dropouts and missing data provided per group; ITT/LOCF
Selective reporting (reporting bias)	High risk	**Comment:** AEs defined as secondary outcome measure in the study report but SAEs not reported
Other bias	Unclear risk	**Comment:** funding received by a pharmaceutical company

Hsia 2011

Study characteristics	
Methods	**Study design:** parallel RCT **Number of study centres:** 1
Participants	**Inclusion criteria:** insulin-naive other than previous use for gestational diabetes or for < 1 week during hospitalisation; aged 18–75 years; type 2 diabetes for ≥ 1 year; HbA1c: 7.5–12.0% despite ≥ 3 months of consistent therapy with maximally tolerated doses of combination of OADs (metformin, SUs, thiazolidinediones, or a combination); BMI 20–40 kg/m^2 **Exclusion criteria:** confirmed or suspected type 1 diabetes; advanced proliferative retinopathy; occupations that required night shift work or any diurnal schedules that caused erratic mealtimes; pregnancy, lactation, any renal, hepatic or other systemic disorders that might complicate glycaemic control

Hsia 2011 *(Continued)*

	Diagnostic criteria: —
Interventions	**Intervention 1:** insulin glargine at bedtime **Intervention 2:** insulin glargine in the morning **Comparator:** NPH insulin at bedtime **Run-in period:** 2 weeks **Extension period:** no
Outcomes	Change of HbA1c from baseline; % participants with HbA1c ≤ 7.0%; fasting SMBG; % fasting SMBG readings < 130 mg/dL; presupper SMBG; % presupper SMBG readings < 130 mg/dL; incidence of hypoglycaemic events (premeal, bedtime, or overnight); % participants reporting any hypoglycaemia; % participants reporting severe hypoglycaemia; weight change; BMI; total daily insulin dose; any AE other than hypoglycaemia; treatment satisfaction (DTSQ) **Composite outcome measures reported:** no
Study details	**Trial terminated early:** yes, "…terminated in February 2009 due to funding limits." **Trial ID:** NCT00686712
Publication details	**Language of publication:** English **Funding:** non-commercial funding **Publication status:** peer-reviewed journal/full article
Stated aim of study	**Quote:** "We compared basal regimens of glargine or NPH among insulin-naïve, U.S. inner city, ethnic minority type 2 diabetic patients who were sub-optimally controlled on maximally tolerated doses of combination oral agents."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "…subjects were then randomized to one of three single-dose basal insulin regimens…" **Comment:** no information on randomisation method.
Allocation concealment (selection bias)	Unclear risk	**Comment:** no information on allocation concealment
Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "…in an open-label fashion."
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Quote:** "…in an open-label fashion."

Hsia 2011 *(Continued)*

Blinding of participants and personnel (performance bias) Diabetes-related complications	Unclear risk	**Quote:** "…in an open-label fashion."
Blinding of participants and personnel (performance bias) HbA1c	Low risk	**Quote:** "…in an open-label fashion." **Comment:** central laboratory
Blinding of participants and personnel (performance bias) Hypoglycaemia	High risk	**Quote:** "…in an open-label fashion."
Blinding of outcome assessment (detection bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "…in an open-label fashion." **Comment:** investigator-assessed and self-reported outcome measurement
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Quote:** "…in an open-label fashion." **Comment:** investigator-assessed outcome measurement
Blinding of outcome assessment (detection bias) Diabetes-related complications	Unclear risk	**Quote:** "…in an open-label fashion." **Comment:** investigator-assessed and self-reported outcome measurement
Blinding of outcome assessment (detection bias) HbA1c	Low risk	**Quote:** "…in an open-label fashion;" "All HbA1c measurements were performed by the Martin Luther King Jr. Multi-Service Ambulatory Clinic (MLK-MACC) clinical chemistry laboratory, utilizing an high-pressure liquid chromatography (HPLC) method that conforms to the Diabetes Control and Complications Trial (DCCT) standard." **Comment:** adjudicated outcome measurement; no information on possible blinding of outcome assessment
Blinding of outcome assessment (detection bias) Hypoglycaemia	High risk	**Quote:** "…in an open-label fashion." **Comment:** self-reported outcome measurement
Incomplete outcome data (attrition bias) Adverse events other than hypoglycaemia	High risk	**Quote:** "All data were analyzed by an intent-to-treat paradigm as a primary analysis using last-value carried-forward imputation of incomplete data." **Comment:** study terminated prematurely; 66% (Glargine bedtime), 56% (Glargine morning) of intervention group and 56.7% of control group finished trial; 30.6% of all randomised participants did not complete due to protocol violations (included confirmed non-compliance with insulin or concurrent oral agents for ≥ 2 weeks; SMBG occurring less than once daily for ≥ 4 days per week over 2 consecutive scheduled visits; or any verified falsification of SMBG readings); other reasons for dropouts (lost to follow-up and AEs) are given per group; ITT; LOCF
Incomplete outcome data (attrition bias) All-cause mortality	High risk	**Quote:** "All data were analyzed by an intent-to-treat paradigm as a primary analysis using last-value carried-forward imputation of incomplete data." **Comment:** study terminated prematurely; 66% (Glargine bedtime), 56% (Glargine morning) of intervention group and 56.7% of control group finished

Hsia 2011 *(Continued)*

		trial; 30.6% of all randomised participants did not complete due to protocol violations (included confirmed non-compliance with insulin or concurrent oral agents for ≥ 2 weeks; SMBG occurring less than once daily for ≥ 4 days per week over 2 consecutive scheduled visits; or any verified falsification of SMBG readings); other reasons for dropouts (lost to follow-up and AEs) are given per group; ITT; LOCF
Incomplete outcome data (attrition bias) Diabetes-related complications	High risk	**Quote:** "All data were analyzed by an intent-to-treat paradigm as a primary analysis using last-value carried-forward imputation of incomplete data." **Comment:** study terminated prematurely; 66% (Glargine bedtime), 56% (Glargine morning) of intervention group and 56.7% of control group finished trial; 30.6% of all randomised participants did not complete due to protocol violations (included confirmed non-compliance with insulin or concurrent oral agents for ≥ 2 weeks; SMBG occurring less than once daily for ≥ 4 days per week over 2 consecutive scheduled visits; or any verified falsification of SMBG readings); other reasons for dropouts (lost to follow-up and AEs) are given per group; ITT; LOCF
Incomplete outcome data (attrition bias) HbA1c	High risk	**Quote:** "All data were analyzed by an intent-to-treat paradigm as a primary analysis using last-value carried-forward imputation of incomplete data." **Comment:** study terminated prematurely; 66% (Glargine bedtime), 56% (Glargine morning) of intervention group and 56.7% of control group finished trial; 30.6% of all randomised participants did not complete due to protocol violations (included confirmed non-compliance with insulin or concurrent oral agents for ≥ 2 weeks; SMBG occurring less than once daily for ≥ 4 days per week over 2 consecutive scheduled visits; or any verified falsification of SMBG readings); other reasons for dropouts (lost to follow-up and AEs) are given per group; ITT; LOCF
Incomplete outcome data (attrition bias) Hypoglycaemia	High risk	**Quote:** "All data were analyzed by an intent-to-treat paradigm as a primary analysis using last-value carried-forward imputation of incomplete data." **Comment:** study terminated prematurely; 66% (Glargine bedtime), 56% (Glargine morning) of intervention group and 56.7% of control group finished trial; 30.6% of all randomised participants did not complete due to protocol violations (included confirmed non-compliance with insulin or concurrent oral agents for ≥ 2 weeks; SMBG occurring less than once daily for ≥ 4 days per week over 2 consecutive scheduled visits; or any verified falsification of SMBG readings); other reasons for dropouts (lost to follow-up and AEs) are given per group; ITT; LOCF
Selective reporting (reporting bias)	Low risk	**Comment:** all announced outcomes reported
Other bias	High risk	**Comment:** study preliminary terminated due to funding limits. Early termination leading to smaller than anticipated enrolment

Kawamori 2003

Study characteristics	
Methods	**Study design:** parallel RCT; non-inferiority design **Number of study centres:** 64

Kawamori 2003 *(Continued)*

Participants	**Inclusion criteria:** type 2 diabetes mellitus, aged 20–70 years; previous therapy with OAD (SU monotherapy or in combination with α-glucosidase-inhibitors, metformin or α-glucosidase-inhibitors and metformin) for ≥ 12 weeks; BMI < 30 kg/m^2; HbA1c > 8.0 to < 12.0% **Exclusion criteria:** clinically relevant major disease other than diabetes; history of ketoacidosis; use of other medication than OAD within 16 weeks before study; history of pancreas resection; nightshift work; pregnancy or breastfeeding; diabetic retinopathy requiring surgical (laser or other) treatment in the 12 weeks before or during the study; current or past history of alcohol abuse; impair liver (ALT, AST: both > 80 IU/L) or renal function (creatinine > 2 mg/dL); use of drugs likely to interfere with study medications **Diagnostic criteria:** —
Interventions	**Intervention:** insulin glargine **Comparator:** NPH insulin **Run-in period:** no (4 weeks' screening period) **Extension period:** no
Outcomes	**Primary outcome measure:** change in HbA1c level from baseline to study end **Secondary outcome measures:** FPG; insulin dose; hypoglycaemic events **Other outcome measures:** AEs; SAEs **Composite outcome measures reported:** no
Study details	**Trial terminated early (for benefit/because of AEs):** no **Trial ID:** —
Publication details	**Language of publication:** Japanese **Funding:** commercial funding (Sanofi) **Publication status:** peer-reviewed journal/full article
Stated aim of study	**Quote:** "…to investigate the efficacy and safety of insulin glargine in comparison to NPH insulin in patients with type 2 diabetes mellitus pretreated with OAD."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** no information from publication, but according to IQWiG report adequate.
Allocation concealment (selection bias)	Unclear risk	**Comment:** no information from publication; according to IQWiG report unclear
Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "…open label." **Comment:** investigator-assessed and self-reported outcome measurement

Kawamori 2003 *(Continued)*

Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Quote:** "…open label." **Comment:** investigator-assessed outcome measurement
Blinding of participants and personnel (performance bias) HbA1c	Unclear risk	**Quote:** "…open label." **Comment:** investigator-assessed outcome measurement
Blinding of participants and personnel (performance bias) Hypoglycaemia	High risk	**Quote:** "…open label." **Comment:** self-reported outcome measurement
Blinding of outcome assessment (detection bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "…open-label…" **Comment:** investigator-assessed and self-reported outcome measurement; there was no indication that the endpoint assessment was blinded
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Quote:** "…open-label…" **Comment:** investigator-assessed outcome measurement; there was no indication that the endpoint assessment was blinded
Blinding of outcome assessment (detection bias) HbA1c	Unclear risk	**Quote:** "…open-label…" **Comment:** investigator-assessed outcome measurement; there is no indication that the endpoint assessment was blinded
Blinding of outcome assessment (detection bias) Hypoglycaemia	High risk	**Quote:** "…open-label…" **Comment:** self-reported outcome measurement; there is no indication that the endpoint assessment was blinded
Incomplete outcome data (attrition bias) Adverse events other than hypoglycaemia	Low risk	**Comment:** ITT analyses for safety parameters
Incomplete outcome data (attrition bias) All-cause mortality	Low risk	**Comment:** ITT analyses for safety parameters
Incomplete outcome data (attrition bias) HbA1c	High risk	**Comment:** per-protocol analyses for efficacy parameters; 17.9% of participants not included
Incomplete outcome data (attrition bias) Hypoglycaemia	Low risk	**Comment:** ITT analyses for safety parameters; 17.9% of participants not included
Selective reporting (reporting bias)	Low risk	**Comment:** none detected
Other bias	Unclear risk	**Comment:** funding received by a pharmaceutical company

Kobayashi 2007 A

Study characteristics	
Methods	**Study design:** parallel RCT; non-inferiority design **Number of study centres:** 52
Participants	**Inclusion criteria:** people with diabetes (type 1 and type 2 diabetes); aged ≥ 20 years, HbA1c < 11%; BMI < 30.0 kg/m^2, who had been receiving for ≥ 12 weeks basal-bolus therapy comprising the concomitant use of intermediate- or long-acting human insulin preparation once a day before bedtime, or twice a day, before breakfast and before bedtime, and insulin aspart 3 times a day immediately before every meal **Exclusion criteria:** impaired renal or hepatic function; serious heart diseases; known hypoglycaemia unawareness or recurrent major hypoglycaemia; proliferative retinopathy or maculopathy requiring acute treatment; uncontrolled treated or untreated hypertension; current treatment with total insulin dose > 100 IU/day; current treatment or expected at the screening to start treatment with systemic corticosteroids **Diagnostic criteria:** —
Interventions	**Intervention:** insulin detemir **Comparator:** NPH insulin **Run-in period:** — **Extension period:** no
Outcomes	HbA1c; SMBG > 7 days; intraindividual variation in FPG over 7 days; 7-point measurement blood sugar profile; hypoglycaemia, AEs, laboratory tests, ECG, fundus examination/fundus photograph, bodyweight; blood pressure; satisfaction with the insulin therapy method; nocturnal QoL associated with the insulin therapy **Composite outcome measures reported:** no
Study details	**Trial terminated early (for benefit/because of AEs):** no **Trial ID:** NCT00604344; NN304-1476
Publication details	**Language of publication:** Japanese **Funding:** commercial funding (Novo Nordisk) **Publication status:** peer-reviewed journal/full article
Stated aim of study	**Quote:** "The aim of the present study was to investigate the non-inferiority of detemir to NPH for blood sugar control with HbA1c as indicator, on 48-week administration to type 1 diabetes patients during basal-bolus therapy. Type 1 and type 2 diabetes patients were subjects in the investigation of other evaluation items."
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Quote:** "The randomisation was stratified according to diabetes type." **Comment:** no information on sequence generation

Kobayashi 2007 A *(Continued)*

Allocation concealment (selection bias)	Unclear risk	**Comment:** no information on allocation concealment
Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "This was a multi-centre, non-blind, randomised study drug and control parallel group (detemir group: NPH group = 2:1) comparative study." **Comment:** investigator-assessed and self-reported outcome measurement
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Quote:** "This was a multi-centre, non-blind, randomised study drug and control parallel group (detemir group: NPH group = 2:1) comparative study." **Comment:** investigator-assessed outcome measurement
Blinding of participants and personnel (performance bias) HbA1c	Unclear risk	**Quote:** "This was a multi-centre, non-blind, randomised study drug and control parallel group (detemir group: NPH group = 2:1) comparative study." **Comment:** probably investigator assessed outcome measurement
Blinding of participants and personnel (performance bias) Health-related quality of life	High risk	**Quote:** "This was a multi-centre, non-blind, randomised study drug and control parallel group (detemir group: NPH group = 2:1) comparative study." **Comment:** self-reported outcome measurement
Blinding of participants and personnel (performance bias) Hypoglycaemia	High risk	**Quote:** "self-monitored pre-breakfast fasting blood sugar level; cases where the patient complained of any subjective symptom thought to be caused by hypoglycaemia were treated as hypoglycaemia, as were cases where the blood sugar level was 55 mg/dL or lower, whether or not there were symptoms." **Comment:** self-reported outcome measurement
Blinding of outcome assessment (detection bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "This was a multi-centre, non-blind, randomised study drug and control parallel group (detemir group: NPH group = 2:1) comparative study." **Comment:** investigator-assessed and self-reported outcome measurement
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Quote:** "This was a multi-centre, non-blind, randomised study drug and control parallel group (detemir group: NPH group = 2:1) comparative study." **Comment:** investigator-assessed outcome measurement
Blinding of outcome assessment (detection bias) HbA1c	Unclear risk	**Quote:** "This was a multi-centre, non-blind, randomised study drug and control parallel group (detemir group: NPH group = 2:1) comparative study." **Comment:** probably investigator assessed outcome measurement
Blinding of outcome assessment (detection bias) Health-related quality of life	High risk	**Quote:** "This was a multi-centre, non-blind, randomised study drug and control parallel group (detemir group: NPH group = 2:1) comparative study." **Comment:** self-reported outcome measurement
Blinding of outcome assessment (detection bias) Hypoglycaemia	High risk	**Quote:** "self-monitored pre-breakfast fasting blood sugar level; cases where the patient complained of any subjective symptom thought to be caused by hypoglycaemia were treated as hypoglycaemia, as were cases where the blood sugar level was 55 mg/dL or lower, whether or not there were symptoms." **Comment:** self-reported outcome measurement

Kobayashi 2007 A *(Continued)*

Incomplete outcome data (attrition bias) Adverse events other than hypoglycaemia	Low risk	**Quote:** "All subjects who received at least one dose of trial product were included in the safety analysis" "The last observation carried forward (LOCF) approach was used for all endpoints at week 48 for subjects who had at least one valid post-baseline measurement." **Comment:** 97% of intervention and 91.4% of control group finished the trial; reasons for withdrawals are given per group; modified ITT and LOCF
Incomplete outcome data (attrition bias) All-cause mortality	Low risk	**Quote:** "All subjects who received at least one dose of trial product were included in the safety analysis" "The last observation carried forward (LOCF) approach was used for all endpoints at week 48 for subjects who had at least one valid post-baseline measurement." **Comment:** 97% of intervention and 91.4% of control group finished the trial; reasons for withdrawals are given per group; modified ITT and LOCF
Incomplete outcome data (attrition bias) HbA1c	Low risk	**Quote:** "For all efficacy endpoints the analysis was performed on the FAS. The FAS consisted of all randomised subjects who had any available efficacy data after receiving the trial product;" "The last observation carried forward (LOCF) approach was used for all endpoints at week 48 for subjects who had at least one valid post-baseline measurement." **Comment:** 97% of intervention and 91.4% of control group finished the trial; reasons for withdrawals are given per group; modified ITT and LOCF
Incomplete outcome data (attrition bias) Health-related quality of life	High risk	**Comment:** essential differences in dropout rates: 8% in the glargine group and 23% in the NPH group
Incomplete outcome data (attrition bias) Hypoglycaemia	Low risk	**Quote:** "All subjects who received at least one dose of trial product were included in the safety analysis" "The last observation carried forward (LOCF) approach was used for all endpoints at week 48 for subjects who had at least one valid post-baseline measurement." **Comment:** 97% of intervention and 91.4% of control group finished the trial; reasons for withdrawals are given per group; modified ITT and LOCF
Selective reporting (reporting bias)	High risk	**Quote:** "All cases of hypoglycaemia were classified as either serious hypoglycaemia (when the hypoglycaemia was accompanied by subjective symptoms, and treatment by a third party was required), non severe hypoglycaemia (when the patient could treat himself, and the blood sugar was 55 mg/dL or lower), hypoglycaemic symptoms (when the patient could treat himself, and the blood sugar level was 56 mg/dL or higher or the blood sugar level could not be measured), or biochemical hypoglycaemia (when the measured blood sugar level was 55 mg/dL or lower but there were no subjective symptoms)." **Comment:** whereas in the methods section of the paper differentiation according to the severity of hypoglycaemia is described, results are reported only for overall daily and overall nocturnal hypoglycaemia
Other bias	Unclear risk	**Comment:** funding received by a pharmaceutical company

Kobayashi 2007 B

Study characteristics	
Methods	**Study design:** parallel RCT; non-inferiority design

Kobayashi 2007 B *(Continued)*

	Number of study centres: 65
Participants	**Inclusion criteria**: people with insulin-naive type 2 diabetes; aged ≥ 20 years, HbA1c ≥ 7.5% but < 10.0%; BMI < 30.0 kg/m^2, who had been receiving for ≥ 12 weeks oral diabetes drug therapy (SU agent, SU agent + biguanide agent, SU agent + α-glucosidase inhibitor (hereafter, α-glucosidase inhibitor) or SU agent + biguanide agent + α-glucosidase inhibitor) **Exclusion criteria:** — **Diagnostic criteria:** —
Interventions	**Intervention:** insulin detemir **Comparator:** NPH insulin **Run-in period:** — **Extension period:** no
Outcomes	**Primary outcome measure:** HbA1c **Secondary outcome measures:** FPG, 7-point BG profile **Other outcome measures:** hypoglycaemia, AEs, laboratory tests, ECG, fundus examinations/photographs, blood pressure, bodyweight **Composite outcome measures reported:** no
Study details	**Trial terminated early (for benefit/because of AEs):** no **Trial ID:** NCT00604253; NN304-1477
Publication details	**Language of publication:** Japanese **Funding:** commercial funding Novo Nordisk **Publication status:** peer-reviewed journal, full article
Stated aim of study	**Quote:** "The aim of the present study was to investigate the non-inferiority of detemir to NPH for blood sugar control with HbA1c as indicator, on 36-week administration of either detemir or NPH concomitantly, at one administration per day, to type 2 diabetes patients during oral diabetes drug therapy."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** no information available
Allocation concealment (selection bias)	Unclear risk	**Comment:** no information available
Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "non-blind." **Comment:** investigator assessed and self-reported outcome measurement

Kobayashi 2007 B *(Continued)*

Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Quote:** "non-blind." **Comment:** investigator-assessed outcome measurement
Blinding of participants and personnel (performance bias) Diabetes-related complications	Unclear risk	**Quote:** "non-blind." **Comment:** investigator assessed and self-reported outcome measurement
Blinding of participants and personnel (performance bias) HbA1c	Unclear risk	**Quote:** "non-blind." **Comment:** no information available
Blinding of participants and personnel (performance bias) Hypoglycaemia	High risk	**Quote:** "non-blind." **Comment:** self-reported outcome measurement
Blinding of outcome assessment (detection bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "non-blind." **Comment:** investigator assessed and self-reported outcome measurement
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Quote:** "non-blind." **Comment:** investigator assessed outcome measurement
Blinding of outcome assessment (detection bias) Diabetes-related complications	Unclear risk	**Quote:** "non-blind." **Comment:** investigator assessed and self-reported outcome measurement
Blinding of outcome assessment (detection bias) HbA1c	Unclear risk	**Quote:** "non-blind." **Comment:** no information available
Blinding of outcome assessment (detection bias) Hypoglycaemia	High risk	**Quote:** "non-blind." **Comment:** self-reported outcome measurement
Incomplete outcome data (attrition bias) Adverse events other than hypoglycaemia	Low risk	**Quote:** "…and study drug administration was completed for 160 detemir group patients and for 172 NPH group patients. All subjects to whom study drug was administered were included in the safety analysis set and in the full analysis set." **Comment:** no information on management of missing data available; ITT/LOCF
Incomplete outcome data (attrition bias) All-cause mortality	Low risk	**Quote:** "…and study drug administration was completed for 160 detemir group patients and for 172 NPH group patients. All subjects to whom study drug was administered were included in the safety analysis set and in the full analysis set." **Comment:** no information on management of missing data available; ITT/LOCF

Kobayashi 2007 B *(Continued)*

Incomplete outcome data (attrition bias) Diabetes-related complications	Low risk	**Quote:** "…and study drug administration was completed for 160 detemir group patients and for 172 NPH group patients. All subjects to whom study drug was administered were included in the safety analysis set and in the full analysis set." **Comment:** no information on management of missing data available; ITT/LOCF
Incomplete outcome data (attrition bias) HbA1c	Low risk	**Quote:** "…and study drug administration was completed for 160 detemir group patients and for 172 NPH group patients. All subjects to whom study drug was administered were included in the safety analysis set and in the full analysis set." **Comment:** no information on management of missing data available; ITT/LOCF
Incomplete outcome data (attrition bias) Hypoglycaemia	Low risk	**Quote:** "…and study drug administration was completed for 160 detemir group patients and for 172 NPH group patients. All subjects to whom study drug was administered were included in the safety analysis set and in the full analysis set." **Comment:** no information on management of missing data available; ITT/LOCF
Selective reporting (reporting bias)	Low risk	**Comment:** none detected.
Other bias	Unclear risk	**Comment:** funding received by a pharmaceutical company

Massi 2003

Study characteristics	
Methods	**Study design:** parallel RCT **Number of study centres:** 57
Participants	**Inclusion criteria:** diabetes duration ≥ 3 years; aged 40–80 years; oral therapy with SUs alone or in combination with acarbose, metformin, or metformin alone, or insulin once daily + OADs for ≥ 1 year; BMI < 40 kg/m^2; HbA1c > 7.5% to < 12.0%; negative history of ketoacidosis **Exclusion criteria:** regular insulin therapy during the last 4 weeks before screening; diabetic retinopathy with surgical treatment in the 3 months before study entry or requiring treatment within 3 months of study entry; night shift worker; treatment with any investigational drugs in the last 2 months before study entry; clinically relevant cardiovascular, hepatic, neurological, endocrine or other major systemic diseases that would make implementation of the study protocol or interpretation of the study results difficult; drug or alcohol abuse; likelihood of requiring treatment during the study period with drugs not permitted by the protocol; impaired hepatic function as shown by but not limited to alanine aminotransferase or aspartate aminotransferase > 2 × the upper limit measured at visit 1; impaired renal function as shown by but not limited to serum creatinine > 1.5 mg/dL; mental condition rendering the person unable to understand the nature, scope and possible consequences of the study; evidence of an uncooperative attitude; inability to attend follow-up visits **Diagnostic criteria:** —
Interventions	**Intervention:** insulin glargine **Comparator:** NPH insulin

Massi 2003 *(Continued)*

	Run-in period: no (4 weeks screening period) **Titrations period:** as needed according to self-monitored FPG (optimal dose was defined by an FPG target of 6.66 mol/L over ≥ 2–4 days without nocturnal hypoglycaemia) **Treatment before study:** oral therapy with SUs alone or in combination with acarbose, metformin, or metformin alone, or insulin once daily + OADs **Extension period:** no
Outcomes	**Primary outcome:** change in HbA1c from baseline to endpoint **Secondary outcomes:** FPG; FBG; FBG variability; 24-hour BG **Additional published outcomes:** hypoglycaemia: symptomatic, severe, nocturnal; AEs; insulin dose; bodyweight **Composite outcome measures reported:** no
Study details	**Trial terminated early (for benefit/because of AEs):** no **Trial ID:** —
Publication details	**Language of publication:** English **Funding:** commercial funding (Sanofi) **Publication status:** peer-reviewed journal/full article
Stated aim of study	**Quote:** "to compare the effects of insulin glargine and NPH human insulin on glycated haemoglobin values, fasting plasma glucose and FBG levels, the blood glucose profile, hypoglycaemia, and safety for a treatment period of 52 weeks in patients with Type 2 diabetes."
Notes	In regard to inclusion and exclusion criteria, information from the present paper is scarce. Most of the information is available only from the paper by H Yki-Järvinen which reports on the insulin-naive subgroup. According to the Food and Drug Administration report and the publication by Yki-Järvinen eye examinations and funduscopy were done. No results concerning retinopathy were presented.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "A randomization schedule was generated, pairing sequential subject numbers with treatment codes…" **Comment:** adequate
Allocation concealment (selection bias)	Low risk	**Quote:** "A randomization schedule was generated, pairing sequential subject numbers with treatment codes…" **Comment:** adequate
Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "The comparison was open-label due to the nature of the insulin glargine formulation…" **Comment:** investigator-assessed and self-reported outcome measurement
Blinding of participants and personnel (performance bias)	Low risk	**Quote:** "The comparison was open-label due to the nature of the insulin glargine formulation…" **Comment:** investigator-assessed outcome measurement

Massi 2003 *(Continued)*
All-cause mortality

Blinding of participants and personnel (performance bias) Diabetes-related complications	Unclear risk	**Quote:** "The comparison was open-label due to the nature of the insulin glargine formulation…" **Comment:** investigator-assessed outcome measurement
Blinding of participants and personnel (performance bias) HbA1c	Low risk	**Quote:** "The comparison was open-label due to the nature of the insulin glargine formulation…" **Comment:** centrally measured outcome measurement
Blinding of participants and personnel (performance bias) Health-related quality of life	High risk	**Quote:** "The comparison was open-label due to the nature of the insulin glargine formulation…" **Comment:** self-reported outcome measurement
Blinding of participants and personnel (performance bias) Hypoglycaemia	High risk	**Quote:** "The comparison was open-label due to the nature of the insulin glargine formulation…" **Comment:** self-reported and investigator-assessed outcome measurement
Blinding of outcome assessment (detection bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "The comparison was open-label due to the nature of the insulin glargine formulation…" **Comment:** self-reported and investigator-assessed outcome measurement; there was no indication that the endpoint assessment was blinded
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Quote:** "The comparison was open-label due to the nature of the insulin glargine formulation…" **Comment:** investigator-assessed outcome measurement; there was no indication that the endpoint assessment was blinded
Blinding of outcome assessment (detection bias) Diabetes-related complications	Unclear risk	**Quote:** "The comparison was open-label due to the nature of the insulin glargine formulation…" **Comment:** investigator-assessed; there was no indication that the endpoint assessment was blinded
Blinding of outcome assessment (detection bias) HbA1c	Low risk	**Quote:** "The comparison was open-label due to the nature of the insulin glargine formulation…" **Comment:** centrally measured outcome measurement
Blinding of outcome assessment (detection bias) Health-related quality of life	High risk	**Quote:** "The comparison was open-label due to the nature of the insulin glargine formulation…" **Comment:** self-reported outcome measurement; there is no indication that the endpoint assessment was blinded
Blinding of outcome assessment (detection bias) Hypoglycaemia	High risk	**Quote:** "The comparison was open-label due to the nature of the insulin glargine formulation…" **Comment:** self-reported and investigator-assessed outcome measurement; there was no indication that the endpoint assessment was blinded
Incomplete outcome data (attrition bias)	Low risk	**Quote:** "The safety population included all 570 patients who were randomized and treated."

Massi 2003 *(Continued)*

Adverse events other than hypoglycaemia		**Comment:** ITT analyses
Incomplete outcome data (attrition bias) All-cause mortality	Low risk	**Quote:** "The safety population included all 570 patients who were randomized and treated." **Comment:** ITT analyses
Incomplete outcome data (attrition bias) Diabetes-related complications	Low risk	**Quote:** "The safety population included all 570 patients who were randomized and treated." **Comment:** ITT analyses
Incomplete outcome data (attrition bias) HbA1c	Low risk	**Quote:** "…analyses were performed using the intent to treat (ITT) population. The ITT population was defined as all subjects randomized and treated and having both pre-treatment and on-treatment value." **Comment:** ITT analyses
Incomplete outcome data (attrition bias) Health-related quality of life	High risk	**Comment:** 12% (glargine) and 15% (NPH) of study population not included in analyses, because validated questionnaires were not available in all languages
Incomplete outcome data (attrition bias) Hypoglycaemia	Low risk	**Quote:** "The safety population included all 570 patients who were randomized and treated." **Comment:** ITT analyses
Selective reporting (reporting bias)	Low risk	**Comment:** none detected
Other bias	Unclear risk	**Comment:** funding received by a pharmaceutical company

NCT00687453

Study characteristics	
Methods	**Study design:** parallel RCT; non-inferiority design **Number of study centres:** 1
Participants	**Inclusion criteria:** type 2 diabetes mellitus for ≥ 1 year; HbA1c ≥ 7.5% and < 12% on stable and maximum-tolerated doses of a SU, metformin, thiazolidinedione + a single bedtime injection of NPH insulin; mean FPG < 130 mg/dL without fasting hypoglycaemia; except for current NPH insulin no other history of chronic insulin use (other than treatment of gestational diabetes or hospitalisation of < 1 week' duration); BMI 20–40 kg/m^2; aged 18–75 years **Exclusion criteria:** confirmed or suspicion of type 1 diabetes mellitus; female of childbearing potential without reliable form of contraception; current pregnancy or lactation; contraindication for intensive insulin therapy; advanced proliferative retinopathy; participants unable to stay on consistent daily meal schedule; history of renal, hepatic, cardiovascular, neurological or other major systemic disease; participants who likely required therapy with drugs interfering with glucose metabolism; participants who were in another study or received another investigational medication within 30 days of study entry; participants who were unable or unwilling to comply with protocol **Diagnostic criteria:** —

NCT00687453 *(Continued)*

Interventions	**Intervention:** insulin glargine **Comparator:** NPH insulin **Run-in period:** yes (duration not specified). There was a baseline run-in period to document baseline control and reinforce dietary/lifestyle principles. **Extension period:** —
Outcomes	HbA1c change from baseline; frequency of presupper glucose readings ≤ 120 mg/dL; hypoglycaemic reactions; severe hypoglycaemic reactions; change of BMI from baseline; total daily insulin dose; AEs **Composite outcome measures reported:** no
Study details	**Trial terminated early (for benefit/because of AEs):** yes (reasons for early termination not specified) **Trial ID:** NCT00687453
Publication details	**Language of publication:** English **Funding:** non-commercial funding (US NIH grant U54RR014616) **Publication status:** other (study results on Clinical.Trials.gov)
Stated aim of study	**Quote:** "To compare the efficacy and safety of once-nightly insulin glargine versus twice-daily NPH insulin in [low income] ethnic minority type 2 diabetic patients inadequately treated with once-nightly NPH insulin alone. This study investigates whether insulin glargine may be more or less effective and safe than twice-daily NPH insulin in this population."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** process of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	**Comment:** method of concealment not described
Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "Masking: open label." **Comment:** investigator-assessed and self-reported outcome measurement
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Quote:** "Masking: open label." **Comment:** investigator-assessed outcome measurement
Blinding of participants and personnel (performance bias) HbA1c	Unclear risk	**Quote:** "Masking: open label." **Comment:** investigator-assessed outcome measurement
Blinding of participants and personnel (performance bias)	High risk	**Quote:** "Masking: open label." **Comment:** investigator-assessed and self-reported outcome measurement

NCT00687453 *(Continued)*
Hypoglycaemia

Blinding of outcome assessment (detection bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "Masking: open label." **Comment:** investigator-assessed and self-reported outcome measurement
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Quote:** "Masking: open label." **Comment:** investigator-assessed outcome measurement
Blinding of outcome assessment (detection bias) HbA1c	Unclear risk	**Quote:** "Masking: open label." **Comment:** investigator-assessed outcome measurement
Blinding of outcome assessment (detection bias) Hypoglycaemia	High risk	**Quote:** "Masking: open label." **Comment:** investigator-assessed and self-reported outcome measurement
Incomplete outcome data (attrition bias) Adverse events other than hypoglycaemia	High risk	**Comment:** insufficient reporting
Incomplete outcome data (attrition bias) All-cause mortality	High risk	**Comment:** insufficient reporting
Incomplete outcome data (attrition bias) HbA1c	High risk	**Quote:** "ITT (LOCF)." **Comment:** study terminated prematurely
Incomplete outcome data (attrition bias) Hypoglycaemia	High risk	**Comment:** insufficient reporting
Selective reporting (reporting bias)	High risk	**Comment:** some predefined secondary outcome measures such as total hypoglycaemic reactions, severe hypoglycaemic reactions or change in BMI were not reported
Other bias	High risk	**Comment:** study preliminary terminated; reason for termination not stated

NN304-1337

Study characteristics	
Methods	**Study design:** parallel RCT **Number of study centres:** —
Participants	**Inclusion criteria:** people with type 2 diabetes ≥ 1 year; aged ≥ 35 years; treatment with metformin (> 1000 mg/day) alone or in combination with other OADs; HbA1c ≥ 8.0% to ≤ 10.0% if pretreated with ≥ 3 OADs or HbA1c ≥ 8.0% to ≤ 12.0% if pretreated with < 2 OADs; BMI ≤ 40 kg/m^2 **Exclusion criteria:** daily dose of metformin < 1000 mg; known severe Ischaemic heart disease; hypoglycaemia unawareness or recurrent major hypoglycaemia; proliferative retinopathy; uncontrolled

NN304-1337 *(Continued)*

	hypertension; impair liver or renal function; insulin treatment > 7 consecutive days within the last 3 months before screening **Diagnostic criteria:** ADA 2000
Interventions	**Intervention:** insulin detemir **Comparator:** NPH insulin **Run-in period:** 2 weeks; treatment unclear **Extension period:** no
Outcomes	**Primary outcome measure:** HbA1c at study end **Secondary outcome measures:** — **Other outcome measures:** hypoglycaemia (overall, severe, nocturnal, severe nocturnal); AEs, bodyweight; funduscopy **Composite outcome measures reported:** no
Study details	**Trial terminated early (for benefit/because of AEs):** no **Trial ID:** NN304-1337
Publication details	**Language of publication:** German **Funding:** commercial funding (Novo Nordisk) **Publication status:** other (IQWiG report 2009)
Stated aim of study	—
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** according to IQWiG report adequate
Allocation concealment (selection bias)	Low risk	**Comment:** according to IQWiG report IVRS; appropriate allocation concealment
Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemia	Unclear risk	**Comment:** according to IQWiG report "open-label;" investigator-assessed and self-reported outcome measurement
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Comment:** according to IQWiG report "open-label;" investigator-assessed outcome measurement
Blinding of participants and personnel (performance bias)	Unclear risk	**Comment:** according to IQWiG report "open-label;" investigator-assessed outcome measurement

NN304-1337 *(Continued)*

Diabetes-related complications		
Blinding of participants and personnel (performance bias) HbA1c	Low risk	**Comment:** according to IQWiG report "open-label;" centrally measured outcome measurement
Blinding of participants and personnel (performance bias) Hypoglycaemia	High risk	**Comment:** according to IQWiG report "open-label;" investigator-assessed and self-reported outcome measurement
Blinding of outcome assessment (detection bias) Adverse events other than hypoglycaemia	Unclear risk	**Comment:** according to IQWiG report "open-label;" investigator-assessed and self-reported outcome measurement
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Comment:** according to IQWiG report "open-label;" investigator-assessed outcome measurement
Blinding of outcome assessment (detection bias) Diabetes-related complications	Unclear risk	**Comment:** according to IQWiG report "open-label;" investigator-assessed outcome measurement
Blinding of outcome assessment (detection bias) HbA1c	Low risk	**Comment:** according to IQWiG report "open-label;" centrally measured outcome measurement
Blinding of outcome assessment (detection bias) Hypoglycaemia	High risk	**Comment:** according to IQWiG report "open-label;" investigator-assessed and self-reported outcome measurement
Incomplete outcome data (attrition bias) Adverse events other than hypoglycaemia	Low risk	**Comment:** ITT/LOCF analyses according to IQWiG report
Incomplete outcome data (attrition bias) All-cause mortality	Low risk	**Comment:** ITT/LOCF analyses according to IQWiG report
Incomplete outcome data (attrition bias) Diabetes-related complications	Low risk	**Comment:** ITT/LOCF analyses according to IQWiG report
Incomplete outcome data (attrition bias) HbA1c	Low risk	**Comment:** ITT/LOCF analyses according to IQWiG report
Incomplete outcome data (attrition bias) Hypoglycaemia	Low risk	**Comment:** ITT/LOCF analyses according to IQWiG report

NN304-1337 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	**Comment:** no publication available
Other bias	Unclear risk	**Comment:** funding received by a pharmaceutical company

NN304-1808

Study characteristics	
Methods	**Study design:** parallel RCT; non-inferiority design **Number of study centres:** 57
Participants	**Inclusion criteria:** type 2 diabetes; aged ≥ 70 years; insulin naive and treated with OADs at the maximum tolerated dose for ≥ 3 months and not achieving therapeutic targets (HbA1c 7.0–8.0%); 8.0% ≤ HbA1c ≤ 10.5% (local dosage within last 6 months); able to comply with the requirements of the trial **Exclusion criteria:** secondary diabetes; maturity-onset diabetes of the young; previous treatment with insulin; proliferative retinopathy or maculopathy, requiring treatment; hypoglycaemia unawareness as judged by the investigator, recurrent major hypoglycaemia; end-stage liver disease; end-stage renal disease; acute heart failure; any acute cardiovascular event or cerebrovascular event < 6 months; acute disease with poor prognosis; history of alcoholism; drug abuse; psychiatric disease or personality disorders likely to invalidate voluntary consent or to prevent good compliance with the trial protocol; mental incapacity, unwillingness or language barrier precluding adequate understanding or co-operation and any conditions as judged by the investigator; legal incapacity or limited legal capacity (patients under guardianship or curatorship); concomitant medication for Alzheimer's treatment (memantine, anticholinesterase treatment); participation in another clinical trial < 1 month before inclusion in the trial; illness requiring repeated hospitalisation; known or suspected allergy to insulin or any compositional component **Diagnostic criteria:** —
Interventions	**Intervention:** insulin detemir **Comparator:** NPH insulin **Run-in period:** no (2 weeks screening period) **Titration period:** 1 months **Treatment before study:** OADs at maximum tolerated doses for ≥ 3 months **Extension period:** no
Outcomes	HbA1c; percentage of participants with HbA1c ≤ 8.0%; percentage of participants with HbA1c ≤ 7.0%; percentage of participants with HbA1c < 7/7–8/8–9/9–10/10–11/> 11%; SMPG fasting, prelunch, predinner); within-subject variation of bodyweight during the trial; percentage of participants achieving FPG ≤ 8.8 ml/L (160 mg/dL); mean fasting capillary glucose; within-subject variation of plasma glucose; incidence of hyperglycaemic events (> 300 mg/dL); major hypoglycaemic episodes; minor hypoglycaemic episodes; symptoms-only hypoglycaemic episodes; nocturnal hypoglycaemic episodes; total hypoglycaemic episodes; hypoglycaemic episodes defined as SMPG < 56 mg/dL (3.1 mmol/L); AEs; vital signs; physical examination; QoL; insulin dose requirements **Composite outcome measures reported:** percentage of participants with HbA1c ≤ 8.0% without hypoglycaemia; percentage of participants with HbA1c ≤ 7.0% without hypoglycaemia
Study details	**Trial terminated early (for benefit/because of AEs):** yes (recruitment problems)

NN304-1808 *(Continued)*

	Trial ID: NCT00506662; NN304-1808; EUCTR2006-006589-41
Publication details	**Language of publication:** English **Funding:** commercial funding (Novo Nordisk) **Publication status:** other (Novo Nordisk Clinical Trial report NN304-1808)
Stated aim of study	**Quote:** "The aim of the trial is to compare insulin detemir once daily to NPH insulin once daily as measured by blood sugar control in ageing subjects with type 2 diabetes naive to previous insulin therapy " "To investigate if once daily insulin detemir was non inferior compared with once daily NPH insulin as measured by HbA1c in ageing subjects with type 2 diabetes naive to previous insulin therapy after 7 months of treatment (including a one-month titration period). Insulin detemir and NPH insulin were both to be administered before breakfast."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "Clinical Supplies Coordination, Novo Nordisk A/S generated the randomisation lists and supplied two sets of sealed codes." **Comment:** adequate
Allocation concealment (selection bias)	Low risk	**Quote:** "Investigators were blinded to randomisation prior to the inclusion of patients. Randomisation was carried out using two sets of sealed codes as the randomisation was not stratified with the initial treatment of the patient (OAD treatment with metformin or not). At the time of randomisation, the investigator assigned the lowest available sealed code number corresponding to the appropriate set to the patient and revealed the treatment for the number by scratching off the protective surface of the sealed code. One randomisation number was printed on each visible sealed code and the treatment for the patients was sealed." **Comment:** adequate
Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "open-labelled." **Comment:** investigator-assessed and self-reported outcome measurement; neither the investigators nor the participants were blinded to the interventions
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Quote:** "open-labelled." **Comment:** investigator-assessed outcome measurement; neither the investigators nor the participants were blinded to the interventions
Blinding of participants and personnel (performance bias) Diabetes-related complications	Unclear risk	**Quote:** "open-labelled." **Comment:** investigator-assessed and self-reported outcome measurement; neither the investigators nor the participants were blinded to the interventions
Blinding of participants and personnel (performance bias) Hypoglycaemia	High risk	**Quote:** "open-labelled." **Comment:** investigator-assessed and self-reported outcome measurement; neither the investigators nor the participants were blinded to the interventions

NN304-1808 *(Continued)*

Blinding of outcome assessment (detection bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "open-labelled." **Comment:** investigator-assessed and self-reported outcome measurement; there are also no indication that the endpoint assessment was blinded
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Quote:** "open-labelled." **Comment:** investigator-assessed outcome measurement; there are also no indication that the endpoint assessment was blinded
Blinding of outcome assessment (detection bias) Diabetes-related complications	Unclear risk	**Quote:** "open-labelled." **Comment:** investigator-assessed and self-reported outcome measurement; there are also no indication that the endpoint assessment was blinded
Blinding of outcome assessment (detection bias) Hypoglycaemia	High risk	**Quote:** "open-labelled." **Comment:** investigator-assessed and self-reported outcome measurement; there are also no indication that the endpoint assessment was blinded
Incomplete outcome data (attrition bias) Adverse events other than hypoglycaemia	High risk	**Quote:** "…the trial was prematurely discontinued; the required number of completers was not achieved to obtain the required statistical power needed to perform between-group comparisons. Only descriptive statistics at baseline and safety analysis were performed for the results of this trial." **Comment:** only 41.7% of study population finished trial. For 11.6% results were "not recorded," 7% were excluded because of "protocol violation," 30.3% were not assessed because trial was terminated early
Incomplete outcome data (attrition bias) All-cause mortality	High risk	**Quote:** "…the trial was prematurely discontinued; the required number of completers was not achieved to obtain the required statistical power needed to perform between-group comparisons. Only descriptive statistics at baseline and safety analysis were performed for the results of this trial." **Comment:** only 41.7% of study population finished trial. For 11.6% results were "not recorded," 7% were excluded because of "protocol violation," 30.3% were not assessed because trial was terminated early
Incomplete outcome data (attrition bias) Diabetes-related complications	High risk	**Quote:** "…the trial was prematurely discontinued; the required number of completers was not achieved to obtain the required statistical power needed to perform between-group comparisons. Only descriptive statistics at baseline and safety analysis were performed for the results of this trial." **Comment:** only 41.7% of study population finished trial. For 11.6% results were "not recorded," 7% were excluded because of "protocol violation," 30.3% were not assessed because trial was terminated early
Incomplete outcome data (attrition bias) Hypoglycaemia	High risk	**Quote:** "…the trial was prematurely discontinued; the required number of completers was not achieved to obtain the required statistical power needed to perform between-group comparisons. Only descriptive statistics at baseline and safety analysis were performed for the results of this trial." **Comment:** only 41.7% of study population finished trial. For 11.6% results were "not recorded," 7% were excluded because of "protocol violation," 30.3% were not assessed because trial terminated early; outcome not reported for total study duration, only for periods of 2 months
Selective reporting (reporting bias)	High risk	**Comment:** efficacy results not reported due to the small number of participants in each group. Also: quote: "Since the trial was prematurely discontinued the required number of completers was not achieved to obtain the re-

NN304-1808 *(Continued)*

		quired statistical power to be able to do between-group comparisons. Instead only descriptive statistics at baseline and a safety analysis were performed for the trial results."
Other bias	High risk	**Comment:** study prematurely terminated because of recruitment problems; high number of participants not finishing the study with a higher rate of participants lost to follow-up in the NPH insulin treatment group; uneven number of participants randomised to the respective comparison groups; funding received by a pharmaceutical company

NN304-3614

Study characteristics	
Methods	**Study design:** parallel RCT **Number of study centres:** 5
Participants	**Inclusion criteria:** people with type 2 diabetes; treated with 2 or 3 doses of insulin for ≥ 3 months prior to inclusion; aged ≥ 18 years; BMI ≥ 27.5 kg/m² and ≤ 40 kg/m²; HbA1c ≥ 7% to ≤ 11.0% centrally measured **Exclusion criteria:** treatment with any OADs in the last 6 months except metformin; use of approved weight-lowering pharmacotherapy or obesity induced by drug treatment; previous or planned surgical treatment of obesity; total daily insulin dose ≥ 2 IU/kg; proliferative retinopathy or maculopathy that has required acute treatment within the last 6 months; receipt of any investigational drug within 1 month prior to trial; cardiac disease New York Heart Association III or IV; unstable angina pectoris or myocardial infarction (or both) within last 6 months **Diagnostic criteria:** —
Interventions	**Intervention:** insulin detemir **Comparator:** NPH insulin **Run-in period:** — **Extension period:** no
Outcomes	Whole body fat mass; whole body lean mass; trunk lean mass; whole body fat percentage; trunk fat percentage; visceral adipose tissue area; subcutaneous adipose tissue area; visceral/subcutaneous adipose tissue ratio; liver/spleen attenuation ratio; HbA1c; FPG; relationship between BMI and dose of insulin detemir; cytokine in adipose tissue; inflammatory; weight; waist and hip circumference; hypoglycaemia; lipid profile; AEs; laboratory safety parameters; physical examination/vital signs **Composite outcome measures reported:** no
Study details	**Trial terminated early (for benefit/because of AEs):** no **Trial ID:** NCT00795600; NN304-3614; EUCTR2008-003739-19
Publication details	**Language of publication:** English **Funding:** commercial funding (Novo Nordisk) **Publication status:** other (Novo Nordisk Clinical Trial report NN304-1808)

NN304-3614 *(Continued)*

Stated aim of study	**Quote:** "…to compare the change in trunk fat mass, assessed by DEXA (Double Energy X-ray Absorptiometry), after 26 weeks of treatment with insulin detemir or insulin NPH [Neutral Protamine Hagedorn] (both with insulin aspart in the main meals) in overweight and obese type 2 diabetic subjects."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "were randomized." **Comment:** no information provided.
Allocation concealment (selection bias)	Unclear risk	**Quote:** "were randomized." **Comment:** no information provided
Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "open-labelled." **Comment:** neither the investigators nor the participants were blinded to the interventions
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Quote:** "open-labelled." **Comment:** neither the investigators nor the participants were blinded to the interventions
Blinding of participants and personnel (performance bias) Diabetes-related complications	Unclear risk	**Quote:** "open-labelled." **Comment:** neither the investigators nor the participants were blinded to the interventions
Blinding of participants and personnel (performance bias) HbA1c	Unclear risk	**Quote:** "open-labelled." **Comment:** neither the investigators nor the participants were blinded to the interventions
Blinding of participants and personnel (performance bias) Hypoglycaemia	High risk	**Quote:** "open-labelled." **Comment:** neither the investigators nor the participants were blinded to the interventions
Blinding of outcome assessment (detection bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "open-labelled." **Comment:** there is no indication that the endpoint assessment was blinded
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Quote:** "open-labelled." **Comment:** there is no indication that the endpoint assessment was blinded
Blinding of outcome assessment (detection bias) Diabetes-related complications	Unclear risk	**Quote:** "open-labelled." **Comment:** there is no indication that the endpoint assessment was blinded

NN304-3614 *(Continued)*

Blinding of outcome assessment (detection bias) HbA1c	Unclear risk	**Quote:** "open-labelled." **Comment:** there is no indication that the endpoint assessment was blinded
Blinding of outcome assessment (detection bias) Hypoglycaemia	High risk	**Quote:** "open-labelled." **Comment:** there is no indication that the endpoint assessment was blinded
Incomplete outcome data (attrition bias) Adverse events other than hypoglycaemia	Low risk	**Comment:** FAS is of all randomised participants who were exposed to ≥ 1 dose of the trial product
Incomplete outcome data (attrition bias) All-cause mortality	Low risk	**Comment:** FAS is of all randomised participants who were exposed to ≥ 1 dose of the trial product
Incomplete outcome data (attrition bias) Diabetes-related complications	Low risk	**Comment:** FAS is of all randomised participants who were exposed to ≥ 1 dose of the trial product
Incomplete outcome data (attrition bias) HbA1c	Low risk	**Comment:** ITT analysis set using LOCF was of all randomised participants exposed to ≥ 1 dose of the trial product. 2 participants in the insulin detemir group and 3 participants in the insulin NPH group did not present an HbA1c value in week 26
Incomplete outcome data (attrition bias) Hypoglycaemia	Low risk	**Comment:** FAS is of all randomised participants who were exposed to ≥ 1 dose of the trial product
Selective reporting (reporting bias)	Unclear risk	**Comment:** no publication available; results at ClinicalTrials.gov not fully reported
Other bias	Unclear risk	**Comment:** funding received by a pharmaceutical company

Pan 2007

Study characteristics	
Methods	**Study design:** parallel RCT; non-inferiority design **Number of study centres:** 31
Participants	**Inclusion criteria:** insulin-naive people from Asia aged ≥ 40 and ≤ 80 years with type 2 diabetes poorly controlled on OHA therapy (SU alone or in combination with metformin or acarbose) for ≥ 3 months prior to study entry (previous doses of SUs were equal to or greater than equivalent doses of glimepiride 3 mg) + a random venous plasma glucose concentration ≥ 11.1 mmol/L or FPG concentration ≥ 7 mmol/mol or 2-hour plasma glucose concentration ≥ 11.1 mmol/L in an oral glucose tolerance test (glucose 75 g); BMI 20–35 kg/m^2; HbA1c: ≥ 7.5% and ≤ 10.5%; FBG levels > 120 mg/dL (> 6.7 mmol/L) **Exclusion criteria:** pregnancy; history of ketoacidosis; likelihood of requiring treatment with drugs prohibited in the study protocol (e.g. non-selective beta-blockers, systemic corticosteroids), retinopathy with necessity of surgical intervention or with possible necessity of surgical intervention within 3 months, pancreatectomy, despaired hepatic or renal function, night shift workers

Pan 2007 *(Continued)*

	Diagnostic criteria: World Health Organization criteria: diabetes symptoms + BG ≥ 11.1 mmol/L or FPG ≥ 7.0 mmol/L in random measurement or BG ≥ 11.1 mmol/L 2 hours in oral glucose tolerance test
Interventions	**Intervention:** insulin glargine **Comparator:** NPH insulin **Run-in period:** no **Extension period:** no
Outcomes	**Primary outcome:** change of HbA1c levels from baseline to study end **Secondary outcome:** FBG levels, proportion of participants with FBG levels ≤ 6.7 mmol/L (≤ 120 mg/dL), mean daily BG, nocturnal BG profiles, proportion of participants with HbA1c levels < 58 mmol/mol (< 7.5%), insulin dose, proportion of participants with hypoglycaemia (severe, serious, nocturnal, all), change in BMI, AEs **Additional published outcomes:** 8-point BG profiles **Composite outcome measures reported:** proportion of participants of combined responders (HbA1c < 7.5% (58 mmol/mol) and FPG ≤ 6.7 mmol/L), proportion of participants HbA1c < 7.5% (58 mmol/mol) and without hypoglycaemia (post hoc analysis)
Study details	**Trial terminated early (for benefit/because of AEs):** no
Publication details	**Language of publication:** English **Funding:** commercial funding (Sanofi-Aventis) **Publication status:** peer-reviewed journal/full article
Stated aim of study	**Quote:** "The aim of the LEAD (LANTUS Evaluation in Asian Diabetics) study was to compare metabolic control with insulin glargine versus NPH insulin (Novo Nordisk, Denmark) in combination with glimepiride (Amaryl, Sanofi-Aventis, Paris, France) in Asian patients with Type 2 diabetes."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "This is an open-label, randomized, 24-week, non-inferiority study." **Comment:** method of randomisation sequence generation not clearly stated, but based on IQWiG report adequate
Allocation concealment (selection bias)	Low risk	**Comment:** method of allocation concealment not clearly stated, but satisfactory according to IQWiG report
Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "open-label." **Comment:** neither the investigators nor the participants were blinded to the interventions
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Quote:** "open-label." **Comment:** neither the investigators nor the participants were blinded to the interventions

Pan 2007 *(Continued)*

Blinding of participants and personnel (performance bias) Diabetes-related complications	Unclear risk	**Quote:** "open-label." **Comment:** neither the investigators nor the participants were blinded to the interventions
Blinding of participants and personnel (performance bias) HbA1c	Unclear risk	**Quote:** "open-label." **Comment:** neither the investigators nor the participants were blinded to the interventions
Blinding of participants and personnel (performance bias) Hypoglycaemia	High risk	**Quote:** "open-label." **Comment:** neither the investigators nor the participants were blinded to the interventions
Blinding of outcome assessment (detection bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "open-label." **Comment:** there is no indication that the endpoint assessment was blinded
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Quote:** "open-label." **Comment:** there is no indication that the endpoint assessment was blinded
Blinding of outcome assessment (detection bias) Diabetes-related complications	Unclear risk	**Quote:** "open-label." **Comment:** there is no indication that the endpoint assessment was blinded
Blinding of outcome assessment (detection bias) HbA1c	Unclear risk	**Quote:** "open-label." **Comment:** there is no indication that HbA1c was measured in a central laboratory
Blinding of outcome assessment (detection bias) Hypoglycaemia	High risk	**Quote:** "open-label." **Comment:** there is no indication that the endpoint assessment was blinded
Incomplete outcome data (attrition bias) Adverse events other than hypoglycaemia	Low risk	**Comment:** no specific information available. According to the IQWiG report, primary efficacy variable was HbA1c in per-protocol population; in addition, ITT/LOCF analysis available from IQWiG report
Incomplete outcome data (attrition bias) All-cause mortality	Low risk	**Comment:** no specific information available. According to the IQWiG report, ITT analyses were satisfactory and methodological quality was ranked as "minor deficiency."
Incomplete outcome data (attrition bias) Diabetes-related complications	Low risk	**Comment:** no specific information available. According to the IQWiG report, ITT analyses were satisfactory and methodological quality was ranked as "minor deficiency."
Incomplete outcome data (attrition bias) HbA1c	Low risk	**Comment:** no specific information available. According to the IQWiG report, ITT analyses were satisfactory and methodological quality was ranked as "minor deficiency."

Pan 2007 *(Continued)*

Incomplete outcome data (attrition bias) Hypoglycaemia	Low risk	**Comment:** no specific information available. According to the IQWiG report, ITT analyses were satisfactory and methodological quality was ranked as "minor deficiency."
Selective reporting (reporting bias)	Unclear risk	**Comment:** diabetic-related complications such as myocardial infarction, stroke or end-stage renal disease reported only as not being significantly different in the treatment groups
Other bias	Unclear risk	**Comment:** funding received by a pharmaceutical company

Riddle 2003

Study characteristics	
Methods	**Study design:** parallel RCT **Number of study centres:** 80
Participants	**Inclusion criteria:** people with type 2 diabetes for ≥ 2 years; aged 30–70 years; stable dose of 1 or 2 oral antihyperglycaemic agents (SUs, metformin, glitazone) for ≥ 3 months; BMI 26–40 kg/m^2; HbA1c ≥ 7.5% to ≤ 10.0%; FPG ≥ 7.8 mmol/L **Exclusion criteria:** prior use of insulin (except for gestational diabetes < 1 week); current use of α-glucosidase inhibitor or rapid-acting insulin secretagogues; use of other agents affecting glycaemic control; history of ketoacidosis or inability to recognise hypoglycaemia; history of drug or alcohol abuse; serum alanine or aspartate aminotransferase more than 2 × upper limit of normal; serum creatinine ≥ 1.5 mg/dL (men) or 1.4 mg/dL (women); positive test for GAD antibody; fasting plasma C-peptide ≤ 0.25 pmol/mL **Diagnostic criteria:** —
Interventions	**Intervention:** insulin glargine **Comparator:** NPH insulin **Run-in period:** 4 weeks; treatment unclear **Titration period:** as needed to achieve target FPG ≤ 5.6 mmol/L (predefined algorithm) **Extension period:** no **Treatment before study:** 1 or 2 oral antihyperglycaemic agents (SU, metformin, pioglitazone, rosiglitazone)
Outcomes	**Primary outcome:** percentage of participants achieving HbA1c ≤ 7.0% without a single instance of symptomatic nocturnal hypoglycaemia confirmed by plasma-referenced glucose ≤ 4 mmol/L or meeting criteria for severe hypoglycaemia or both **Secondary outcome:** — **Additional published outcomes:** changes from baseline for HbA1c, FPG and weight; percentage of participants achieving HbA1c ≤ 7.0% or FPG ≤ 5.6 mmol/L independent of occurrence of hypoglycaemia; participants achieving FPG ≤ 5.6 mmol/L without confirmed hypoglycaemia; within-participant variability between 7 sequential fasting glucose measures; rates of symptomatic hypoglycaemia including unconfirmed, confirmed and severe hypoglycaemia **Composite outcome measures reported:** no
Study details	**Trial terminated early (for benefit/because of AEs):** no

Riddle 2003 *(Continued)*

	Trial ID: NCT00653341
Publication details	**Language of publication:** English **Funding:** commercial funding (Sanofi) **Publication status:** peer-reviewed journal/full article
Stated aim of study	**Quote:** "…to compare the abilities of glargine and NPH to reduce HbA1c to 7% when added to ongoing oral therapy and the hypoglycaemia accompanying this effort using a simple algorithm for insulin dosage titration seeking a FPG target of 5.6 mmol/L."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "…randomization schedule generated by Quintiles linked sequential numbers to random treatment codes…using a centralized telephone system." **Comment:** adequate.
Allocation concealment (selection bias)	Low risk	**Quote:** "…randomization schedule generated by Quintiles linked sequential numbers to random treatment codes…using a centralized telephone system." **Comment:** adequate
Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "…open-label." **Comment:** investigator-assessed and self-reported outcome measurement
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Quote:** "…open-label." **Comment:** investigator-assessed outcome measurement
Blinding of participants and personnel (performance bias) HbA1c	Low risk	**Quote:** "…open-label." **Comment:** centrally measured outcome measurement
Blinding of participants and personnel (performance bias) Hypoglycaemia	High risk	**Quote:** "…open-label." **Comment:** investigator-assessed and self-reported outcome measurement
Blinding of outcome assessment (detection bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "…open-label." **Comment:** self-reported and investigator-assessed outcome measurement; there is no indication that the endpoint assessment was blinded
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Quote:** "…open-label." **Comment:** investigator-assessed outcome measurement; there is no indication that the endpoint assessment was blinded

Riddle 2003 *(Continued)*

Blinding of outcome assessment (detection bias) HbA1c	Low risk	**Quote:** "…open-label." **Comment:** centrally measured
Blinding of outcome assessment (detection bias) Hypoglycaemia	High risk	**Quote:** "…open-label." **Comment:** self-reported and investigator-assessed outcome measurement; there is no indication that the endpoint assessment was blinded
Incomplete outcome data (attrition bias) Adverse events other than hypoglycaemia	Low risk	**Quote:** "The intent-to-treat (ITT) population included all subjects randomized who received at least one dose of study medication. The last measurement before discontinuation or completion of the protocol was considered the end point measurement (last observation carried forward)."
Incomplete outcome data (attrition bias) All-cause mortality	Low risk	**Quote:** "The intent-to-treat (ITT) population included all subjects randomized who received at least one dose of study medication. The last measurement before discontinuation or completion of the protocol was considered the end point measurement (last observation carried forward)."
Incomplete outcome data (attrition bias) HbA1c	Low risk	**Quote:** "The intent-to-treat (ITT) population included all subjects randomized who received at least one dose of study medication. The last measurement before discontinuation or completion of the protocol was considered the end point measurement (last observation carried forward)."
Incomplete outcome data (attrition bias) Hypoglycaemia	Low risk	**Quote:** "The intent-to-treat (ITT) population included all subjects randomized who received at least one dose of study medication. The last measurement before discontinuation or completion of the protocol was considered the end point measurement (last observation carried forward)."
Selective reporting (reporting bias)	Low risk	**Comment:** none detected
Other bias	Unclear risk	**Comment:** funding received by a pharmaceutical company

Rosenstock 2001

Study characteristics	
Methods	**Study design:** parallel RCT **Number of study centres:** 59
Participants	**Inclusion criteria:** people with type 2 diabetes; aged 40–80 years; insulin treatment for ≥ 3 months; BMI < 40 kg/m^2; HbA1c ≥ 7.0% to ≤ 12.0% **Exclusion criteria:** OAD treatment within 3 months prior to study inclusion; history of drug or alcohol abuse; significant hepatic or renal impairment **Diagnostic criteria**: —
Interventions	**Intervention:** insulin glargine **Comparator:** NPH insulin **Run-in period:** no (1–4 weeks' screening period)

Rosenstock 2001 *(Continued)*

	Titration period: as needed to achieve target FPG 4.4–7.8 mmol/L (the evening dose of the basal insulin was increased if FPG was ≥ 10 mmol/L on 3 consecutive measurements unless nocturnal hypoglycaemia occurred; premeal insulin target: premeal BG 4.4–7.8 mmol/L and bedtime BG 6.7–10.0 mmol/L **Extension period:** no **Treatment before study:** insulin
Outcomes	**Primary outcome:** change of HbA1c from baseline to endpoint **Secondary outcomes:** — **Additional published outcomes:** changes from baseline for FBG at weeks 8, 20, 28, and at study endpoint; hypoglycaemia insulin doses; AEs; insulin antibody levels; bodyweight **Composite outcome measures reported:** no
Study details	**Trial terminated early (for benefit/because of AEs):** no **Trial ID:** —
Publication details	**Language of publication:** English **Funding:** commercial funding (Sanofi) **Publication status:** peer-reviewed journal/full article
Stated aim of study	**Quote:** "to compare the safety and effectiveness of once daily insulin glargine with once or twice daily NPH insulin in patients who were not taking oral agents and who had previously received basal insulin with or without regular insulin for postprandial glycaemic control."
Notes	According to the European Medicines Agency (EMA) report: "…additional antidiabetic treatment was provided by oral antidiabetic drugs."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** no information from publication, but according to IQWiG report adequate
Allocation concealment (selection bias)	Low risk	**Comment:** no information from publication, but according to IQWiG report adequate
Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "…open-label comparison…" **Comment:** investigator-assessed and self-reported outcome measurement
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Quote:** "…open-label comparison…" **Comment:** investigator-assessed outcome measurement
Blinding of participants and personnel (performance bias) Diabetes-related complications	Unclear risk	**Quote:** "…open-label comparison…" **Comment:** investigator-assessed outcome measurement

Rosenstock 2001 *(Continued)*

Blinding of participants and personnel (performance bias) HbA1c	Low risk	**Quote:** "…open-label comparison…" **Comment:** centrally measured outcome measurement
Blinding of participants and personnel (performance bias) Health-related quality of life	High risk	**Quote:** "…open-label comparison…" **Comment:** self-reported outcome measurement
Blinding of participants and personnel (performance bias) Hypoglycaemia	High risk	**Quote:** "…open-label comparison…" **Comment:** investigator-assessed and self-reported outcome measurement
Blinding of outcome assessment (detection bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "…open-label comparison…" **Comment:** self-reported and investigator-assessed outcome measurement; no indications that the endpoint assessment was blinded
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Quote:** "…open-label comparison…" **Comment:** investigator-assessed outcome measurement; no indications that the endpoint assessment was blinded
Blinding of outcome assessment (detection bias) Diabetes-related complications	Unclear risk	**Quote:** "…open-label comparison…" **Comment:** self-reported and investigator-assessed outcome measurement; no indications that the endpoint assessment was blinded
Blinding of outcome assessment (detection bias) HbA1c	Low risk	**Quote:** "…open-label comparison…" **Comment:** centrally measured outcome measurement
Blinding of outcome assessment (detection bias) Health-related quality of life	High risk	**Quote:** "…open-label comparison…" **Comment:** self-reported outcome measurement; no indications that the endpoint assessment was blinded
Blinding of outcome assessment (detection bias) Hypoglycaemia	High risk	**Quote:** "…open-label comparison…" **Comment:** self-reported and investigator-assessed outcome measurement; no indications that the endpoint assessment was blinded
Incomplete outcome data (attrition bias) Adverse events other than hypoglycaemia	Low risk	**Quote:** "All analyses were based on intent to treat and included all subjects with post-baseline data." **Comment:** ITT/LOCF according to IQWiG report
Incomplete outcome data (attrition bias) All-cause mortality	Low risk	**Quote:** "All analyses were based on intent to treat and included all subjects with post-baseline data." **Comment:** ITT/LOCF according to IQWiG report
Incomplete outcome data (attrition bias) Diabetes-related complications	Low risk	**Quote:** "All analyses were based on intent to treat and included all subjects with post-baseline data." **Comment:** ITT/LOCF according to IQWiG report

Rosenstock 2001 *(Continued)*

Incomplete outcome data (attrition bias) HbA1c	Low risk	**Quote:** "All analyses were based on intent to treat and included all subjects with post-baseline data." **Comment:** ITT/LOCF according to IQWiG report
Incomplete outcome data (attrition bias) Health-related quality of life	Low risk	**Quote:** "All analyses were based on intent to treat and included all subjects with post-baseline data." **Comment:** ITT/LOCF according to IQWiG report
Incomplete outcome data (attrition bias) Hypoglycaemia	Low risk	**Quote:** "All analyses were based on intent to treat and included all subjects with post-baseline data." **Comment:** ITT/LOCF according to IQWiG report
Selective reporting (reporting bias)	Low risk	**Comment:** none detected
Other bias	Unclear risk	**Comment:** funding received by a pharmaceutical company

Rosenstock 2009

Study characteristics	
Methods	**Study design:** parallel RCT; non-inferiority design **Number of study centres:** 62
Participants	**Inclusion criteria:** aged 30–70 years; diagnosis of type 2 diabetes mellitus for ≥ 1 year; treated with OHAs or insulin alone or a combination of OADs and insulin for ≥ 1 year prior to screening, with a stable dose(s) for ≥ 3 months prior to screening; HbA1c 6.0–12.0% at screening; baseline retinopathy severity not to exceed 53/<53 on the ETDRS scale; unlikely to require laser surgery or vitrectomy within upcoming year **Exclusion criteria:** presence of proliferative or severe non-proliferative diabetic retinopathy in either eye; laser photocoagulation or vitrectomy prior to study entry; use of any insulin analogues ≥ 3 months prior to screening; systolic blood pressure > 150 mmHg or diastolic blood pressure > 95 mmHg at screening; history of hypoglycaemia unawareness (> 2 severe hypoglycaemia episodes without warning in the past year) **Diagnostic criteria**: type 2 diabetes mellitus: not reported; proliferative or severe non-proliferative diabetic retinopathy: ETDRS level ≥ 53
Interventions	**Intervention:** insulin glargine **Comparator:** NPH insulin **Run-in period:** no (1–6 weeks' screening phase) **Extension period:** no
Outcomes	Percentage of participants with ≥ 3 step progression in ETDRS score after 5 years of treatment; percentage of participants with ≥ 3 step progression in ETDRS score after 3, 6, 12, 24, 36, 48 and 60 months of treatment; percentage of participants who developed proliferative diabetic retinopathy; distribution of change on the ETDRS scale; percentage of participants who developed clinically significant macular oedema; change from baseline in overall HbA1c and FPG levels; overall incidence and rate of symptomatic hypoglycaemia (all episodes of symptomatic hypoglycaemia), symptomatic nocturnal hypoglycaemia and severe hypoglycaemia (symptomatic hypoglycaemia requiring assistance and either with

Rosenstock 2009 *(Continued)*

	BG levels of ≤ 3.1 mmol/L or treated with oral or injectable carbohydrate or glucagon injection); insulin doses **Composite outcome measures reported:** no
Study details	**Trial terminated early (for benefit/because of AEs):** no **Trial ID:** NCT00174824
Publication details	**Language of publication:** English **Funding:** commercial funding (Sanofi-Aventis) **Publication status:** peer-reviewed journal
Stated aim of study	**Quote:** "This long-term study was designed to further characterise the retinal safety profile of insulin glargine and human neutral protamine Hagedorn (NPH) insulin in patients with type 2 diabetes mellitus."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "Patients entering the screening phase received a participant number and, following fulfilment of inclusion criteria (at the end of the screening phase), were randomised by the investigator according to the centralised interactive voice response system (IVRS). The randomisation schedule (1:1) was stratified by investigational centre and baseline HbA1c levels (6.0–9.0% and > 9.0–12.0%)." **Comment:** method of randomisation sequence generation not clearly stated, but adequate according to IQWiG report
Allocation concealment (selection bias)	Low risk	**Quote:** "Patients entering the screening phase received a participant number and, following fulfilment of inclusion criteria (at the end of the screening phase), were randomised by the investigator according to the centralised interactive voice response system (IVRS)." **Comment:** central allocation
Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "open-label;" "Safety was assessed by the evaluation of reported adverse events using the Medical Dictionary for Regulatory Activities (MedDRA) coding (Version 10.0; MSSO, Chantilly, VA, USA)." **Comment:** any AE (investigator-assessed and self-reported); any treatment-emergent AEs (investigator-assessed and self-reported)
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Quote:** "open-label;" "Safety was assessed by the evaluation of reported adverse events using the Medical Dictionary for Regulatory Activities (MedDRA) coding (Version 10.0; MSSO, Chantilly, VA, USA)." **Comment:** treatment-emergent AEs leading to death (investigator-assessed outcome measurement)
Blinding of participants and personnel (performance bias) Diabetes-related complications	Unclear risk	**Quote:** "open-label;" "Diabetic retinopathy status was assessed in seven-field stereoscopic fundus photographs obtained at screening and after 3, 6, 12, 24, 36, 48 and 60 months of treatment [19–21]. Photographs underwent treatment-group-masked grading, without comparison with other photographs, at the University of Wisconsin Fundus Photograph Reading Centre (FPRC). To

Rosenstock 2009 *(Continued)*

		verify progression status, a side-by-side comparison of baseline and follow-up photographs masked to treatment was conducted by a senior grader for any patient whose ETDRS score demonstrated a three step or greater progression over baseline at any time point during the study." **Comment:** adjudicated outcome measurement
Blinding of participants and personnel (performance bias) HbA1c	Low risk	**Quote:** "open-label;" "HbA1c (performed by the Diabetes Diagnostic Laboratories, Columbia, MO, USA, using the National Glycohemoglobin Standardization Programme [level 1])." **Comment:** adjudicated outcome measurement
Blinding of participants and personnel (performance bias) Hypoglycaemia	High risk	**Quote:** "open-label." **Comment:** all episodes of symptomatic hypoglycaemia (self-reported outcome measurement); symptomatic nocturnal hypoglycaemia (self-reported outcome measurement); severe hypoglycaemia (self-reported outcome measurement)
Blinding of outcome assessment (detection bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "open-label;" "The investigator was not blinded to the treatment group to which each participant had been assigned;" "Safety was assessed by the evaluation of reported adverse events using the Medical Dictionary for Regulatory Activities (MedDRA) coding (Version 10.0; MSSO, Chantilly, VA, USA)." **Comment:** any AE (investigator-assessed outcome measurement); any treatment-emergent AEs (investigator-assessed outcome measurement)
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Quote:** "open-label;" "treatment-emergent adverse events leading to death." **Comment:** investigator-assessed outcome measurement
Blinding of outcome assessment (detection bias) Diabetes-related complications	Low risk	**Quote:** "open-label;" "Diabetic retinopathy status was assessed in seven-field stereoscopic fundus photographs obtained at screening and after 3, 6, 12, 24, 36, 48 and 60 months of treatment [19–21]. Photographs underwent treatment-group-masked grading, without comparison with other photographs, at the University of Wisconsin Fundus Photograph Reading Centre (FPRC). To verify progression status, a side-by-side comparison of baseline and follow-up photographs masked to treatment was conducted by a senior grader for any patient whose ETDRS score demonstrated a three step or greater progression over baseline at any time point during the study." **Comment:** percentage of participants who developed clinically significant macular oedema (adjudicated outcome measurement); percentage of participants who developed proliferative diabetic retinopathy (adjudicated outcome measurement); distribution of change on the ETDRS scale (adjudicated outcome measurement)
Blinding of outcome assessment (detection bias) HbA1c	Low risk	**Quote:** "open-label;" "HbA1c (performed by the Diabetes Diagnostic Laboratories, Columbia, MO, USA, using the National Glycohemoglobin Standardization Programme [level 1])." **Comment:** adjudicated outcome measurement
Blinding of outcome assessment (detection bias) Hypoglycaemia	High risk	**Quote:** "open-label." **Comment:** all episodes of symptomatic hypoglycaemia (self-reported outcome measurement); symptomatic nocturnal hypoglycaemia (self-reported outcome measurement); severe hypoglycaemia (self-reported outcome measurement)

Rosenstock 2009 *(Continued)*

Incomplete outcome data (attrition bias) Adverse events other than hypoglycaemia	Low risk	**Quote:** "Total randomised to insulin glargine n=515…ITT population n=513… Total completed n=374…Safety population n=514" "Total randomised to NPH insulin n=509… ITT population n=504…Total completed n=364…Safety population n=503;" "One patient who was randomised to receive NPH insulin received insulin glargine throughout the study." **Comment:** 72.6% of intervention and 71.5% of control group completed trial; reasons for premature withdrawals reported for treatment groups, according to IQWiG report LOCF
Incomplete outcome data (attrition bias) All-cause mortality	Low risk	**Quote:** "Total randomised to insulin glargine n=515…ITT population n=513… Total completed n=374…Safety population n=514" "Total randomised to NPH insulin n=509…ITT population n=504…Total completed n=364…Safety population n=503;" "One patient who was randomised to receive NPH insulin received insulin glargine throughout the study." **Comment:** 72.6% of intervention and 71.5% of control group completed trial; reasons for premature withdrawals reported for treatment groups, according to IQWiG report LOCF
Incomplete outcome data (attrition bias) Diabetes-related complications	Low risk	**Quote:** "Total randomised to insulin glargine n=515…ITT population n=513… Total completed n=374" "Total randomised to NPH insulin n=509…ITT population n=504…Total completed n=364." **Comment:** 72.6% of intervention and 71.5% of control group completed trial; reasons for premature withdrawals reported for treatment groups; about 3% of ITT-population not included in analysis
Incomplete outcome data (attrition bias) HbA1c	Low risk	**Quote:** "Total randomised to insulin glargine n=515…ITT population n=513… Total completed n=374" "Total randomised to NPH insulin n=509…ITT population n=504…Total completed n=364;" "Metabolic changes (mean ± SD) during the course of the study from baseline to endpoint (last observation carried forward)…" **Comment:** 72.6% of intervention and 71.5% of control group completed trial; reasons for premature withdrawals reported for treatment groups
Incomplete outcome data (attrition bias) Hypoglycaemia	Low risk	**Quote:** "Total randomised to insulin glargine n=515…ITT population n=513… Total completed n=374" "Total randomised to NPH insulin n=509…ITT population n=504…Total completed n=364;" "Metabolic changes (mean ± SD) during the course of the study from baseline to endpoint (last observation carried forward)…" **Comment:** 72.6% of intervention and 71.5% of control group completed trial; reasons for premature withdrawals reported for treatment groups; also according to IQWiG report LOCF
Selective reporting (reporting bias)	Low risk	**Comment:** none detected
Other bias	Unclear risk	**Comment:** funding received by a pharmaceutical company

Yki-Järvinen 2006

Study characteristics	
Methods	**Study design:** parallel RCT

Yki-Järvinen 2006 *(Continued)*

	Number of study centres: 7
Participants	**Inclusion criteria:** men or women; aged 35–75 years; type 2 diabetes mellitus; had been treated with a stable dose of SU (any dose) and metformin (≥ 1.5 g) or with metformin alone for ≥ 3 months; BMI 20–40 kg/m^2; HbA1c ≥ 8.0%; mean FPG ≥ 7 mmol/L (daily home glucose monitoring); fasting C-peptide ≥ 0.33 nmol/L (reference range 0.33–0.69 nmol/L) **Exclusion criteria:** use of other oral antihyperglycaemic agents; prior use of insulin; positive GAD antibodies; history of ketoacidosis; non-compliance with regard to daily measurements of FPG in the run-in phase, abnormal safety laboratory tests; current or past history of alcohol or drug abuse; night shift work; pregnancy; treatment with any investigational drug in the past 2 months prior start of trial; use of drugs likely to interfere with glucose control; clinically relevant major systemic disease other than diabetes; diabetic retinopathy requiring surgical (laser or other) treatment in the 3 months before or during the study. **Diagnostic criteria:** —
Interventions	**Intervention:** insulin glargine **Comparator:** NPH insulin **Run-in period:** 4 weeks **Titration period:** — **Treatment before study:** oral antihyperglycaemic agents: SU and metformin or metformin alone; with a stable dose **Extension period:** no
Outcomes	**Primary outcome:** change in HbA1c from baseline to end of study **Secondary outcomes:** diurnal glucose concentrations; symptomatic hypoglycaemia **Additional published outcomes:** weight; serum ALT; triglycerides; insulin doses between groups; FPG, AEs **Composite outcome measures reported:** no
Study details	**Trial terminated early (for benefit/because of AEs):** no **Trial ID:** —
Publication details	**Language of publication:** English **Funding:** commercial and non-commercial funding (Academy of Finland; Sanofi) **Publication status:** peer-reviewed journal; full article
Stated aim of study	**Quote:** "…we compared the combination therapy insulin glargine + metformin (G+MET) with NPH insulin + metformin (NPH+MET)."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** no information from publication, but according to IQWiG report adequate

Yki-Järvinen 2006 *(Continued)*

Allocation concealment (selection bias)	Low risk	**Comment:** no information from publication, but according to IQWiG report adequate
Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "open." **Comment:** self-reported and investigator assessed outcome measurement
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Quote:** "open." **Comment:** investigator assessed outcome measurement
Blinding of participants and personnel (performance bias) Diabetes-related complications	Unclear risk	**Quote:** "open." **Comment:** investigator assessed outcome measurement
Blinding of participants and personnel (performance bias) HbA1c	Unclear risk	**Quote:** "open." **Comment:** investigator assessed outcome measurement, local laboratories
Blinding of participants and personnel (performance bias) Hypoglycaemia	High risk	**Quote:** "open." **Comment:** self-reported and investigator assessed outcome measurement
Blinding of outcome assessment (detection bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "open." **Comment:** self-reported and investigator assessed outcome measurement; no indication that the endpoint assessment was blinded
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Quote:** "open." **Comment:** investigator assessed outcome measurement; no indication that the endpoint assessment was blinded
Blinding of outcome assessment (detection bias) Diabetes-related complications	Unclear risk	**Quote:** "open." **Comment:** self-reported and investigator assessed; no indication that the endpoint assessment was blinded
Blinding of outcome assessment (detection bias) HbA1c	Unclear risk	**Quote:** "open." **Comment:** investigator assessed outcome measurement, local laboratories; no indication that the endpoint assessment was blinded
Blinding of outcome assessment (detection bias) Hypoglycaemia	High risk	**Quote:** "open." **Comment:** self-reported and investigator assessed outcome measurement; no indication that the endpoint assessment was blinded
Incomplete outcome data (attrition bias) Adverse events other than hypoglycaemia	Low risk	**Quote:** "All statistical analyses were performed on an intent-to-treat basis, defined as randomised patients who received at least one injection of insulin."

Yki-Järvinen 2006 *(Continued)*

		Comment: after randomisation, 2 participants discontinued the study (1 on glargine + metformin because of pancreatic cancer, and 1 on NPH + metformin because of a pulmonary tumour, which was benign)
Incomplete outcome data (attrition bias) All-cause mortality	Low risk	**Quote:** "All statistical analyses were performed on an intent-to-treat basis, defined as randomised patients who received at least one injection of insulin." **Comment:** after randomisation, 2 participants discontinued the study (1 on glargine + metformin because of pancreatic cancer, and 1 on NPH + metformin because of a pulmonary tumour, which was benign)
Incomplete outcome data (attrition bias) Diabetes-related complications	Low risk	**Quote:** "All statistical analyses were performed on an intent-to-treat basis, defined as randomised patients who received at least one injection of insulin." **Comment:** after randomisation, 2 participants discontinued the study (1 on glargine + metformin because of pancreatic cancer, and 1 on NPH + metformin because of a pulmonary tumour, which was benign)
Incomplete outcome data (attrition bias) HbA1c	Low risk	**Quote:** "All statistical analyses were performed on an intent-to-treat basis, defined as randomised patients who received at least one injection of insulin." **Comment:** after randomisation, 2 participants discontinued the study (1 on glargine + metformin because of pancreatic cancer, and 1 on NPH + metformin because of a pulmonary tumour, which was benign)
Incomplete outcome data (attrition bias) Hypoglycaemia	Low risk	**Quote:** "All statistical analyses were performed on an intent-to-treat basis, defined as randomised patients who received at least one injection of insulin." **Comment:** after randomisation, 2 participants discontinued the study (1 on glargine + metformin because of pancreatic cancer, and 1 on NPH + metformin because of a pulmonary tumour, which was benign)
Selective reporting (reporting bias)	Low risk	**Comment:** none detected
Other bias	Unclear risk	**Comment:** funding received by a pharmaceutical company

Yokoyama 2006

Study characteristics	
Methods	**Study design:** parallel RCT **Number of study centres:** 1
Participants	**Inclusion criteria:** type 2 diabetes mellitus; 2 years' duration of diabetes mellitus; aged ≥ 35 years; negative GAD test; without any episodes of ketoacidosis; BMI ≤ 40 kg/m^2; HbA1c ≤ 10%; people had once had poor glycaemic control (HbA1c ≥ 8%) despite optimal dose of SUs in addition to diet and exercise; for > 1 year on basal/prandial insulin therapy using aspart/lispro at each meal and NPH at bedtime with or without any antidiabetic oral agents **Exclusion criteria:** impaired hepatic, renal or cardiac function; recurrent major hypoglycaemia **Diagnostic criteria:** —
Interventions	**Intervention:** insulin glargine **Comparator:** NPH insulin

Yokoyama 2006 *(Continued)*

	Run-in period: 3 months **Titration period:** — **Treatment before study:** SUs in addition to diet and exercise then having been treated for > 1 year with basal-prandial insulin therapy using aspart/lispro at each meal and NPH at bedtime with or without OADs **Extension period:** no
Outcomes	**Primary outcome:** HbA1c (not specified in publication) **Secondary outcomes:** total daily insulin dose; fasting and postprandial BG; BMI; hypoglycaemia **Additional published outcomes:** — **Composite outcome measures reported:** no
Study details	**Trial terminated early (for benefit/because of AEs):** no **Trial ID:** —
Publication details	**Language of publication:** English **Funding:** unclear **Publication status:** peer-reviewed journal/full article
Stated aim of study	**Quote:** "…we hypothesized that increasing the dose of morning glargine up to half the total insulin requirement may lead to better glycaemic control."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "…the patients were randomized to…" **Comment:** no information on randomisation method.
Allocation concealment (selection bias)	Unclear risk	**Comment:** no information on allocation concealment
Blinding of participants and personnel (performance bias) HbA1c	Unclear risk	**Comment:** no information regarding blinding, but due to the differences in the treatment strategies in the study groups certainly open labelled
Blinding of participants and personnel (performance bias) Hypoglycaemia	High risk	**Comment:** no information regarding blinding, but due to the differences in the treatment strategies in the study groups certainly open labelled
Blinding of outcome assessment (detection bias) HbA1c	Unclear risk	**Comment:** no indications that the endpoint assessment was blinded
Blinding of outcome assessment (detection bias) Hypoglycaemia	High risk	**Comment:** no indications that the endpoint assessment was blinded

Yokoyama 2006 *(Continued)*

Incomplete outcome data (attrition bias) HbA1c	Unclear risk	**Comment:** no specific information available
Incomplete outcome data (attrition bias) Hypoglycaemia	Unclear risk	**Comment:** no specific information available
Selective reporting (reporting bias)	High risk	**Comment:** data on hypoglycaemic episodes are provided for 3 months only, not for the whole follow-up period of 6 months; no data provided for nocturnal hypoglycaemia: quote: "There were few episodes of nocturnal hypoglycaemia in either groups;" no data on adverse events and mortality
Other bias	Unclear risk	**Comment:** there were some inconsistencies regarding the HbA1c value in the abstract and the text of the trial; funding source not reported

— denotes not reported.
ACCORD: Action to Control Cardiovascular Disease; ADA: American Diabetes Association; AE: adverse event; ALT: alanine transaminase; AST: aspartate transaminase; BG: blood glucose; BMI: body mass index; CI: confidence interval; DRQoL: diabetes-related quality of life; DTSQ (s/c): Diabetes Treatment Satisfaction Questionnaire (status/change); ECG: electrocardiogram; EQ-5D: EuroQol 5 Dimension; ETDRS: Early Treatment of Diabetic Retinopathy Study; FAS: Full Analysis Set; FBG: fasting blood glucose; FPG: fasting plasma (blood) glucose; FPRC: Fundus Photograph Reading Centre; GAD: glutamic acid decarboxylase; GLP-1: glucagon-like peptide; HbA1c: glycosylated haemoglobin A1c; ID: identifier; IQWiG: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care); ITEQ: Insulin Therapy Experience Questionnaire; ITT: intention-to-treat; IU: international unit; IVRS: interactive voice response system; LOCF: last observation carried forward; MedDRA: Medical Dictionary for Regulatory Activities; MSSO: Maintenance and Support Services Organization; NPH: neutral protamine Hagedorn; OAD: oral antihyperglycaemic drug; OHA: oral hypoglycaemic agent(s); PAID: Problem Areas In Diabetes; QoL: quality of life; RCT: randomised controlled trial; SAE: serious adverse event; SD: standard deviation; SF-12: 12-item Short Form Health Survey; SMBG: self-monitoring of blood glucose; SMPG: self-monitored plasma glucose; SU: sulphonylurea.

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

Study	Reason for exclusion
Bellido 2014	Comparison inadequate.
Bi 2012	Systematic review/meta-analysis, HTA report.
Bolli 2012	Not an RCT.
Currie 2009	Not an RCT.
Dailey 2013	Systematic review/meta-analysis, HTA report.
Freemantle 2016	Systematic review/meta-analysis, HTA report.
Freemantle 2020a	Comparison inadequate.
Freemantle 2020b	Comparison inadequate.
Frier 2013	Systematic review/meta-analysis, HTA report.
Fritsche 2010	Comparison inadequate.
Hoogwerf 2016	Intervention not long-acting insulin analogues.

Study	Reason for exclusion
ISRCTN76123473	Study withdrawn.
Jensen 2010	Systematic review/meta-analysis, HTA report.
Jiang 2008	Study duration < 24 weeks.
Johnson 2009	Not an RCT.
Leal 2008	Not an RCT.
Lin 2014	Systematic review/meta-analysis, HTA report.
Mu 2011	Study duration < 24 weeks.
NCT01854723	Study withdrawn.
Oster 2016	Comparison inadequate.
Owens 2014	Systematic review/meta-analysis, HTA report.
Owens 2017	Systematic review/meta-analysis, HTA report.
Peterson 2006	Systematic review/meta-analysis, HTA report.
Philis-Tsimikas 2008	Systematic review/meta-analysis, HTA report.
Porcellati 2017	Systematic review/meta-analysis, HTA report.
Puig 2012	Study duration < 24 weeks.
Ramirez de Arellano 2014	Not an RCT.
Rys 2015	Systematic review/meta-analysis, HTA report.
Schwartz 2011	Not an RCT.
Smith 2008	Not an RCT.
Tamaki 2008	Control not NPH insulin.
Tilling 2011	Comparison inadequate.
Van Avendonk 2009	Systematic review/meta-analysis, HTA report.
Vora 2011	Different antihyperglycaemic cotherapy.
Wang 2015	Systematic review/meta-analysis, HTA report.
Wojciechowski 2013	Systematic review/meta-analysis, HTA report.

HTA: health technology assessment; RCT: randomised controlled trial.

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

NCT00788840

Methods	**Type of trial:** interventional **Allocation:** randomised **Intervention model:** parallel assignment **Masking:** open label **Primary purpose:** treatment
Participants	**Condition:** type 2 diabetes **Enrollment:** estimated 30 **Inclusion criteria:** type 2 diabetes mellitus; treated with metformin; already on treatment with a long-acting or intermediate insulin; aged > 18 years; HbA1c > 7.0%; BMI 27–40 kg/m^2; able and willing to perform self-BG monitoring; able and willing to maintain consistent eating habits throughout the entire trial period; able and willing to maintain consistent physical activity level during the entire trial period **Exclusion criteria:** people taking sulphonylureas or TZDs; proliferative retinopathy that has required acute treatment within the last 6 months; impaired hepatic or renal functions; cardiac problems; uncontrolled hypertension (treated or untreated); mental incapacity, unwillingness or a language barrier precluding adequate understanding or co-operation
Interventions	**Intervention:** insulatard insulin used as long-acting insulin for 16-week treatment phase of study **Comparator:** insulin detemir used as long-acting insulin in treatment phase of study
Outcomes	**Primary outcome:** weight change after 6 months **Secondary outcomes:** energy expenditure; fat composition; fat and muscle gene expression; glycaemic control **Other outcomes:** —
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 compare the effects of 2 long-acting insulins, detemir and insulatard, on energy expenditure, weight, fat composition, gut hormone profiles, glycaemic control and fat and muscle gene expression over a 6 month period."
Trial identifier	NCT00788840
Notes	No publication or trial results available. No information provided by trial investigators.

NCT01310452

Methods	**Type of trial:** interventional **Allocation:** randomised **Intervention model:** parallel assignment **Masking:** open label **Primary purpose:** basic science
Participants	**Condition:** type 2 diabetes mellitus

NCT01310452 *(Continued)*

	Enrollment: estimated 50 **Inclusion criteria:** women or men, aged 18–70 years; participants with insulin-naive type 2 diabetes who have been treated with metformin (> 1 g/day) alone for ≥ 3 months prior to screening; HbA1c 7.5–11% based on analysis from a central laboratory; BMI 24–40 kg/m^2; weight fluctuation < 2 kg in 1 month prior to screening; able and willing to perform self-monitoring of BG; willing to accept basal insulin therapy; able to self-inject all required doses of insulin **Exclusion criteria:** treatment with any OADs in the last 6 months, except metformin; use of approved weight-lowering pharmacotherapy (e.g. orlistat, sibutramine, rimonabant) or obesity induced by drug treatment (e.g. corticosteroids, NSAIDS, tricyclic antidepressants, atypical antipsychotics); participation in a clinical study of weight control within the last 3 months prior to screening; previous or planned surgical treatment of obesity; any disease or condition (such as renal, hepatic or cardiac) according to the judgement of the investigator makes the person unsuitable for participation in the trial; anticipated change in concomitant medication known to interfere with glucose metabolism, such as systemic steroids, non-selective beta-blockers or monoaminoxidase inhibitors; anticipated change in concomitant medication known to interfere with lipid metabolism, such as lipid-lowering drugs; proliferative retinopathy or maculopathy that has required acute treatment within the last 6 months; uncontrolled hypertension (treated or untreated) as judged by the investigator; known or suspected allergy to trial product(s) or related products; previous participation in this trial; pregnant, breastfeeding or the intention of becoming pregnant or not using adequate contraceptive measures; mental incapacity, unwillingness or language barriers precluding adequate understanding or co-operation; any condition that the investigator feels would interfere with trial participation or evaluation of results; receipt of any investigational drug (NPH or insulin detemir) within 1 month prior to trial; cardiac disease defined according to the New York Heart Association class III or IV, unstable angina pectoris or myocardial infarction (or both) within the last 6 months previous to the selection; history of hypoglycaemic unawareness; with mental implant (such as cardiac pacemaker, insulin pump) in vivo
Interventions	**Intervention:** insulin detemir once daily with metformin **Comparator:** NPH insulin once daily with metformin
Outcomes	**Primary outcomes:** change in liver fat content and visceral fat mass after 26 weeks of treatment **Secondary outcomes:** magnetic resonance image for abdominal subcutaneous fat mass and calculated visceral/subcutaneous adipose tissue ratio; change in HbA1c; change in FPG; bodyweight; waist and hip circumference; hypoglycaemia; lipid profile; adverse events; safety profile (haematology, biochemistry) and physical examination/vital signs **Other outcomes:** —
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 compare the change in liver fat content and visceral fat mass (cm^2) assessed by MRS (Magnetic Resonance Spectroscopy) and MRI (Magnetic Resonance Image), after 26 weeks of treatment with insulin detemir once daily or insulin NPH once daily both with metformin in overweight and obese type 2 diabetic subjects."
Trial identifier	NCT01310452
Notes	No publication or trial results available. No information provided by trial investigators.

NCT01500850

Methods	**Type of trial:** interventional **Allocation:** randomised

NCT01500850 *(Continued)*

	Intervention model: parallel assignment **Masking:** open label **Primary purpose:** treatment
Participants	**Condition:** type 2 diabetes **Enrollment:** estimated 60 **Inclusion criteria:** type 2 diabetes mellitus ≥ 1 year of diagnosis (men and women); experienced in self-BG measurement for ≥ 3 months; HbA1c > 6.5% to ≤ 9%; BMI > 30 kg/m^2; aged ≥ 18 years; waist circumference > 88 cm (women) and > 102 cm (men); NPH insulin treatment + 1 or 2 OAD (except TZD) **Exclusion criteria:** history of drug or alcohol abuse within the last 5 years prior to screening; 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, haematological disease (or a combination) as judged by the investigator; pregnant or lactating women; sexually active women of childbearing potential not consistently and correctly practicing contraception; treatment with GLP-1-analog or TZD; hsCRP > 10 mg/L; type 1 diabetes mellitus; already treated with intensified conventional insulin therapy
Interventions	**Intervention 1:** insulin glargine + insulin glulisine **Intervention 2:** insulin glargine + human insulin **Comparator 1:** NPH insulin + insulin glulisine **Comparator 2:** NPH insulin + human insulin
Outcomes	**Primary outcome:** fasting intact proinsulin after 24 weeks of treatment **Secondary outcomes:** bodyweight; hsCRP; adiponectin ; matrix metalloproteinase-9; oral glucose tolerance test parameters (insulin, intact proinsulin, glucose); homeostatic model assessment for insulin resistance score; HbA1c; glucose; responder rate; hypoglycaemic events defined as BG < 63 mg/dL **Other outcomes:** —
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
Notes	No publication or trial results available. No information provided by trial investigators.

BG: blood glucose; BMI: body mass index; DPP-4: dipeptidyl peptidase 4; FPG: fasting plasma glucose; GLP-1: glucagon-like peptide; HbA1c: glycosylated haemoglobin A1c; hsCRP: high-sensitivity C-reactive protein; NPH: neutral protamine Hagedorn; NSAID: non-steroidal anti-inflammatory drug; OAD: oral antihyperglycaemic drug; SGLT-2: sodium/glucose co-transporter 2; TZD: thiazolidinedione.

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

EUCTR2017-004454-42-ES

Study name	An interventional study to arrest the progression of cognitive decline in diabetic patients at high risk of developing Alzheimer's disease by reducing hypoglycaemic events (low blood glucose)
Methods	**Type of trial:** interventional **Allocation:** randomised **Intervention model:** parallel assignment **Masking:** open label **Primary purpose:** treatment
Participants	**Condition:** type 2 diabetes mellitus **Enrollment:** estimated 188 **Inclusion criteria:** people with type 2 diabetes mellitus under treatment with insulin (with or without metformin) ≥ 5 years prior randomisation; mild cognitive impaired confirmed by the neuropsychological tests at screening; aged 60–75 years **Exclusion criteria:** family history of Alzheimer's disease; people with any type of dementia; history of neurological or psychiatric conditions likely to substantially affect cognition, sensory deficits or mobility limitations that would prevent or substantially restrict the delivery of the assessment or intervention, as well as other significant health problems (e.g. recent cardiovascular event, renal failure, treatment for cancer)
Interventions	**Intervention:** insulin degludec **Comparator 1:** insulin detemir **Comparator 2:** insulin glargine (U100) **Comparator 3:** NPH insulin
Outcomes	**Primary outcomes:** Alzheimer's disease diagnosis at 6, 12, 18 and 24 months **Secondary outcomes:** rate of hypoglycaemic events and measurements of glycaemic variability, respectively, in relation with Alzheimer's disease diagnosis at 6, 12, 18 and 24 months **Other outcomes:** —
Starting date	**Trial start date:** January 2018 **Trial completion date:** unknown (status: ongoing)
Contact information	**Responsible party/principal investigator:** Vall d'Hebron Research Institute, Barcelona, Spain
Trial identifier	EUCTR2017-004454-42-ES
Notes	

NCT03389490

Study name	A pilot study to describe the glycaemic variability of insulin glargine 300U/mL versus NPH (neutral protamine Hagedorn) in the insulin-naïve type 2 diabetes patients following a patient-adjusted insulin algorithm in Hong Kong
Methods	**Type of trial:** interventional

NCT03389490 *(Continued)*

	Allocation: randomised **Intervention model:** parallel assignment **Masking:** single (outcomes assessor) **Primary purpose:** treatment
Participants	**Condition:** type 2 diabetes **Enrolment:** estimated 80 **Inclusion criteria:** insulin-naive people with type 2 diabetes mellitus suboptimally controlled on their previous antidiabetic treatment; aged 18–75 years; stable dose of oral antidiabetic treatment for > 8 weeks; number of OADs that the participants used should be "3" or less; HbA1c level > 7.0% and < 10%; FPG > 8 mmol/L and < 15 mmol/L; BMI < 40 kg/m^2 **Exclusion criteria:** participation in a clinical trial with any investigational drug used with curative intent and within 30 days prior to study entry; person known to have hypoglycaemia unawareness or recurrent major hypoglycaemia; any product containing prandial insulin; concomitant medication known to interface with glucose metabolism (such as systematic steroids); change in dose of non-insulin antidiabetic treatment or initiation of new antidiabetic medications in the last 8 weeks prior to screening; people treated with steroid or non-steroidal anti-inflammatory drugs; people who had experienced an acute concurrent illness during the 3-month period before the investigation; people with hepatic disease and end-stage renal disease; people unable to comply with follow-up visits; pregnant or breastfeeding women
Interventions	**Intervention:** insulin glargine (U300) **Comparator:** NPH insulin
Outcomes	**Primary outcome:** glycaemic variability at 24 weeks **Secondary outcomes:** percentage time in target; HbA1c; FPG; incidence of hypoglycaemia; proportion of participants achieving HbA1c < 7.0%; treatment satisfaction; inflammatory markers; heart rate variability **Other outcomes:** —
Starting date	**Trial start date:** January 2018 **Trial completion date:** December 2019
Contact information	**Responsible party/principal investigator:** Elaine Chow, Chinese University of Hong Kong
Trial identifier	NCT03389490
Notes	

BMI: body mass index; FPG: fasting plasma glucose; HbA1c: glycosylated haemoglobin A1c; NPH: neutral protamine Hagedorn; OAD: oral antidiabetic drug.

DATA AND ANALYSES

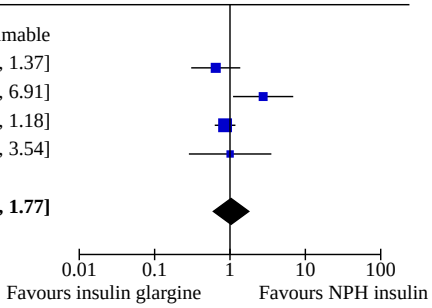
Comparison 1. Insulin glargine versus NPH insulin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Diabetes-related complications (progression in retinopathy)	5	1947	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.60, 1.77]
1.2 Severe hypoglycaemia	14	6164	Risk Ratio (IV, Random, 95% CI)	0.68 [0.46, 1.01]
1.3 Serious hypoglycaemia	10	4685	Risk Ratio (IV, Random, 95% CI)	0.75 [0.52, 1.09]
1.4 Confirmed hypoglycaemia (blood glucose (BG) < 75 mg/dL)	7	4115	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.85, 1.01]
1.5 Confirmed hypoglycaemia (BG < 55 mg/dL)	8	4388	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.81, 0.96]
1.6 Confirmed nocturnal hypoglycaemia (BG < 75 mg/dL)	8	4225	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.68, 0.89]
1.7 Confirmed nocturnal hypoglycaemia (BG < 55 mg/dL)	8	4759	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.64, 0.85]
1.8 All-cause mortality	14	6173	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.06 [0.62, 1.82]
1.9 Adverse events other than hypoglycaemia (serious adverse effects)	13	5499	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.87, 1.10]
1.10 Adverse events other than hypoglycaemia (all adverse events (AE))	14	6170	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.98, 1.03]
1.11 Adverse events other than hypoglycaemia (AEs leading to discontinuation)	13	6149	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.84, 1.76]
1.12 Adverse events other than hypoglycaemia (weight gain)	8	2405	Mean Difference (IV, Random, 95% CI)	0.12 [0.02, 0.22]
1.13 Adverse events other than hypoglycaemia (skin reactions)	10	4735	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.83, 1.35]
1.14 Adverse events other than hypoglycaemia (eye related AEs)	9	4204	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.86, 1.35]
1.15 Glycosylated haemoglobin (HbA1c)	16	5809	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.18, 0.03]

Analysis 1.1. Comparison 1: Insulin glargine versus NPH insulin, Outcome 1: Diabetes-related complications (progression in retinopathy)

Study or Subgroup	Insulin glargine Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Betônico 2019	0	31	0	32		Not estimable
Massi 2003	11	187	15	165	25.0%	0.65 [0.31 , 1.37]
Rosenstock 2001	16	213	6	220	20.1%	2.75 [1.10 , 6.91]
Rosenstock 2009	63	502	71	487	41.5%	0.86 [0.63 , 1.18]
Yki-Järvinen 2006	5	61	4	49	13.3%	1.00 [0.28 , 3.54]
Total (95% CI)		**994**		**953**	**100.0%**	**1.03 [0.60 , 1.77]**
Total events:	95		96			

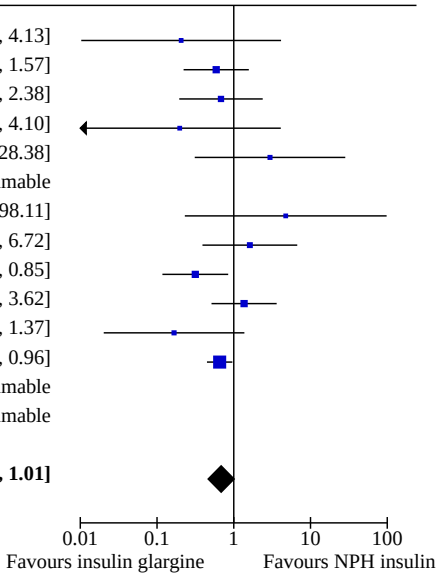
Heterogeneity: Tau² = 0.16; Chi² = 6.53, df = 3 (P = 0.09); I² = 54%
Test for overall effect: Z = 0.12 (P = 0.90)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Insulin glargine versus NPH insulin, Outcome 2: Severe hypoglycaemia

Study or Subgroup	Insulin glargine Events	Total	NPH insulin Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Betônico 2019	0	31	2	32	1.6%	0.21 [0.01 , 4.13]
Eliaschewitz 2006	6	231	11	250	12.4%	0.59 [0.22 , 1.57]
Fritsche 2003	4	227	6	232	8.3%	0.68 [0.19 , 2.38]
Hermanns 2015	0	327	2	323	1.6%	0.20 [0.01 , 4.10]
Home 2015	3	354	1	350	2.8%	2.97 [0.31 , 28.38]
Hsia 2011	0	25	0	30		Not estimable
Kawamori 2003	2	141	0	134	1.6%	4.75 [0.23 , 98.11]
Massi 2003	5	289	3	281	6.6%	1.62 [0.39 , 6.72]
Pan 2007	5	221	16	223	12.2%	0.32 [0.12 , 0.85]
Riddle 2003	9	367	7	389	12.4%	1.36 [0.51 , 3.62]
Rosenstock 2001	1	259	6	259	3.2%	0.17 [0.02 , 1.37]
Rosenstock 2009	40	513	60	504	37.1%	0.65 [0.45 , 0.96]
Yki-Järvinen 2006	0	61	0	49		Not estimable
Yokoyama 2006	0	31	0	31		Not estimable
Total (95% CI)		**3077**		**3087**	**100.0%**	**0.68 [0.46 , 1.01]**
Total events:	75		114			

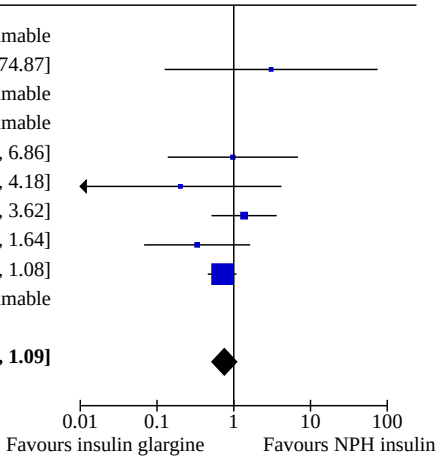
Heterogeneity: Tau² = 0.07; Chi² = 11.99, df = 10 (P = 0.29); I² = 17%
Test for overall effect: Z = 1.91 (P = 0.06)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Insulin glargine versus NPH insulin, Outcome 3: Serious hypoglycaemia

Study or Subgroup	Insulin glargine Events	Total	NPH insulin Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Eliaschewitz 2006	0	231	0	250		Not estimable
Fritsche 2003	1	227	0	232	1.3%	3.07 [0.13 , 74.87]
Hsia 2011	0	25	0	30		Not estimable
Kawamori 2003	0	141	0	134		Not estimable
Massi 2003	2	289	2	281	3.6%	0.97 [0.14 , 6.86]
Pan 2007	0	221	2	223	1.5%	0.20 [0.01 , 4.18]
Riddle 2003	9	367	7	389	14.3%	1.36 [0.51 , 3.62]
Rosenstock 2001	2	259	6	259	5.4%	0.33 [0.07 , 1.64]
Rosenstock 2009	33	513	46	504	73.9%	0.70 [0.46 , 1.08]
Yki-Järvinen 2006	0	61	0	49		Not estimable
Total (95% CI)		**2334**		**2351**	**100.0%**	**0.75 [0.52 , 1.09]**
Total events:	47		63			

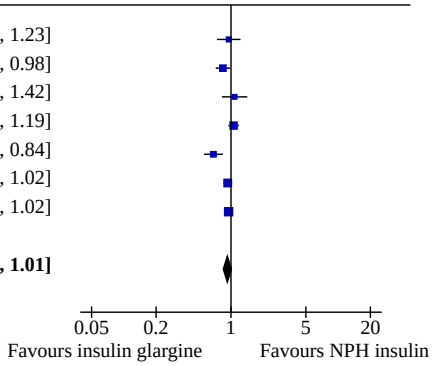
Heterogeneity: Tau² = 0.00; Chi² = 4.05, df = 5 (P = 0.54); I² = 0%
Test for overall effect: Z = 1.50 (P = 0.13)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Insulin glargine versus NPH insulin, Outcome 4: Confirmed hypoglycaemia (blood glucose (BG) < 75 mg/dL)

Study or Subgroup	Insulin glargine Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Betônico 2019	24	31	26	32	8.1%	0.95 [0.74 , 1.23]
Eliaschewitz 2006	122	231	157	250	14.1%	0.84 [0.72 , 0.98]
Hermanns 2015	82	327	75	323	7.2%	1.08 [0.82 , 1.42]
Home 2015	229	354	214	350	17.9%	1.06 [0.94 , 1.19]
Pan 2007	85	221	125	223	10.7%	0.69 [0.56 , 0.84]
Riddle 2003	248	367	282	389	19.8%	0.93 [0.85 , 1.02]
Rosenstock 2009	381	513	394	504	22.2%	0.95 [0.89 , 1.02]
Total (95% CI)		**2044**		**2071**	**100.0%**	**0.92 [0.85 , 1.01]**
Total events:	1171		1273			

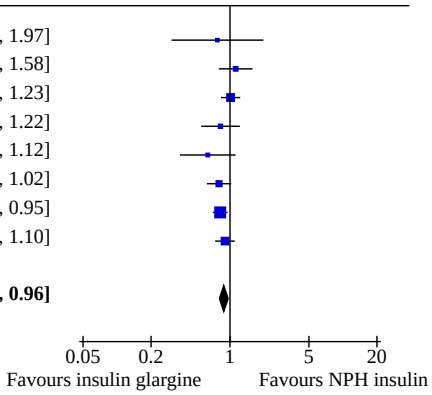
Heterogeneity: Tau² = 0.01; Chi² = 16.60, df = 6 (P = 0.01); I² = 64%
Test for overall effect: Z = 1.77 (P = 0.08)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: Insulin glargine versus NPH insulin, Outcome 5: Confirmed hypoglycaemia (BG < 55 mg/dL)

Study or Subgroup	Insulin glargine Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Betônico 2019	6	31	8	32	0.9%	0.77 [0.30 , 1.97]
Hermanns 2015	58	327	51	323	6.5%	1.12 [0.80 , 1.58]
Home 2015	129	354	126	350	20.0%	1.01 [0.83 , 1.23]
Massi 2003	39	289	46	281	5.0%	0.82 [0.56 , 1.22]
Riddle 2003	18	367	30	389	2.4%	0.64 [0.36 , 1.12]
Rosenstock 2001	76	259	95	259	12.5%	0.80 [0.62 , 1.02]
Rosenstock 2009	185	513	222	504	33.5%	0.82 [0.70 , 0.95]
Yki-Järvinen 2006	45	61	40	49	19.2%	0.90 [0.74 , 1.10]
Total (95% CI)		**2201**		**2187**	**100.0%**	**0.88 [0.81 , 0.96]**
Total events:	556		618			

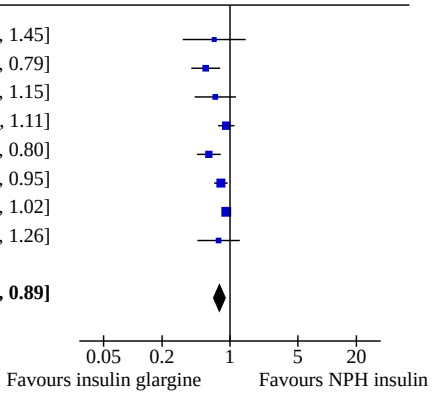
Heterogeneity: Tau² = 0.00; Chi² = 6.86, df = 7 (P = 0.44); I² = 0%
Test for overall effect: Z = 2.84 (P = 0.005)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: Insulin glargine versus NPH insulin, Outcome 6: Confirmed nocturnal hypoglycaemia (BG < 75 mg/dL)

Study or Subgroup	Insulin glargine Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Betônico 2019	8	31	12	32	3.0%	0.69 [0.33 , 1.45]
Eliaschewitz 2006	39	231	75	250	10.1%	0.56 [0.40 , 0.79]
Hermanns 2015	25	327	35	323	6.0%	0.71 [0.43 , 1.15]
Home 2015	123	354	133	350	17.9%	0.91 [0.75 , 1.11]
Pan 2007	54	221	90	223	12.8%	0.61 [0.46 , 0.80]
Riddle 2003	146	367	192	389	20.3%	0.81 [0.69 , 0.95]
Rosenstock 2009	275	513	295	504	24.1%	0.92 [0.82 , 1.02]
Yki-Järvinen 2006	19	61	20	49	5.8%	0.76 [0.46 , 1.26]
Total (95% CI)		**2105**		**2120**	**100.0%**	**0.78 [0.68 , 0.89]**
Total events:	689		852			

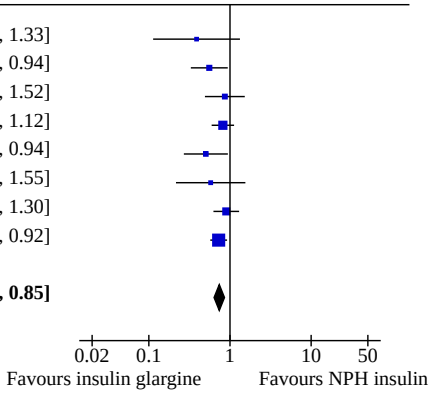
Heterogeneity: Tau² = 0.02; Chi² = 15.20, df = 7 (P = 0.03); I² = 54%
Test for overall effect: Z = 3.63 (P = 0.0003)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: Insulin glargine versus NPH insulin, Outcome 7: Confirmed nocturnal hypoglycaemia (BG < 55 mg/dL)

Study or Subgroup	Insulin glargine Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Betônico 2019	3	31	8	32	1.4%	0.39 [0.11 , 1.33]
Eliaschewitz 2006	19	231	37	250	7.9%	0.56 [0.33 , 0.94]
Hermanns 2015	21	327	24	323	6.8%	0.86 [0.49 , 1.52]
Home 2015	57	354	69	350	21.4%	0.82 [0.59 , 1.12]
Massi 2003	14	289	27	281	5.6%	0.50 [0.27 , 0.94]
Riddle 2003	6	367	11	389	2.2%	0.58 [0.22 , 1.55]
Rosenstock 2001	45	259	50	259	16.4%	0.90 [0.63 , 1.30]
Rosenstock 2009	93	513	126	504	38.3%	0.73 [0.57 , 0.92]
Total (95% CI)		**2371**		**2388**	**100.0%**	**0.74 [0.64 , 0.85]**
Total events:	258		352			

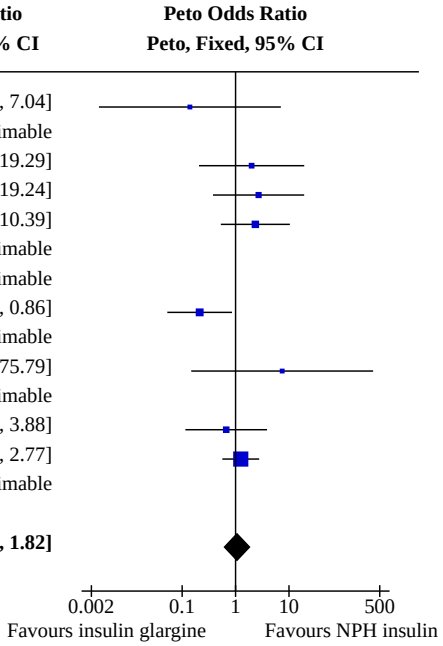
Heterogeneity: Tau² = 0.00; Chi² = 5.72, df = 7 (P = 0.57); I² = 0%
Test for overall effect: Z = 4.05 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1: Insulin glargine versus NPH insulin, Outcome 8: All-cause mortality

Study or Subgroup	Insulin glargine Events	Total	NPH insulin Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Betônico 2019	0	31	1	32	1.9%	0.14 [0.00 , 7.04]
Eliaschewitz 2006	0	231	0	250		Not estimable
Fritsche 2003	2	227	1	232	5.6%	2.00 [0.21 , 19.29]
Hermanns 2015	3	327	1	323	7.5%	2.70 [0.38 , 19.24]
Home 2015	5	354	2	350	13.1%	2.35 [0.53 , 10.39]
Hsia 2011	0	30	0	30		Not estimable
Kawamori 2003	0	158	0	159		Not estimable
Massi 2003	1	289	7	281	14.9%	0.21 [0.05 , 0.86]
NCT00687453	0	11	0	13		Not estimable
Pan 2007	1	221	0	223	1.9%	7.46 [0.15 , 375.79]
Riddle 2003	0	367	0	389		Not estimable
Rosenstock 2001	2	259	3	259	9.3%	0.67 [0.11 , 3.88]
Rosenstock 2009	14	514	11	503	45.9%	1.25 [0.57 , 2.77]
Yki-Järvinen 2006	0	61	0	49		Not estimable
Total (95% CI)		**3080**		**3093**	**100.0%**	**1.06 [0.62 , 1.82]**
Total events:	28		26			

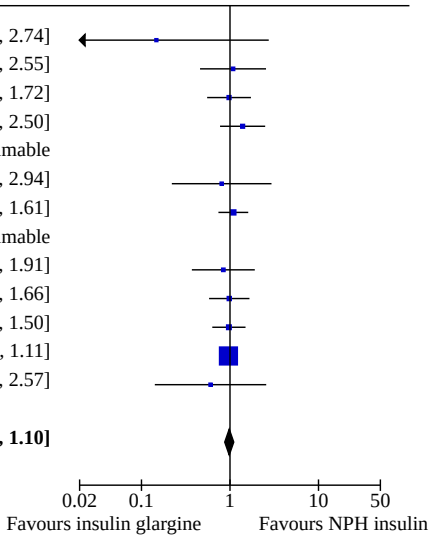
Heterogeneity: Chi² = 9.77, df = 7 (P = 0.20); I² = 28%
Test for overall effect: Z = 0.22 (P = 0.83)
Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1: Insulin glargine versus NPH insulin, Outcome 9: Adverse events other than hypoglycaemia (serious adverse effects)

Study or Subgroup	Insulin glargine Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Betônico 2019	0	31	3	32	0.2%	0.15 [0.01 , 2.74]
Eliaschewitz 2006	10	231	10	250	1.9%	1.08 [0.46 , 2.55]
Fritsche 2003	21	227	22	232	4.2%	0.98 [0.55 , 1.72]
Hermanns 2015	25	340	18	340	4.0%	1.39 [0.77 , 2.50]
Hsia 2011	0	30	0	30		Not estimable
Kawamori 2003	4	158	5	159	0.8%	0.81 [0.22 , 2.94]
Massi 2003	46	289	41	281	9.1%	1.09 [0.74 , 1.61]
NCT00687453	0	11	0	13		Not estimable
Pan 2007	10	221	12	223	2.0%	0.84 [0.37 , 1.91]
Riddle 2003	25	367	27	389	4.9%	0.98 [0.58 , 1.66]
Rosenstock 2001	35	259	36	259	7.3%	0.97 [0.63 , 1.50]
Rosenstock 2009	211	514	215	503	65.0%	0.96 [0.83 , 1.11]
Yki-Järvinen 2006	3	61	4	49	0.6%	0.60 [0.14 , 2.57]
Total (95% CI)		**2739**		**2760**	**100.0%**	**0.98 [0.87 , 1.10]**
Total events:	390		393			

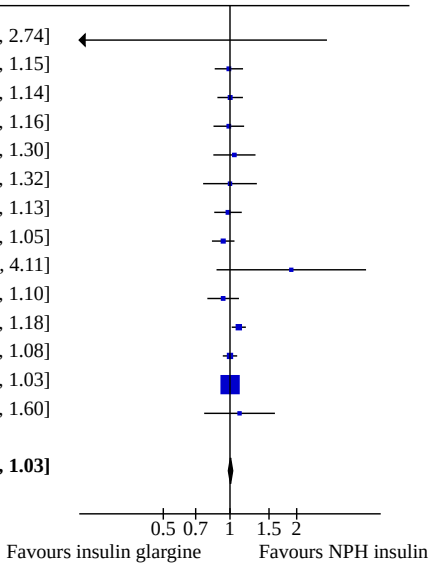
Heterogeneity: Tau² = 0.00; Chi² = 4.05, df = 10 (P = 0.95); I² = 0%
Test for overall effect: Z = 0.33 (P = 0.74)
Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1: Insulin glargine versus NPH insulin, Outcome 10: Adverse events other than hypoglycaemia (all adverse events (AE))

Study or Subgroup	Insulin glargine Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Betônico 2019	0	31	3	32	0.0%	0.15 [0.01 , 2.74]
Eliaschewitz 2006	137	231	150	250	2.3%	0.99 [0.85 , 1.15]
Fritsche 2003	149	227	152	232	2.8%	1.00 [0.88 , 1.14]
Hermanns 2015	157	327	157	323	1.9%	0.99 [0.84 , 1.16]
Home 2015	113	352	107	349	1.0%	1.05 [0.84 , 1.30]
Hsia 2011	23	30	23	30	0.6%	1.00 [0.76 , 1.32]
Kawamori 2003	110	158	113	159	2.4%	0.98 [0.85 , 1.13]
Massi 2003	185	289	193	281	3.6%	0.93 [0.83 , 1.05]
NCT00687453	8	11	5	13	0.1%	1.89 [0.87 , 4.11]
Pan 2007	120	221	130	223	1.8%	0.93 [0.79 , 1.10]
Riddle 2003	304	367	294	389	9.1%	1.10 [1.02 , 1.18]
Rosenstock 2001	218	259	218	259	8.8%	1.00 [0.93 , 1.08]
Rosenstock 2009	490	514	479	503	65.3%	1.00 [0.97 , 1.03]
Yki-Järvinen 2006	33	61	24	49	0.4%	1.10 [0.76 , 1.60]
Total (95% CI)		**3078**		**3092**	**100.0%**	**1.01 [0.98 , 1.03]**
Total events:	2047		2048			

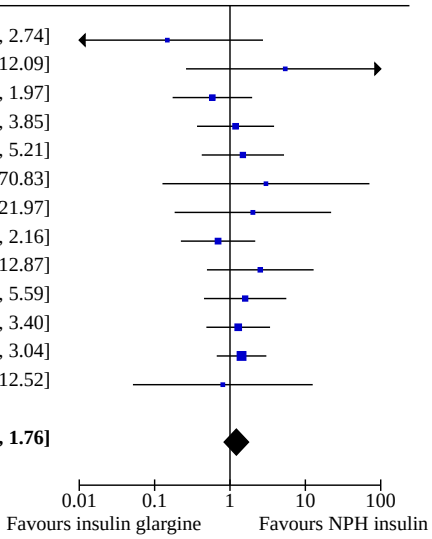
Heterogeneity: Tau² = 0.00; Chi² = 12.71, df = 13 (P = 0.47); I² = 0%
Test for overall effect: Z = 0.49 (P = 0.62)
Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1: Insulin glargine versus NPH insulin, Outcome 11: Adverse events other than hypoglycaemia (AEs leading to discontinuation)

Study or Subgroup	Insulin glargine Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Betônico 2019	0	31	3	32	1.6%	0.15 [0.01 , 2.74]
Eliaschewitz 2006	2	231	0	250	1.5%	5.41 [0.26 , 112.09]
Fritsche 2003	4	227	7	232	9.3%	0.58 [0.17 , 1.97]
Hermanns 2015	6	327	5	323	10.0%	1.19 [0.37 , 3.85]
Home 2015	6	354	4	350	8.7%	1.48 [0.42 , 5.21]
Hsia 2011	1	30	0	30	1.4%	3.00 [0.13 , 70.83]
Kawamori 2003	2	158	1	159	2.4%	2.01 [0.18 , 21.97]
Massi 2003	5	289	7	281	10.7%	0.69 [0.22 , 2.16]
Pan 2007	5	221	2	223	5.2%	2.52 [0.49 , 12.87]
Riddle 2003	6	367	4	389	8.7%	1.59 [0.45 , 5.59]
Rosenstock 2001	9	259	7	259	14.6%	1.29 [0.49 , 3.40]
Rosenstock 2009	16	514	11	503	24.0%	1.42 [0.67 , 3.04]
Yki-Järvinen 2006	1	61	1	49	1.8%	0.80 [0.05 , 12.52]
Total (95% CI)		**3069**		**3080**	**100.0%**	**1.21 [0.84 , 1.76]**
Total events:	63		52			

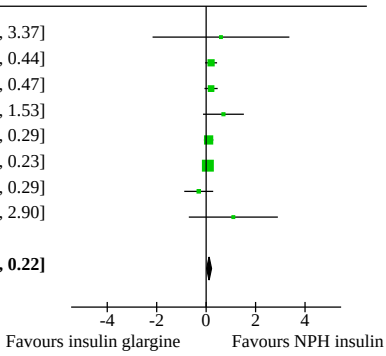
Heterogeneity: Tau² = 0.00; Chi² = 7.07, df = 12 (P = 0.85); I² = 0%
Test for overall effect: Z = 1.03 (P = 0.30)
Test for subgroup differences: Not applicable



Analysis 1.12. Comparison 1: Insulin glargine versus NPH insulin, Outcome 12: Adverse events other than hypoglycaemia (weight gain)

Study or Subgroup	Insulin glargine Mean	SD	Total	NPH insulin Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Betônico 2019	1	4.21	16	0.4	3.99	18	0.1%	0.60 [-2.17 , 3.37]
Eliaschewitz 2006	1.5	1.4	231	1.3	1.3	250	16.4%	0.20 [-0.04 , 0.44]
Fritsche 2003	1.3	1.3	227	1.1	1.6	232	13.5%	0.20 [-0.07 , 0.47]
Hsia 2011	0.7	1.6	25	0	1.5	30	1.4%	0.70 [-0.13 , 1.53]
Pan 2007	1.18	0.99	220	1.08	1.08	232	26.3%	0.10 [-0.09 , 0.29]
Riddle 2003	1.01	1.14	364	0.94	1.04	388	39.2%	0.07 [-0.09 , 0.23]
Yki-Järvinen 2006	0.9	1.5	61	1.2	1.6	49	2.8%	-0.30 [-0.89 , 0.29]
Yokoyama 2006	0.5	4.24	31	-0.6	2.86	31	0.3%	1.10 [-0.70 , 2.90]
Total (95% CI)			**1175**			**1230**	**100.0%**	**0.12 [0.02 , 0.22]**

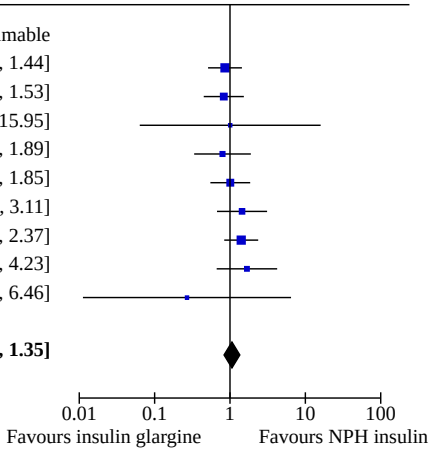
Heterogeneity: Tau² = 0.00; Chi² = 6.33, df = 7 (P = 0.50); I² = 0%
Test for overall effect: Z = 2.38 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 1.13. Comparison 1: Insulin glargine versus NPH insulin, Outcome 13: Adverse events other than hypoglycaemia (skin reactions)

Study or Subgroup	Insulin glargine Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Betônico 2019	0	31	0	32		Not estimable
Eliaschewitz 2006	23	231	29	250	21.6%	0.86 [0.51 , 1.44]
Fritsche 2003	17	227	21	232	15.4%	0.83 [0.45 , 1.53]
Kawamori 2003	1	158	1	159	0.8%	1.01 [0.06 , 15.95]
Massi 2003	9	289	11	281	7.7%	0.80 [0.33 , 1.89]
Pan 2007	19	221	19	223	15.7%	1.01 [0.55 , 1.85]
Riddle 2003	15	367	11	389	9.9%	1.45 [0.67 , 3.11]
Rosenstock 2001	31	259	22	259	21.5%	1.41 [0.84 , 2.37]
Rosenstock 2009	12	514	7	503	6.8%	1.68 [0.67 , 4.23]
Yki-Järvinen 2006	0	61	1	49	0.6%	0.27 [0.01 , 6.46]
Total (95% CI)		**2358**		**2377**	**100.0%**	**1.06 [0.83 , 1.35]**
Total events:	127		122			

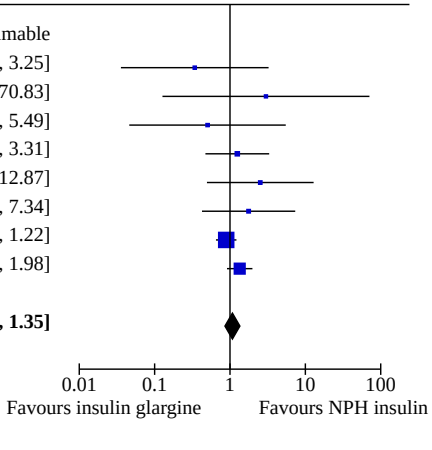
Heterogeneity: Tau² = 0.00; Chi² = 5.17, df = 8 (P = 0.74); I² = 0%
Test for overall effect: Z = 0.48 (P = 0.63)
Test for subgroup differences: Not applicable



Analysis 1.14. Comparison 1: Insulin glargine versus NPH insulin, Outcome 14: Adverse events other than hypoglycaemia (eye related AEs)

Study or Subgroup	Insulin glargine Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Betônico 2019	0	31	0	32		Not estimable
Fritsche 2003	1	227	3	232	1.0%	0.34 [0.04 , 3.25]
Hsia 2011	1	30	0	30	0.5%	3.00 [0.13 , 70.83]
Kawamori 2003	1	158	2	159	0.9%	0.50 [0.05 , 5.49]
Massi 2003	9	289	7	281	5.5%	1.25 [0.47 , 3.31]
Pan 2007	5	221	2	223	2.0%	2.52 [0.49 , 12.87]
Riddle 2003	5	367	3	389	2.6%	1.77 [0.43 , 7.34]
Rosenstock 2001	57	259	64	259	53.1%	0.89 [0.65 , 1.22]
Rosenstock 2009	55	514	40	503	34.4%	1.35 [0.91 , 1.98]
Total (95% CI)		**2096**		**2108**	**100.0%**	**1.08 [0.86 , 1.35]**
Total events:	134		121			

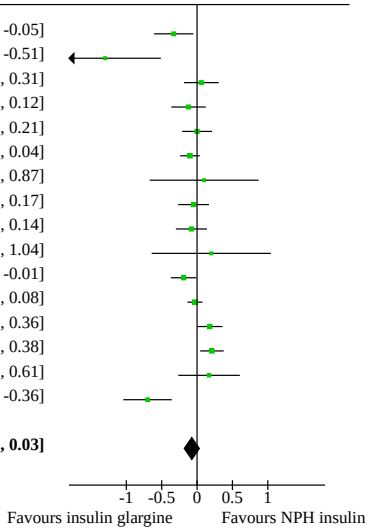
Heterogeneity: Tau² = 0.00; Chi² = 6.11, df = 7 (P = 0.53); I² = 0%
Test for overall effect: Z = 0.64 (P = 0.52)
Test for subgroup differences: Not applicable



Analysis 1.15. Comparison 1: Insulin glargine versus NPH insulin, Outcome 15: Glycosylated haemoglobin (HbA1c)

Study or Subgroup	Insulin glargine Mean [%]	SD [%]	Total	NPH insulin Mean [%]	SD [%]	Total	Weight	Mean Difference IV, Random, 95% CI [%]
Berard 2015	-0.34	0.57	32	-0.01	0.58	34	6.2%	-0.33 [-0.61 , -0.05]
Betônico 2019	-1.2	0.98	16	0.1	1.35	18	1.6%	-1.30 [-2.09 , -0.51]
Eliaschewitz 2006	-1.38	1.32	213	-1.44	1.33	237	6.9%	0.06 [-0.19 , 0.31]
Fritsche 2003	-0.96	1.32	227	-0.84	1.34	232	6.9%	-0.12 [-0.36 , 0.12]
Hermanns 2015	-1.17	1.05	175	-1.17	0.93	164	7.6%	0.00 [-0.21 , 0.21]
Home 2015	-1.07	0.94	352	-0.97	0.93	349	9.1%	-0.10 [-0.24 , 0.04]
Hsia 2011	-1.3	1.2	25	-1.4	1.7	30	1.6%	0.10 [-0.67 , 0.87]
Kawamori 2003	-1.1	0.93	141	-1.05	0.91	134	7.5%	-0.05 [-0.27 , 0.17]
Massi 2003	-0.46	1.32	280	-0.38	1.3	266	7.4%	-0.08 [-0.30 , 0.14]
NCT00687453	-0.8	0.9	11	-1	1.2	13	1.4%	0.20 [-0.64 , 1.04]
Pan 2007	-0.98	0.98	220	-0.79	0.96	223	8.2%	-0.19 [-0.37 , -0.01]
Riddle 2003	-1.65	0.75	367	-1.62	0.75	389	9.8%	-0.03 [-0.14 , 0.08]
Rosenstock 2001	-0.41	1.02	246	-0.59	1.02	255	8.3%	0.18 [0.00 , 0.36]
Rosenstock 2009	-0.55	1.34	497	-0.76	1.32	487	8.6%	0.21 [0.04 , 0.38]
Yki-Järvinen 2006	-1.95	1.19	61	-2.12	1.13	49	3.9%	0.17 [-0.27 , 0.61]
Yokoyama 2006	-0.6	0.77	32	0.1	0.64	34	5.1%	-0.70 [-1.04 , -0.36]
Total (95% CI)			**2895**			**2914**	**100.0%**	**-0.07 [-0.18 , 0.03]**

Heterogeneity: Tau² = 0.03; Chi² = 48.87, df = 15 (P < 0.0001); I² = 69%
Test for overall effect: Z = 1.37 (P = 0.17)
Test for subgroup differences: Not applicable



Comparison 2. Insulin detemir vs NPH insulin

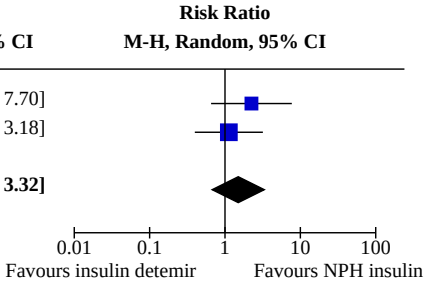
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Diabetes-related complications (progression in retinopathy)	2	972	Risk Ratio (M-H, Random, 95% CI)	1.50 [0.68, 3.32]
2.2 Severe hypoglycaemia	5	1804	Risk Ratio (IV, Random, 95% CI)	0.45 [0.17, 1.20]
2.3 Serious hypoglycaemia	5	1777	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.16 [0.04, 0.61]
2.4 Confirmed hypoglycaemia (blood glucose (BG) < 75 mg/dL)	4	1718	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.61, 0.86]
2.5 Confirmed hypoglycaemia (BG < 55 mg/dL)	4	1718	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.32, 0.71]
2.6 Confirmed nocturnal hypoglycaemia (BG < 75 mg/dL)	4	1718	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.47, 0.68]
2.7 Confirmed nocturnal hypoglycaemia (BG < 55 mg/dL)	4	1718	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.16, 0.63]
2.8 All-cause mortality	8	2328	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.74 [0.20, 2.65]
2.9 Adverse events other than hypoglycaemia (serious adverse events)	8	2328	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.64, 1.20]
2.10 Adverse events other than hypoglycaemia (all adverse events (AE))	8	2328	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.96, 1.11]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.11 Adverse events other than hypoglycaemia (AEs leading to discontinuation)	8	2328	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.67, 2.25]
2.12 Adverse events other than hypoglycaemia (skin reactions)	5	1777	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.63, 2.59]
2.13 Adverse events other than hypoglycaemia (eye-related AEs)	6	1386	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.41, 1.37]
2.14 Glycosylated haemoglobin (HbA1c)	7	2233	Mean Difference (IV, Random, 95% CI)	0.13 [-0.02, 0.28]

Analysis 2.1. Comparison 2: Insulin detemir vs NPH insulin, Outcome 1: Diabetes-related complications (progression in retinopathy)

Study or Subgroup	insulin detemir Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Haak 2005	14	341	3	164	41.6%	2.24 [0.65 , 7.70]
NN304-1337	11	309	5	158	58.4%	1.12 [0.40 , 3.18]
Total (95% CI)		**650**		**322**	**100.0%**	**1.50 [0.68 , 3.32]**
Total events:	25		8			

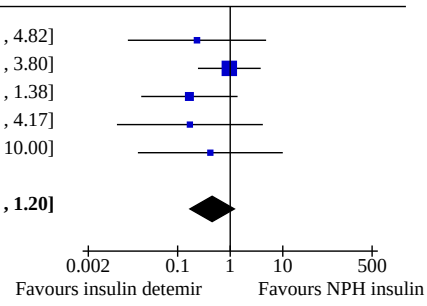
Heterogeneity: Tau² = 0.00; Chi² = 0.71, df = 1 (P = 0.40); I² = 0%
Test for overall effect: Z = 1.00 (P = 0.32)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Insulin detemir vs NPH insulin, Outcome 2: Severe hypoglycaemia

Study or Subgroup	insulin detemir Events	Total	NPH insulin Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Fajardo Montañana 2008	0	125	2	146	10.3%	0.23 [0.01 , 4.82]
Haak 2005	6	341	3	164	50.0%	0.96 [0.24 , 3.80]
Hermansen 2006	1	237	6	238	21.2%	0.17 [0.02 , 1.38]
NN304-1337	0	309	1	158	9.2%	0.17 [0.01 , 4.17]
NN304-1808	0	38	1	48	9.4%	0.42 [0.02 , 10.00]
Total (95% CI)		**1050**		**754**	**100.0%**	**0.45 [0.17 , 1.20]**
Total events:	7		13			

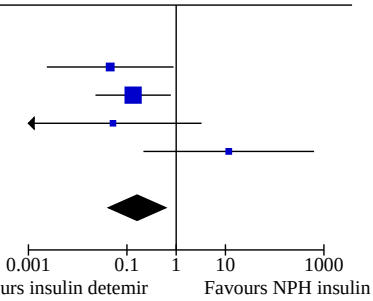
Heterogeneity: Tau² = 0.00; Chi² = 2.56, df = 4 (P = 0.63); I² = 0%
Test for overall effect: Z = 1.60 (P = 0.11)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Insulin detemir vs NPH insulin, Outcome 3: Serious hypoglycaemia

Study or Subgroup	insulin detemir Events	Total	NPH insulin Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Fajardo Montañana 2008	0	125	0	146		Not estimable
Haak 2005	0	341	2	164	20.4%	0.05 [0.00 , 0.88]
Hermansen 2006	0	237	5	238	57.9%	0.13 [0.02 , 0.78]
NN304-1337	0	309	1	158	10.4%	0.05 [0.00 , 3.28]
NN304-3614	1	24	0	35	11.3%	11.69 [0.22 , 631.58]
Total (95% CI)		**1036**		**741**	**100.0%**	**0.16 [0.04 , 0.61]**
Total events:	1		8			

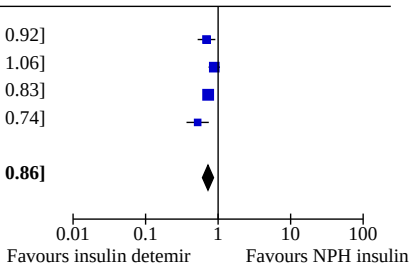
Heterogeneity: Chi² = 5.45, df = 3 (P = 0.14); I² = 45%
Test for overall effect: Z = 2.67 (P = 0.007)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: Insulin detemir vs NPH insulin, Outcome 4: Confirmed hypoglycaemia (blood glucose (BG) < 75 mg/dL)

Study or Subgroup	Insulin detemir Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Fajardo Montañana 2008	45	125	76	146	20.3%	0.69 [0.52 , 0.92]
Haak 2005	162	341	88	164	29.4%	0.89 [0.74 , 1.06]
Hermansen 2006	135	237	186	238	34.7%	0.73 [0.64 , 0.83]
NN304-1337	48	309	47	158	15.5%	0.52 [0.37 , 0.74]
Total (95% CI)		**1012**		**706**	**100.0%**	**0.73 [0.61 , 0.86]**
Total events:	390		397			

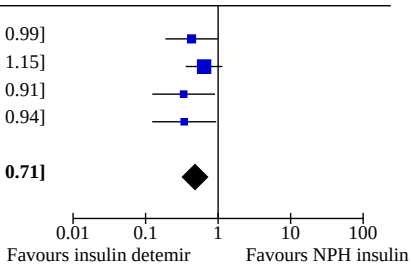
Heterogeneity: Tau² = 0.02; Chi² = 7.84, df = 3 (P = 0.05); I² = 62%
Test for overall effect: Z = 3.61 (P = 0.0003)
Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2: Insulin detemir vs NPH insulin, Outcome 5: Confirmed hypoglycaemia (BG < 55 mg/dL)

Study or Subgroup	Insulin detemir Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Fajardo Montañana 2008	7	125	19	146	22.6%	0.43 [0.19 , 0.99]
Haak 2005	24	341	18	164	46.3%	0.64 [0.36 , 1.15]
Hermansen 2006	5	237	15	238	15.8%	0.33 [0.12 , 0.91]
NN304-1337	6	309	9	158	15.2%	0.34 [0.12 , 0.94]
Total (95% CI)		**1012**		**706**	**100.0%**	**0.48 [0.32 , 0.71]**
Total events:	42		61			

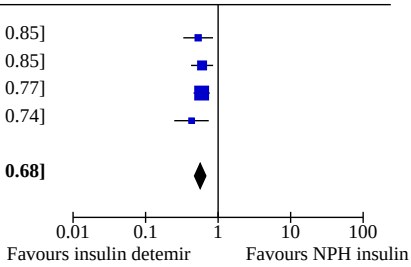
Heterogeneity: Tau² = 0.00; Chi² = 1.97, df = 3 (P = 0.58); I² = 0%
Test for overall effect: Z = 3.63 (P = 0.0003)
Test for subgroup differences: Not applicable



Analysis 2.6. Comparison 2: Insulin detemir vs NPH insulin, Outcome 6: Confirmed nocturnal hypoglycaemia (BG < 75 mg/dL)

Study or Subgroup	Insulin detemir Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Fajardo Montañana 2008	20	125	44	146	14.5%	0.53 [0.33 , 0.85]
Haak 2005	55	341	44	164	26.3%	0.60 [0.42 , 0.85]
Hermansen 2006	62	237	105	238	48.6%	0.59 [0.46 , 0.77]
NN304-1337	21	309	25	158	10.7%	0.43 [0.25 , 0.74]
Total (95% CI)		**1012**		**706**	**100.0%**	**0.57 [0.47 , 0.68]**
Total events:	158		218			

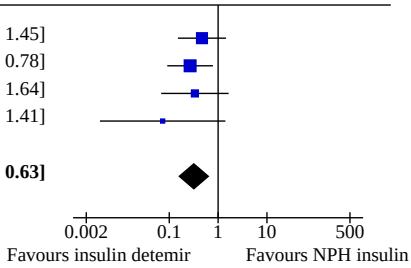
Heterogeneity: Tau² = 0.00; Chi² = 1.29, df = 3 (P = 0.73); I² = 0%
Test for overall effect: Z = 6.23 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 2.7. Comparison 2: Insulin detemir vs NPH insulin, Outcome 7: Confirmed nocturnal hypoglycaemia (BG < 55 mg/dL)

Study or Subgroup	Insulin detemir Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Fajardo Montañana 2008	4	125	10	146	36.2%	0.47 [0.15 , 1.45]
Haak 2005	5	341	9	164	40.1%	0.27 [0.09 , 0.78]
Hermansen 2006	2	237	6	238	18.4%	0.33 [0.07 , 1.64]
NN304-1337	0	309	3	158	5.3%	0.07 [0.00 , 1.41]
Total (95% CI)		**1012**		**706**	**100.0%**	**0.32 [0.16 , 0.63]**
Total events:	11		28			

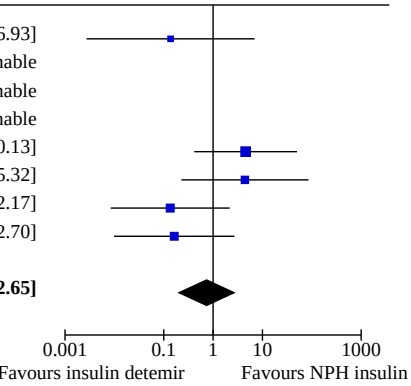
Heterogeneity: Tau² = 0.00; Chi² = 1.50, df = 3 (P = 0.68); I² = 0%
Test for overall effect: Z = 3.29 (P = 0.001)
Test for subgroup differences: Not applicable



Analysis 2.8. Comparison 2: Insulin detemir vs NPH insulin, Outcome 8: All-cause mortality

Study or Subgroup	Insulin detemir Events	Total	NPH insulin Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
NN304-1808	0	180	1	183	10.7%	0.14 [0.00 , 6.93]
NN304-1337	0	67	0	35		Not estimable
NN304-3614	0	24	0	35		Not estimable
Haak 2005	0	125	0	146		Not estimable
Hermansen 2006	3	309	0	158	28.5%	4.56 [0.42 , 50.13]
Kobayashi 2007 A	2	341	0	164	18.7%	4.41 [0.23 , 85.32]
Kobayashi 2007 B	0	237	2	238	21.3%	0.14 [0.01 , 2.17]
Fajardo Montañana 2008	0	38	2	48	20.8%	0.16 [0.01 , 2.70]
Total (95% CI)		**1321**		**1007**	**100.0%**	**0.74 [0.20 , 2.65]**
Total events:	5		5			

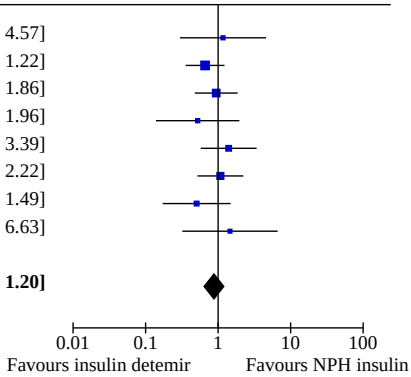
Heterogeneity: Chi² = 6.87, df = 4 (P = 0.14); I² = 42%
Test for overall effect: Z = 0.47 (P = 0.64)
Test for subgroup differences: Not applicable



Analysis 2.9. Comparison 2: Insulin detemir vs NPH insulin, Outcome 9: Adverse events other than hypoglycaemia (serious adverse events)

Study or Subgroup	Insulin detemir Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Fajardo Montañana 2008	4	125	4	146	5.2%	1.17 [0.30 , 4.57]
Haak 2005	22	341	16	164	25.4%	0.66 [0.36 , 1.22]
Hermansen 2006	15	237	16	238	20.8%	0.94 [0.48 , 1.86]
Kobayashi 2007 A	4	67	4	35	5.5%	0.52 [0.14 , 1.96]
Kobayashi 2007 B	11	180	8	183	12.3%	1.40 [0.58 , 3.39]
NN304-1337	21	309	10	158	18.2%	1.07 [0.52 , 2.22]
NN304-1808	4	38	10	48	8.3%	0.51 [0.17 , 1.49]
NN304-3614	3	24	3	35	4.2%	1.46 [0.32 , 6.63]
Total (95% CI)		**1321**		**1007**	**100.0%**	**0.88 [0.64 , 1.20]**
Total events:	84		71			

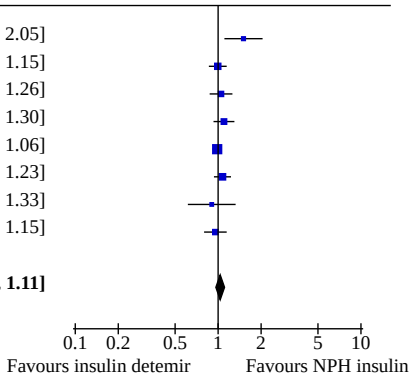
Heterogeneity: Tau² = 0.00; Chi² = 4.40, df = 7 (P = 0.73); I² = 0%
Test for overall effect: Z = 0.83 (P = 0.40)
Test for subgroup differences: Not applicable



Analysis 2.10. Comparison 2: Insulin detemir vs NPH insulin, Outcome 10: Adverse events other than hypoglycaemia (all adverse events (AE))

Study or Subgroup	Insulin detemir Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Fajardo Montañana 2008	58	125	45	146	4.6%	1.51 [1.11 , 2.05]
Haak 2005	213	341	103	164	15.0%	0.99 [0.86 , 1.15]
Hermansen 2006	119	237	114	238	10.7%	1.05 [0.87 , 1.26]
Kobayashi 2007 A	61	67	29	35	12.2%	1.10 [0.93 , 1.30]
Kobayashi 2007 B	157	180	162	183	27.7%	0.99 [0.91 , 1.06]
NN304-1337	214	309	102	158	15.9%	1.07 [0.94 , 1.23]
NN304-1808	20	38	28	48	3.0%	0.90 [0.61 , 1.33]
NN304-3614	21	24	32	35	10.9%	0.96 [0.80 , 1.15]
Total (95% CI)		**1321**		**1007**	**100.0%**	**1.03 [0.96 , 1.11]**
Total events:	863		615			

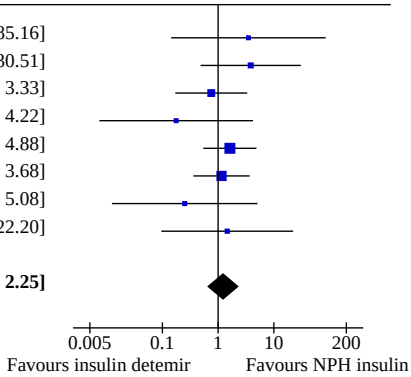
Heterogeneity: Tau² = 0.00; Chi² = 10.38, df = 7 (P = 0.17); I² = 33%
Test for overall effect: Z = 0.94 (P = 0.35)
Test for subgroup differences: Not applicable



Analysis 2.11. Comparison 2: Insulin detemir vs NPH insulin, Outcome 11: Adverse events other than hypoglycaemia (AEs leading to discontinuation)

Study or Subgroup	Insulin detemir Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Fajardo Montañana 2008	1	125	0	146	3.6%	3.50 [0.14 , 85.16]
Haak 2005	8	341	1	164	8.6%	3.85 [0.49 , 30.51]
Hermansen 2006	3	237	4	238	16.8%	0.75 [0.17 , 3.33]
Kobayashi 2007 A	0	67	1	35	3.7%	0.18 [0.01 , 4.22]
Kobayashi 2007 B	8	180	5	183	30.7%	1.63 [0.54 , 4.88]
NN304-1337	9	309	4	158	27.4%	1.15 [0.36 , 3.68]
NN304-1808	0	38	2	48	4.1%	0.25 [0.01 , 5.08]
NN304-3614	1	24	1	35	5.0%	1.46 [0.10 , 22.20]
Total (95% CI)		**1321**		**1007**	**100.0%**	**1.22 [0.67 , 2.25]**
Total events:	30		18			

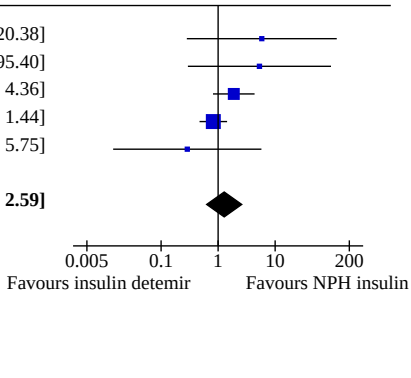
Heterogeneity: Tau² = 0.00; Chi² = 4.78, df = 7 (P = 0.69); I² = 0%
Test for overall effect: Z = 0.65 (P = 0.52)
Test for subgroup differences: Not applicable



Analysis 2.12. Comparison 2: Insulin detemir vs NPH insulin, Outcome 12: Adverse events other than hypoglycaemia (skin reactions)

Study or Subgroup	Insulin detemir Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Fajardo Montañana 2008	2	125	0	146	5.1%	5.83 [0.28 , 120.38]
Haak 2005	5	341	0	164	5.5%	5.31 [0.30 , 95.40]
Hermansen 2006	15	237	8	238	35.3%	1.88 [0.81 , 4.36]
NN304-1337	29	309	18	158	48.9%	0.82 [0.47 , 1.44]
NN304-3614	0	24	2	35	5.2%	0.29 [0.01 , 5.75]
Total (95% CI)		**1036**		**741**	**100.0%**	**1.28 [0.63 , 2.59]**
Total events:	51		28			

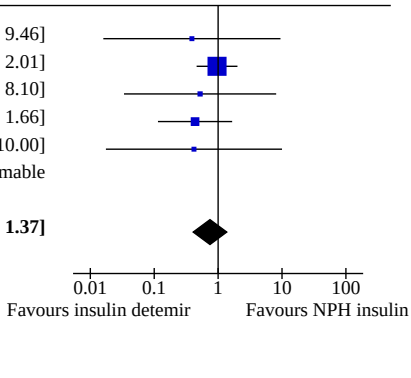
Heterogeneity: Tau² = 0.19; Chi² = 5.77, df = 4 (P = 0.22); I² = 31%
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable



Analysis 2.13. Comparison 2: Insulin detemir vs NPH insulin, Outcome 13: Adverse events other than hypoglycaemia (eye-related AEs)

Study or Subgroup	Insulin detemir Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Fajardo Montañana 2008	0	125	1	146	3.6%	0.39 [0.02 , 9.46]
Haak 2005	20	341	10	164	67.5%	0.96 [0.46 , 2.01]
Kobayashi 2007 A	1	67	1	35	4.9%	0.52 [0.03 , 8.10]
Kobayashi 2007 B	3	180	7	183	20.4%	0.44 [0.11 , 1.66]
NN304-1808	0	38	1	48	3.6%	0.42 [0.02 , 10.00]
NN304-3614	0	24	0	35		Not estimable
Total (95% CI)		**775**		**611**	**100.0%**	**0.75 [0.41 , 1.37]**
Total events:	24		20			

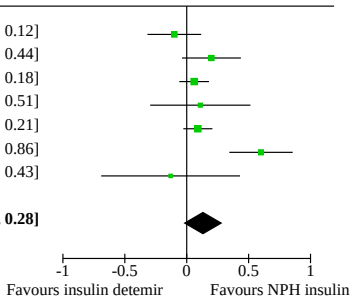
Heterogeneity: Tau² = 0.00; Chi² = 1.44, df = 4 (P = 0.84); I² = 0%
Test for overall effect: Z = 0.95 (P = 0.34)
Test for subgroup differences: Not applicable



Analysis 2.14. Comparison 2: Insulin detemir vs NPH insulin, Outcome 14: Glycosylated haemoglobin (HbA1c)

Study or Subgroup	Insulin detemir Mean [%]	SD [%]	Total	NPH insulin Mean [%]	SD [%]	Total	Weight	Mean Difference IV, Random, 95% CI [%]
Fajardo Montañana 2008	-1.1	0.91	122	-1	0.89	145	15.8%	-0.10 [-0.32 , 0.12]
Haak 2005	-0.2	1.27	341	-0.4	1.28	164	14.8%	0.20 [-0.04 , 0.44]
Hermansen 2006	-1.84	0.67	237	-1.9	0.66	238	20.7%	0.06 [-0.06 , 0.18]
Kobayashi 2007 A	-0.21	0.99	67	-0.32	0.99	35	8.5%	0.11 [-0.29 , 0.51]
Kobayashi 2007 B	-0.49	0.54	180	-0.58	0.6	183	20.9%	0.09 [-0.03 , 0.21]
NN304-1337	-0.9	1.2	309	-1.5	1.4	158	13.9%	0.60 [0.34 , 0.86]
NN304-3614	-0.92	1.08	22	-0.79	0.96	32	5.4%	-0.13 [-0.69 , 0.43]
Total (95% CI)			**1278**			**955**	**100.0%**	**0.13 [-0.02 , 0.28]**

Heterogeneity: Tau² = 0.02; Chi² = 19.68, df = 6 (P = 0.003); I² = 70%
Test for overall effect: Z = 1.74 (P = 0.08)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Overview of trial populations

Trial ID (study design)	Intervention(s) and comparator(s)	Description of power and sample size calculation	Screened/ eligible (n)	Randomised (n)	ITT (n)	Analysed (n)	Finishing trial (n)	Randomised finishing trial (%)	Follow-up (extended follow-up)[a]
Berard 2015 (parallel RCT)	I: insulin glargine once-daily	—	—	32	—	—	—	—	6 months
	C: NPH insulin once daily or twice daily			34	—	—	—	—	
	total:			**66**	**—**	**—**	**—**	**—**	
Eliasche-witz 2006 (parallel RCT, equivalence design)	I: insulin glargine at bedtime + glimepiride 4 mg/ day in the morning	Based on an equivalence region of 0.5% and an SD of 2.0% for the differences in HbA1c between the groups, equivalence can be demonstrated with a statistical power of 80% with 199 participants per group, based on a 1-sided α = 0.05. A 1:1 randomisation would require 199 evaluable participants in each group. Based on an expectation that 20% of the participants would not be evaluable, the study required the enrolment of 240 in each group.	918/—	—	231	Efficacy: 218 Safety: 231	218	—	24 weeks
	C: NPH insulin at bedtime + glimepiride 4 mg/ day in the morning			—	250	Efficacy: 244 Safety: 250	244	—	
	total:			**528**	**481**	**Efficacy: 462** **Safety: 481**	**462**	**87.5**	
Fajardo Montañana 2008 (parallel RCT)	I: insulin detemir at bedtime	272 participants (230 evaluable) were required to detect a difference in weight change of 1.5 kg (SD 4.0) between groups after 26 weeks, using a 2-sided test with a 0.05 significance level.	345/293	126	125	125	119	94.4	26 weeks
	C: NPH insulin at bedtime			151	146	146	139	92.1	
	total:			**277**	**271**	**271**	**252**	**91.0**	

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

Fritsche 2003 (parallel RCT, non-inferiority design)	I1: insulin glargine in the morning + glimepiride 3 mg	Based on the assumption of an SD of σ = 2.0%, a difference of Δ = 0.5% for HbA1c reductions among treatment groups can be detected with an α-error of 0.05 and a β-error of 0.2. This equates to a statistical power of 80% with 199 participants per group. With use of a 1:1:1 randomisation, 597 participants would be required for this study. Assuming a non-evaluable rate of 20%, 720 participants (240 per group) would need to be enrolled in this study.	938/752	237	236	236	225	94.9	24 weeks
	I2: insulin glargine at bedtime + glimepiride 3 mg			229	227	227	210	91.7	
	C: NPH insulin at bedtime + glimepiride 3 mg			234	232	232	205	87.6	
	total:			**700**	**695**	**695**	**640**	**91.4**	
Haak 2005 (parallel RCT, non-inferiority design)	I: detemir once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart	The study had sufficient power (85%) to detect a mean difference of 0.4% in HbA1c between groups. A 95% 2-sided CI was constructed for the difference between the group means (insulin detemir NPH insulin); insulin detemir was deemed non-inferior if the upper limit of the 95% CI was < 0.4% (absolute). Treatments were considered comparable if the non-inferiority criterion was fulfilled.	—/—	341	341	341	315	92.4	26 weeks
	C: detemir once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart			164	164	164	156	95.1	
	total:			**505**	**505**	**505**	**471**	**93.3**	
Hermanns 2015 (cross-over RCT)	I: insulin glargine	In a previous cross-sectional study, different effect sizes of insulin glargine compared to NPH insulin in terms of SF-12 (d = 0.10), PAID (d = 0.22), and ITEQ (d = 0.29) scores were observed. The mean effect size of all 3 scales was d = 0.166. Since the present study had a cross-over design, in which each participant served as his/her own control, an effect size on the primary endpoint DRQoL of d = 0.20 was expected.	460/—	343; sequence A: 176, sequence B: 167	339; sequence A: 175, sequence B: 164 229[b]; sequence A: 118, sequence B: 111	—	296; sequence A: 151, sequence B: 145	86.3; sequence A: 85.8, sequence B: 86.8	48 weeks (efficacy) 49 weeks (safety)
	C: NPH basal insulin								

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

		Such an effect can be detected with 90% power using a paired t-test with a significance level of 5% and with 265 participants.							
	total:			**343**	**339** **229[b]**	**—**	**296**	**86.3**	
Hermansen 2006 (parallel RCT, non-inferiority design)	I: detemir in the morning and evening	A non-inferiority criterion, defined as a < 0.4% difference in HbA1c, was calculated to require 198 completers per arm for 95% power with a 5% significance level and with a maximum baseline-adjusted SD of 1.1%	735/490	237	237	237	227	95.8	24 weeks
	C: NPH insulin in the morning and evening			239	238	238	225	94.1	
	total:			**476**	**475**	**475**	**452**	**95.0**	
Home 2015 (parallel RCT)	I: insulin glargine	It was estimated that at least 568 evaluable participants (670 were randomised with 15% not assessable) needed to be randomised to detect a difference in change of HbA1c of 0.3% (3.3 mmol/mol) at the 5% significance level with 90% power.This assumes an SD of change of HbA1c of 1.1% (12 mmol/mol)	1102/—	355	352	352	335	94.5	36 weeks (efficacy) 37 weeks (safety)
	C: NPH insulin			353	349	349	328	92.9	
	total:			**708**	**701**	**701**	**663**	**93.6**	
Hsia 2011 (parallel RCT)	I1: insulin glargine at bedtime	Based on previously published HbA1c levels in oral agent-treated participants from the study centre, enrolment of 24 in each of the 3 treatment arms (72 total) would provide 95% power to detect an HbA1c difference of 0.8%, at a 5% significance level.	—/108	30	30	30	20[c]	66.7[c]	26 weeks
	I2: insulin glargine in the morning			25	25	25	14[c]	56.0[c]	
	C: NPH insulin at bedtime			30	30	30	17[c]	56.7[c]	
	total:			**85**	**85**	**85**	**51[c]**	**60.0[c]**	

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

Kawamori 2003 (parallel RCT, non-inferiority design)	I: insulin glargine once in the morning + OAD	—	—/400	167	158	Efficacy: 141 Safety: 158	141	84.4	28 weeks
	C: NPH insulin once in the morning + OAD			168	159	Efficacy: 134 Safety: 159	134	79.8	
	total:			**335**	**317**	**Efficacy: 275** **Safety: 317**	**275**	**82.1**	
Kobayashi 2007 A (parallel RCT, non-inferiority design)	I: insulin detemir once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart	—	454/401[d]	70	67	67	65	92.9	48 weeks
	C: NPH insulin once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart			35	35	35	32	91.4	
	total:			**105**	**102**	**102**	**97**	**92.4**	
Kobayashi 2007 B (parallel RCT, non-inferiority design)	I: insulin detemir at bedtime + OAD	—	437/371	183	180	180	160	87.4	36 weeks
	C: NPH insulin at bedtime + OAD			188	183	183	172	97.5	
	total:			**371**	**363**	**363**	**332**	**89.5**	

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

Massi 2003 (parallel RCT)	I: insulin glargine once daily at bedtime + OAD	Based on 1:1 randomisation and using a t-test, a total number of 384 participants (192 for each group) was required to detect a mean difference of 0.5% glycated haemoglobin between insulin glargine and NPH insulin with a significance level of α = 5% and a statistical power of 90%. It was estimated that a total of 480 participants were to be enrolled to have 384 participants evaluable for efficacy analysis,	687/—	293	289	289	277	94.5	52 weeks
	C: NPH insulin once daily at bedtime + OAD			285	281	281	252	88.4	
	total:			**578**	**570**	**570**	**529**	**91.5**	
NCT00687453 (parallel RCT, non-inferiority design)	I: insulin glargine at bedtime	—	27/24 [e]	11	11	11	8[c]	73[c]	6 months
	C: NPH insulin in the morning and at bedtime			13	13	13	7[c]	54[c]	
	total:			**24**	**24**	**24**	**15[c]**	**62.5[c]**	
NN304-1337 (parallel RCT)	I: insulin detemir once daily at bedtime + metformin	—	—	309	309	309	266	86.1	24 weeks
	C: NPH insulin once daily at bedtime + metformin			158	158	158	140	88.6	
	total:			**467**	**467**	**467**	**406**	**86.9**	
NN304-1808 (parallel RCT, non-inferiority design)	I: insulin detemir once daily before breakfast ± metformin at optimal dose	For 80% power and 5% significance level with a baseline-adjusted SD of 1.1, a total of 238 completers (119 per group) was required. Owing to a 20% maximal expected frequency of participants lost for follow-up, 286 were to have been included, 143 in each group.	124/—	38	38	38	21[c]	55.3[c]	7 months
	C: NPH insulin once daily before break-			48	48	48	20[c]	41.7[c]	

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

	fast ± metformin at optimal dose								
	total:			**86**	**86**	**86**	**41**[c]	**47.7**[c]	
NN304-3614 (parallel RCT)	I: insulin detemir in the evening + insulin aspart each meal	As the primary objective was to demonstrate a difference of 5% in the primary endpoint, using an analysis of covariance model with 3 factors and 1 covariate and with an SD of 5%, the number of participants needed would be of 23 per group. Assuming a withdrawal rate of 20%, the total number of randomised participants would be 58. With a planned screening failure of 20%, the total number of participants planned would be 73.	81/—	25	24	24	21	84.0	26 weeks
	C: NPH insulin in the evening + insulin aspart each meal			35	35	35	31	88.6	
	total:			**60**	**59**	**59**	**52**	**86.7**	
Pan 2007 (parallel RCT, non-inferiority design)	I: insulin glargine in the evening + glimepiride 3 mg in the morning	Assuming an SD of 1.6% for the changes from baseline in HbA1c in the 2 groups, and a maximum difference between the groups to be equivalent to 0.4%, the sample size per group was calculated to provide 80% power. The sample size was adjusted for an evaluation rate of 90%, and a total of 440 participants (220 per group) was thus targeted for randomisation.	—	224	220	220[f]	211	94.2	24 weeks
	C: NPH insulin in the evening + glimepiride 3 mg in the morning		—	224	223	223[f]	214	95.5	
	total:			**448**	**443**	**443**	**425**	**94.9**	
Betônico 2019 (cross-over RCT, non-inferiority design)	I: insulin glargine in the morning + insulin lispro at mealtime	A sample size of 34 participants provided 90% power to detect a mean difference of 0.7% (7.7 mmol/mol) in the primary endpoint (HbA1c), considering a 15% dropout rate and assuming an SD of 0.85% and a type I error of 5%.	193/40	Period 1 – glargine/ period 2 – NPH: 16 Period 1 – NPH/period 2 – glargine: 18	After period 1: 16 After period 2: 15 After period 1: 18	After period 1: 16 After period 2: 15 After period 1: 18	Period 1 – glargine/ period 2 – NPH: 14 Period 1 – NPH/period 2 – glargine: 15	Period 1 – glargine/ period 2 – NPH: 87.5 Period 1 – NPH/period 2 – glargine: 83.3	Cross-over trial, 6 months per period
	C: NPH insulin 3 times daily + insulin lispro at mealtime								

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

					After period 2: 14	After period 2: 14			
	total:			**34**	**After period 1: 34** **After period 2: 29**	**After period 1: 34** **After period 2: 29**	**29**	**85.3**	
Riddle 2003 (parallel RCT)	I: insulin glargine once at bedtime + OAD	Based on previous data, randomisation of 750 participants had the power to provide an 85% chance of detecting, with α = 5%, a 10% treatment effect for the primary outcome measure	1381/764	372	367	367	334	89.8	24 weeks
	C: NPH insulin once at bedtime + OAD			392	389	389	357	91.1	
	total:			**764**	**756**	**756**	**691**	**90.4**	
Rosenstock 2001 (parallel RCT)	I: insulin glargine once daily at bedtime + premeal regular insulin	The study was designed to provide 90% power to detect a mean difference of 0.5% in HbA1c between treatment groups	846[g]/—	260	259	259	231	88.8	28 weeks
	C: NPH insulin once at bedtime or twice daily in the morning and at bedtime + premeal regular insulin			261	259	259	238	91.2	
	total:			**521**	**518**	**518**	**469**	**90.0**	
Rosenstock 2009 (parallel RCT, non-inferiority design)	I: insulin glargine once daily, generally at bedtime	Sample size was calculated assuming a 20% 5-year event rate for a ≥ 3 step progression in diabetic retinopathy on the Early Treatment of Diabetic Retinopathy Study scale from baseline to end of study (based on data from the Diabetes Control and Complications Trial), and a non-inferiority margin of 10% (half of the expected background rate of 20%) was chosen. Assuming that approximately 40% of the randomised participants would not be evaluable, a	1413/—	515	513	513 (ITT); 514[h] (safety population)	374	72.6	5 years
	C: NPH insulin twice daily, generally in the morning and at bedtime			509	504	504 (ITT); 503[h] (safety population)	364	71.5	

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

		sample size of 840 randomised participants (420 per group) was calculated to provide at least 80% power for declaring non-inferiority							
	total:			**1024**	**1017**	**1017**	**738**	**72.1**	
Yki-Järvinen 2006 (parallel RCT)	I: insulin glargine at bedtime + metformin	The sample size calculation was based on differences observed in a previous study between 11 insulin-naive participants treated with NPH and metformin and 12 participants treated with glargine and metformin for 1 year in Helsinki. In this study, HbA1c differed by 0.5% at the end of 1 year; the SDs for the groups were not different and averaged 0.87. The mean HbA1c change for the NPH + metformin group was −0.8 (SE 0.2%) (11 participants), and for the glargine + metformin group it was −1.3 (SE 0.3%) (12 participants) at the end of 1 year. Assuming α = 0.05 and 80% power, the required number of participants per group to observe a difference of 0.5% is 50. To allow for a 10% dropout rate, 110 participants were randomised	157/110	61	61	61	60	98.4	36 weeks
	C: NPH insulin at bedtime + metformin			49	49	49	48	98.0	
	total:			**110**	**110**	**110**	**108**	**98.2**	
Yokoyama 2006 (parallel RCT)	I: insulin glargine once at breakfast + aspart/lispro at each meal with or without OADs	—	—/—	31	—	—	—	—	6 months
	C: NPH insulin daily at bedtime + aspart/lispro at each meal with or without OADs			31	—	—	—	—	
	total:			**62**	**—**	**—**	**—**	**—**	

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

Overall total	**All interventions**	—	—
	All comparators	—	—
	All interventions and comparators	**8677**	—

— denotes not reported.

[a]Follow-up under randomised conditions until end of trial or if not available, duration of intervention; extended follow-up refers to follow-up of participants once the original study was terminated as specified in the power calculation.

[b]Modified ITT set for primary endpoint evaluation (including randomised participants with valid values for DRQoL for both treatment periods).

[c]Study prematurely discontinued.

[d]Participants with type 1 and type 2 diabetes.

[e]3 participants not randomised due to protocol violations.

[f]Safety population: 444 participants.

[g]According to European Medical Agency report.

[h]1 participant who was randomised to receive NPH insulin received insulin glargine throughout the study, and was consequently counted in the ITT population as an NPH participant, but in the safety population as an insulin glargine participant, leading to a discrepancy in the numbers for the ITT and safety populations in both the insulin glargine and NPH insulin arms.

C: comparator; CI: confidence interval; DRQoL: diabetes-related quality of life; HbA1c: glycosylated haemoglobin A1c; I: intervention; ITEQ: Insulin Therapy Experience Questionnaire; ITT: intention-to-treat; n: number of participants; NPH: neutral protamine Hagedorn; OAD: oral antihyperglycaemic drug; PAID: Problem Areas In Diabetes; RCT: randomised controlled trial; SD: standard deviation; SE: standard error; SF-12: 12-item Short Form Health Survey.

APPENDICES

Appendix 1. Checklist to aid consistency and reproducibility of GRADE assessment: insulin glargine versus NPH insulin

Insulin glargine vs NPH insulin		Diabetes-related complications *(a) Fatal myocardial infarction* *(b) Fatal stroke* *(c) Progression in retinopathy* *(d) Amputations* *(e) End-stage renal disease*	Hypoglycaemic episodes *(a) Severe hypoglycaemia* *(b) Serious hypoglycaemia* *(c) Confirmed hypoglycaemia (BG < 75 mg/dL)* *(d) Confirmed hypoglycaemia (BG < 55 mg/dL)* *(e) Confirmed nocturnal hypoglycaemia (BG < 75 mg/dL)* *(f) Confirmed nocturnal hypoglycaemia (BG < 55 mg/dL)*	Health-related quality of life	All-cause mortality	AEs other than hypoglycaemia *(a) SAE* *(b) Overall AE* *(c) AE leading to discontinuation*	Socioeconomic effects	HbA1c
Trial limitations (risk of bias)[a]	Was random sequence generation used (i.e. no potential for selection bias)?	(a) + (b) + (c) Yes (d) + (e) Unclear	Yes	Yes	Yes	Yes	NR	Yes
	Was allocation concealment used (i.e. no potential for selection bias)?	(a) + (b) + (c) Yes (d) + (e) Unclear	Yes	Yes	Yes	Yes		Yes
	Was there blinding of participants and personnel (i.e. no potential for perfor-	Unclear	No (↓) (b) Yes	No (↓)	Unclear	Unclear		Unclear

(Continued)

	mance bias) or outcome not likely to be influenced by lack of blinding?					
	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?	Unclear	No (↓) (b) Yes	No (↓)	Unclear	Unclear	Yes
	Was an objective outcome used?	Yes	Yes	Yes	Yes	Yes	Yes
	Were > 80% of participants enrolled in trials included in the analysis (i.e. no potential reporting bias)?[b]	Yes	Yes	Yes	Yes	Yes	Yes
	Were data reported consistently for the outcome of interest (i.e. no potential selective reporting)?	Yes	Yes	Yes	Yes	Yes	Yes
	No other biases reported (i.e. no potential of other bias)?	Yes	Yes	Yes	Yes	Yes	Yes
	Did the trials end up as scheduled (i.e. not stopped early)?	Yes	Yes	Yes	Yes	Yes	Yes
Inconsistency[c]	Point estimates did not vary widely?	(a) + (b) + (c) Yes (d) + (e) NA	Yes	NA	Yes	Yes	Yes
	To what extent did confidence intervals overlap (substantial: all confidence intervals overlap ≥ 1 of the included studies point estimate; some: confidence intervals overlap but not all overlap ≥ 1 point estimate; no: ≥ 1 outlier: where the confidence interval of some of the studies do not overlap with those of most included studies)?	(a) + (b) NA (c) Some (d) + (e) NA	Substantial	NA	Substantial	Substantial	Some
	Was the direction of effect consistent?	(a) + (b) + (c) Yes (d) + (e) NA	(a) + (b) No (↓) (c) + (d) + (e) + (f) Yes	Yes	No	Yes	No

(Continued)

	What was the magnitude of statistical heterogeneity (as measured by I^2) — low (I^2 < 40%), moderate (I^2 40–60%), high I^2 > 60%)?	(a) + (b) NA (c) Moderate (d) + (e) NA	(a) + (b) + (d) + (f) Low (c) High (↓) (e) Moderate	NA	Low	Low	High (↓)
	Was the test for heterogeneity statistically significant (P < 0.1)?	(a) + (b) NA (c) Statistically significant (d) + (e) NA	(a) + (b) + (d) + (f) Not statistically significant (c) + (e) Statistically significant	NA	Not statistically significant	Not statistically significant	Statistically significant
Indirectness	Were the populations in included studies applicable to the decision context?	Highly applicable	Highly applicable	Highly applicable	Highly applicable	Highly applicable	Highly applicable
	Were the interventions in the included studies applicable to the decision context?	Highly applicable	Highly applicable	Highly applicable	Highly applicable	Highly applicable	Highly applicable
	Was the included outcome not a surrogate outcome?	Yes	Yes	Yes	Yes	Yes	No
	Was the outcome timeframe sufficient?	(a) + (b) + (c) Yes (d) + (e) No (↓)	Yes	Yes	Yes	Yes	Yes
	Were the conclusions based on direct comparisons?	Yes	Yes	Yes	Yes	Yes	Yes
Imprecision[d]	Was the confidence interval for the pooled estimate not consistent with benefit and harm?	(a) + (b) NA (c) No (↓) (d) + (e) NA	(a) No (↓) (c) + (d) + (e) + (f) Yes (b) No (↓)	NA	Yes	No (↓)	No (↓)
	What is the magnitude of the median sample size (high: 300 participants, intermediate: 100–300 participants, low: < 100 participants)?[b]	(a) + (b) Intermediate (c) High (d) + (e) Low (↓)	High	High	High	High	High

(Continued)

	What was the magnitude of the number of included studies (large: > 10 studies, moderate: 5–10 studies, small: < 5 studies)?[b]	(a) + (b) Small (↓) (c) Moderate (d) + (e) Small (↓)	(a) + (b) Large (c) + (d) + (e) + (f) Moderate	Small (↓)	Large	Large	Large
	Was the outcome a common event (e.g. occurs more than 1/100)?	(a) + (b) No (↓) (c) Yes (d) + (e) No (↓)	Yes	NA	No (↓)	Yes	NA
Publication bias[e]	Was a comprehensive search conducted?	Yes	Yes	Yes	Yes	Yes	Yes
	Was grey literature searched?	Yes	Yes	Yes	Yes	Yes	Yes
	Were no restrictions applied to study selection on the basis of language?	Yes	Yes	Yes	Yes	Yes	Yes
	There was no industry influence on studies included in the review?	(a) + (b) + (c) No (↓) (d) + (e) Yes	No (↓)	No (↓)	No (↓)	No (↓)	No (↓)
	There was no evidence of funnel plot asymmetry?	NA	Yes	NA	Yes	Yes	Yes
	There was no discrepancy in findings between published and unpublished trials?	NA	NA	NA	NA	NA	NA

[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 the I^2 statistic.
[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 quality of the evidence (GRADE) as shown in the footnotes of the 'Summary of finding' table(s).

AE: adverse event; **BG:** blood glucose; **HbA1c:** glycosylated haemoglobin A1c; **NA:** not applicable; **NPH:** neutral protamine Hagedorn; **NR:** not reported; **SAE:** serious adverse event.

Appendix 2. Checklist to aid consistency and reproducibility of GRADE assessment: insulin detemir versus NPH insulin

Insulin detemir vs NPH insulin		Diabetes-related complications *(a) Fatal myocardial infarction* *(b) Fatal stroke* *(c) Progression in retinopathy* *(d) Amputations* *(e) End-stage renal disease*	Hypoglycaemic episodes *(a) Severe hypoglycaemia* *(b) Serious hypoglycaemia* *(c) Confirmed hypoglycaemia (BG < 75 mg/dL)* *(d) Confirmed hypoglycaemia (BG < 55 mg/dL)* *(e) Confirmed nocturnal hypoglycaemia (BG < 75 mg/dL)* *(f) Confirmed nocturnal hypoglycaemia (BG < 55 mg/dL)*	Health-related quality of life	All-cause mortality	AEs other than hypoglycaemia *(a) SAE* *(b) Overall AE* *(c) AE leading to discontinuation*	Socioeconomic effects	HbA1c
Trial limitations (risk of bias)[a]	Was random sequence generation used (i.e. no potential for selection bias)?	Yes	Yes	Yes	Yes	Yes	NA	Yes
	Was allocation concealment used (i.e. no potential for selection bias)?	Yes	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?	Unclear	No (↓)	No (↓)	Unclear	Unclear		Unclear

(Continued)

	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?	Unclear	No (↓)	No (↓)	Unclear	Unclear	Unclear
	Was an objective outcome used?	Yes	Yes	Yes	Yes	Yes	Yes
	Were > 80% of participants enrolled in trials included in the analysis (i.e. no potential reporting bias)?[b]	Yes	Yes	Yes	Yes	Yes	Yes
	Were data reported consistently for the outcome of interest (i.e. no potential selective reporting)?	Yes	Yes	Yes	Yes	Yes	Yes
	No other biases reported (i.e. no potential of other bias)?	Yes	Yes	Yes	Yes	Yes	Yes
	Did the trials end as scheduled (i.e. not stopped early)?	Yes	Yes	Yes	Yes	Yes	Yes
Inconsistency[c]	Point estimates did not vary widely?	(a) + (b) + (d) + (e) NA (c) Yes	Yes	NA	Yes	Yes	Yes
	To what extent did confidence intervals overlap (substantial: all confidence intervals overlap ≥ 1 of the included studies point estimate; some: confidence intervals overlap but not all overlap ≥ 1 point estimate; no: ≥ 1 outlier: where the confidence interval of some of the studies do not overlap with those of most included studies)?	(a) + (b) + (d) + (e) NA (c) Substantial	Substantial	NA	Substantial	Substantial	Some
	Was the direction of effect consistent?	(a) + (b) + (d) + (e) NA (c) Yes	Yes	Yes	No	No	No
	What was the magnitude of statistical heterogeneity (as measured by the I^2 statis-	(a) + (b) + (d) + (e) NA (c) Low	(a) + (b) + (d) + (e) + (f) Low (c) High (↓)	NA	Low	Low	High (↓)

(Continued)

	tic) — low (I^2 < 40%), moderate (I^2 = 40–60%), high I^2 > 60%)?					
	Was the test for heterogeneity statistically significant (P < 0.1)?	(a) + (b) + (d) + (e) NA (c) Not statistically significant	(a) + (b) + (d) + (e) + (f) Not statistically significant (c) Statistically significant	NA	Not statistically significant	Not statistically significant	Statistically significant
Indirectness	Were the populations in included studies applicable to the decision context?	Highly applicable	Highly applicable	Highly applicable	Highly applicable	Highly applicable	Highly applicable
	Were the interventions in the included studies applicable to the decision context?	Highly applicable	Highly applicable	Highly applicable	Highly applicable	Highly applicable	Highly applicable
	Was the included outcome not a surrogate outcome?	Yes	Yes	Yes	Yes	Yes	No
	Was the outcome timeframe sufficient?	Yes	Yes	Yes	Yes	Yes	Yes
	Were the conclusions based on direct comparisons?	Yes	Yes	Yes	Yes	Yes	Yes
Imprecision[d]	Was the confidence interval for the pooled estimate not consistent with benefit and harm?	(a) + (b) + (d) + (e) NA (c) No	(a) No (↓) (b) + (c) + (d) + (e) + (f) Yes	NA	No	(a) + (b) + (c) No (↓)	No
	What is the magnitude of the median sample size (high: 300 participants, intermediate: 100–300 participants, low: < 100 participants)?[b]	(a) + (b) + (d) + (e) Intermediate (c) High	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate
	What was the magnitude of the number of included studies (large: > 10 studies, moderate: 5–10 studies, small: < 5 studies)?[b]	Small (↓)	(a) + (b) Moderate (c) + (d) + (e) + (f) Small (↓)	Small (↓)	Moderate	Moderate	Moderate
	Was the outcome a common event (e.g. occurs more than 1/100)?	(a) + (b) + (d) + (e) No (↓)	(b) No (↓)	NA	No (↓)	Yes	NA

(Continued)

		(c) Yes	(a) + (c) + (d) + (e) + (f) Yes				
Publication bias[e]	Was a comprehensive search conducted?	Yes	Yes	Yes	Yes	Yes	Yes
	Was grey literature searched?	Yes	Yes	Yes	Yes	Yes	Yes
	Were no restrictions applied to study selection on the basis of language?	Yes	Yes	Yes	Yes	Yes	Yes
	There was no industry influence on studies included in the review?	No (↓)	No (↓)	No (↓)	No (↓)	No (↓)	No (↓)
	There was no evidence of funnel plot asymmetry?	NA	NA	NA	NA	NA	NA
	There was no discrepancy in findings between published and unpublished trials?	NA	NA	NA	NA	NA	NA

[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 the I^2 statistic.

[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 quality of the evidence (GRADE) as shown in the footnotes of the 'Summary of finding' table(s).

AE: adverse event; **BG:** blood glucose; **HbA1c:** glycosylated haemoglobin A1c; **NA:** not applicable; **NPH:** neutral protamine Hagedorn; **SAE:** serious adverse event.

Appendix 3. Search strategy (2006–2017)

Cochrane Central Register of Controlled Trials (Cochrane Register of Studies Online)
1. MESH DESCRIPTOR Insulin Glargine
2. glargin*:TI,AB,KY
3. (lantus OR basaglar OR abasaglar OR abasria OR t?ujeo OR optisulin OR soliqua OR solostar):TI,AB,KY
4. ("HOE 901" OR HOE901):TI,AB,KY
5. (gly?A21 OR A21gly* OR (gly* ADJ1 A21)):TI,AB,KY
6. (arg?B31 OR B31arg* OR (arg* ADJ1 B31)):TI,AB,KY
7. (arg?B32 OR B32?arg* OR (arg* ADJ1 B32)):TI,AB,KY
8. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9. MESH DESCRIPTOR Insulin Detemir
10. detemir*:TI,AB,KY
11. levemir*:TI,AB,KY
12. (lys?B29 OR B29lys* OR (lys* ADJ1 B29)):TI,AB,KY
13. (ala?B30 OR B30ala* OR (ala* ADJ1 B30)):TI,AB,KY
14. ("NN 304" OR NN304):TI,AB,KY
15. #9 OR #10 OR #11 OR #12 OR #13 OR #14
16. degludec:TI,AB,KY
17. (tresiba OR ryzodeg OR xultrophy):TI,AB,KY
18. (B29N* OR (29B ADJ1 N6)):TI,AB,KY
19. ("NN 1250" OR NN1250):TI,AB,KY
20. #16 OR #17 OR #18 OR #19
21. #8 OR #15 OR #20
22. MESH DESCRIPTOR Insulin, Isophane EXPLODE ALL TREES
23. (NPH OR protamine hagedorn):TI,AB,KY
24. (isophan* OR protophan* OR humulin OR novolin OR insulatard OR penfil):TI,AB,KY
25. #22 OR #23 OR #24
26. #21 AND #25
27. MESH DESCRIPTOR Diabetes Mellitus EXPLODE ALL TREES
28. diabet*:TI,AB,KY
29. (IDDM OR MODY OR NIDDM OR T1D* OR T2D*):TI,AB,KY
30. (insulin* depend* OR insulin?depend* OR noninsulin* OR noninsulin?depend*):TI,AB,KY
31. #27 OR #28 OR #29 OR #30

(Continued)

32. #26 AND #31

33. 2006 TO 2017:YR

34. #32 AND #33

MEDLINE (OvidSP)

1. Insulin Glargine/

2. glargin*.mp.

3. (lantus or basaglar or abasaglar or abasria or t?ujeo or optisulin or soliqua or solostar).mp.

4. ("HOE 901" or HOE901).mp.

5. (gly?A21 or A21gly* or (gly* adj1 A21)).mp.

6. (arg?B31 or B31arg* or (arg* adj1 B31)).mp.

7. (arg?B32 or B32?arg* or (arg* adj1 B32)).mp.

8. or/1-7

9. Insulin Detemir/

10. detemir*.mp.

11. levemir*.mp.

12. (lys?B29 or B29lys* or (lys* adj1 B29)).mp.

13. (ala?B30 or B30ala* or (ala* adj1 B30)).mp.

14. (NN 304 or NN304).mp.

15. or/9-14

16. degludec.mp.

17. (tresiba or ryzodeg or xultrophy).mp.

18. (B29N* or (29B adj1 N6)).mp.

19. (NN 1250 or NN1250).mp.

20. or/16-19

21. 8 or 15 or 20 *[long acting insulins]*

22. exp Insulin, Isophane/

23. (NPH or protamine hagedorn).mp.

24. (isophan* or protophan* or humulin or novolin or insulatard or penfil).mp.

25. or/22-24 *[NPH insulin]*

26. 21 and 25 *[long acting insulins + NPH insulin]*

27. exp Diabetes Mellitus/

28. diabet*.mp.

29. (IDDM or MODY or NIDDM or T1D* or T2D*).mp.

30. (insulin* depend* or insulin?depend* or noninsulin* or noninsulin?depend*).mp.

(Continued)

31. or/27-30 *[diabetes]*

32. 26 and 31 *[long acting insulins + NPH insulin + diabetes]*

[33-43: Cochrane Handbook 2019 RCT filter - sensitivity max version (Lefebvre 2019 *)]*

33. randomized controlled trial.pt.

34. controlled clinical trial.pt.

35. randomi?ed.ab.

36. placebo.ab.

37. drug therapy.fs.

38. randomly.ab.

39. trial.ab.

40. groups.ab.

41. or/33-40

42. exp animals/ not humans/

43. 41 not 42

44. 32 and 43 *[long acting insulins + NPH insulin + diabetes + RCTs]*

[45: Wong 2006 *– systematic reviews filter – HSens version]*

45. search*.tw. or meta analysis.mp,pt. or review.pt. or di.xs. or associated.tw.

46. 32 and 45 *[long acting insulins + NPH insulin + diabetes + MAs]*

47. 44 or 46 *[RCTs or MAs]*

48. (200609* or 20061* or 2007* or 2008* or 2009* or 201*).dc.

49. 47 and 48 *[RCTs or MAs + year limit]*

Embase (OvidSP)

1. insulin glargine/

2. glargin*.mp.

3. (lantus or basaglar or abasaglar or abasria or t?ujeo or optisulin or soliqua or solostar).mp.

4. ("HOE 901" or HOE901).mp.

5. (gly?A21 or A21gly* or (gly* adj1 A21)).mp.

6. (arg?B31 or B31arg* or (arg* adj1 B31)).mp.

7. (arg?B32 or B32?arg* or (arg* adj1 B32)).mp.

8. or/1-7

9. insulin detemir/

10. detemir*.mp.

11. levemir*.mp.

12. (lys?B29 or B29lys* or (lys* adj1 B29)).mp.

(Continued)

13. (ala?B30 or B30ala* or (ala* adj1 B30)).mp.

14. (NN 304 or NN304).mp.

15. or/9-14

16. insulin degludec/

17. degludec.mp.

18. (tresiba or ryzodeg or xultrophy).mp.

19. (B29N* or (29B adj1 N6)).mp.

20. (NN 1250 or NN1250).mp.

21. or/16-20

22. 8 or 15 or 21 *[long acting insulins]*

23. isophane insulin/

24. (NPH or protamine hagedorn).mp.

25. (isophan* or protophan* or humulin or novolin or insulatard or penfil).mp.

26. or/23-25 *[NPH insulin]*

27. 22 and 26 *[long acting insulins + NPH insulin]*

28. diabet*.tw.

29. (IDDM or MODY or NIDDM or T1D* or T2D*).mp.

30. (insulin* depend* or insulin?depend* or noninsulin* or noninsulin?depend*).mp.

31. or/28-30 *[diabetes]*

32. 27 and 31 *[long acting insulins + NPH insulin + diabetes]*

[33: Wong 2006b "sound treatment studies" filter – best sensitivity version]

33. random*.tw. or clinical trial*.mp. or exp health care quality/

34. 32 and 33 [long acting insulins + NPH insulin + diabetes + RCTs]

[35: Wong 2006 *– systematic reviews filter – sensitivity specificity balancing version]*

35. meta analysis.mp. or search*.tw. or review.pt.

36. 32 and 35 *[long acting insulins + NPH insulin + diabetes + MAs]*

37. 34 or 36 *[RCTs or MAs]*

38. (200609* or 20061* or 2007* or 2008* or 2009* or 201*).dc.

39. 37 and 38 *[RCTs or MAs + year limit]*

40. limit 39 to embase

ICTRP search portal (standard search)

glargin* AND NPH* AND diabet* OR

glargin* AND hagedorn* AND diabet* OR

detemir* AND NPH* AND diabet* OR

(Continued)

detemir* AND hagedorn* AND diabet* OR

degludec* AND NPH* AND diabet* OR

degludec* AND hagedorn* AND diabet*

ClinicalTrials.gov (expert search)

((glargine OR lantus OR basaglar OR abasaglar OR abasria OR toujeo OR optisulin OR soliqua OR solostar OR "HOE 901" OR HOE901 OR detemir OR levemir OR "NN 304" OR NN304 OR degludec OR tresiba OR ryzodeg OR xultrophy OR "NN 1250" OR NN1250) AND (NPH OR "protamine hagedorn" OR isophane OR protophane OR humulin OR novolin OR insulatard OR penfil)) [TREATMENT] AND EXACT "Interventional" [STUDY-TYPES] AND (diabetes OR diabetic OR IDDM OR MODY OR NIDDM OR T1DM OR T2DM OR T1D OR T2D) [DISEASE]

Appendix 4. Search strategy (2017–2019)

Cochrane Central Register of Controlled Trials (Cochrane Register of Studies Online)

1. MESH DESCRIPTOR Insulin Glargine

2. glargin*:TI,AB,KY

3. ("2ZM8CX04RZ" OR "160337-95-1"):TI,AB,KY

4. (lantus* or basaglar* or abasaglar* or abasria* or t?ujeo* or optisulin* or suliqua* or soliqua* or solostar* or lusduna* or nexvue* or basalin* or bonglixan* or basalog* or vibrenta* or glaritus* or basagin* or glarine* or semglee*):TI,AB,KY

5. ("HOE 901" or HOE901 or "HOE 71GT" or "HOE71GT" or "LY 2963016"):TI,AB,KY

6. (gly?A21 OR A21gly* OR (gly* ADJ1 A21)):TI,AB,KY

7. (arg?B31 OR B31arg* OR (arg* ADJ1 B31)):TI,AB,KY

8. (arg?B32 OR B32?arg* OR (arg* ADJ1 B32)):TI,AB,KY

9. ("MK-1293" or "MK1293"):TI,AB,KY

10. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9

11. MESH DESCRIPTOR Insulin Detemir

12. detemir*:TI,AB,KY

13. ("169148-63-4" or "4FT78T86XV"):TI,AB,KY

14. levemir*:TI,AB,KY

15. (lys?B29 OR B29lys* OR (lys* ADJ1 B29)):TI,AB,KY

16. (ala?B30 OR B30ala* OR (ala* ADJ1 B30)):TI,AB,KY

17. ("NN 304" OR NN304):TI,AB,KY

18. #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17

19. degludec:TI,AB,KY

20. ("844439-96-9" or "54Q18076QB"):TI,AB,KY

21. (tresiba OR ryzodeg OR xultrophy):TI,AB,KY

(Continued)

22. (B29N* OR (29B ADJ1 N6)):TI,AB,KY

23. ("NN 1250" OR NN1250):TI,AB,KY

24. #19 OR #20 OR #21 OR #22 OR #23

25. #10 OR #18 OR #24

26. MESH DESCRIPTOR Diabetes Mellitus EXPLODE ALL TREES

27. diabet*:TI,AB,KY

28. (IDDM OR MODY OR NIDDM OR T1D* OR T2D*):TI,AB,KY

29. #26 OR #27 OR #28

30. #25 AND #29

MEDLINE (OvidSP)

[Glargine insulin and biosimilars]

1. Insulin Glargine/

2. glargin*.mp.

3. ("2ZM8CX04RZ" or "160337-95-1").mp.

4. (lantus* or basaglar* or abasaglar* or abasria* or t?ujeo* or optisulin* or suliqua* or soliqua* or solostar* or lusduna* or nexvue* or basalin* or bonglixan* or basalog* or vibrenta* or glaritus* or basagin* or glarine* or semglee*).mp.

5. ("HOE 901" or HOE901 or "HOE 71GT" or "HOE71GT" or "LY 2963016").mp.

6. (gly?A21 or A21gly* or (gly* adj1 A21)).mp.

7. (arg?B31 or B31arg* or (arg* adj1 B31)).mp.

8. (arg?B32 or B32?arg* or (arg* adj1 B32)).mp.

9. ("MK-1293" or "MK1293").mp.

10. or/1-9

[Detemir insulin]

11. Insulin Detemir/

12. detemir*.mp.

13. ("169148-63-4" or "4FT78T86XV").mp.

14. levemir*.mp.

15. (lys?B29 or B29lys* or (lys* adj1 B29)).mp.

16. (ala?B30 or B30ala* or (ala* adj1 B30)).mp.

17. (NN 304 or NN304).mp.

18. or/11-17

[Degludec insulin]

19. degludec*.mp.

20. ("844439-96-9" or "54Q18076QB").mp.

(Continued)

21. (tresiba* or ryzodeg or xultrophy).mp.

22. (B29N* or (29B adj1 N6)).mp.

23. (NN 1250 or NN1250).mp.

24. or/19-23

[all insulins]

25. 10 or 18 or 24

[diabetes]

26. exp Diabetes Mellitus/

27. diabet*.mp.

28. (IDDM or T1D* or NIDDM or T2D* or MODY).tw.

29. or/26-28

30. 25 and 29

[31-41: Cochrane Handbook 2019 RCT filter - sensitivity max version (Lefebvre 2019 *)]*

31. randomized controlled trial.pt.

32. controlled clinical trial.pt.

33. randomi?ed.ab.

34. placebo.ab.

35. drug therapy.fs.

36. randomly.ab.

37. trial.ab.

38. groups.ab.

39. or/31-38

40. exp animals/ not humans/

41. 39 not 40

[42-44: phase 3 study filter (Cooper 2019 *)]*

42. Clinical Trial, Phase III/

43. ("phase 3" or "phase3" or p3 or "pIII").ti,ab,kw.

44. 42 or 43

45. 41 or 44

[long acting insulins + diabetes + RCTs]

46. 30 and 45

ICTRP search portal (standard search)

glargine AND diabet* OR

levemir AND diabet* OR

(Continued)

detemir AND diabet* OR

degludec AND diabet*

ClinicalTrials.gov (expert search)

(glargine OR lantus OR basaglar OR abasaglar OR abasria OR toujeo OR tujeo OR optisulin OR soliqua OR suliqua OR solostar OR lusduna OR nexvue OR basalin OR bonglixan OR basalog OR vibrenta OR glaritus OR basagin OR glarine OR semglee OR "HOE 901" OR HOE901 OR "HOE 71GT" OR HOE71GT OR "LY 2963016" OR MK-1293 OR MK1293 OR detemir OR levemir OR "NN 304" OR NN304 OR degludec OR tresiba OR ryzodeg OR xultrophy OR "NN 1250" OR NN1250) [TREATMENT] AND EXACT "Interventional" [STUDY-TYPES] AND (diabetes OR diabetic OR IDDM OR MODY OR NIDDM OR T1DM OR T2DM OR T1D OR T2D) [DISEASE]

Note: restriction to publication year 2017 onwards was carried out manually in reference management software.

Appendix 5. 'Risk of bias' assessment

'Risk of bias' domains

Random sequence generation (selection bias due to inadequate generation of a randomised sequence)

For each included study, we described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

- Low risk of bias: study authors achieved sequence generation using computer-generated random numbers or a random numbers table. Drawing of lots, tossing a coin, shuffling cards or envelopes, and throwing dice are adequate if an independent person performed this who was not otherwise involved in the study. 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).

Allocation concealment (selection bias due to inadequate concealment of allocation prior to assignment)

We described for each included study 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: used an open random allocation schedule (e.g. a list of random numbers); assignment envelopes used without appropriate safeguards; alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

We also evaluated study baseline data to incorporate assessment of baseline imbalance into the 'Risk of bias' judgement for selection bias (Corbett 2014).

Chance imbalances may also affect judgements on the risk of attrition bias. In the case of unadjusted analyses, we distinguished between studies that we rate as being at low risk of bias on the basis of both randomisation methods and baseline similarity, and studies that we judge as being at low risk of bias on the basis of baseline similarity alone (Corbett 2014). We reclassified judgements of unclear, low, or high risk of selection bias as specified in Appendix 6.

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

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 (see below).

(Continued)

- 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 judge that the outcome is unlikely to have been influenced by lack of blinding.
- Unclear risk of bias: insufficient information about the blinding of participants and study personnel; the study does not address this outcome.
- High risk of bias: no blinding or incomplete blinding, and the outcome is likely to have been influenced by lack of blinding; blinding of study participants and key personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.

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 (see below).

- Low risk of bias: blinding of outcome assessment is ensured, and it is unlikely that the blinding could have been broken; no blinding of outcome assessment, but we judge that the outcome measurement is unlikely to have been influenced by lack of blinding.
- Unclear risk of bias: insufficient information about the blinding of outcome assessors; the study 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.

Incomplete outcome data (attrition bias due to quantity, nature or handling of incomplete outcome data)

For each included study or each outcome, or both, we described the completeness of data, including attrition and exclusions from the analyses. We stated whether the study reported attrition and exclusions, and we reported the number of participants included in the analysis at each stage (compared with the number of randomised participants per intervention/comparator groups). We also noted if the study 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 study 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 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 study 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 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 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.

Selective reporting (reporting bias due to selective outcome reporting)

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

- Low risk of bias: the study protocol was available and all the study's prespecified (primary and secondary) outcomes that were of interest to this review were reported in the prespecified 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 the study's prespecified 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 prespecified; one or more reported primary outcomes were not prespecified (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 cannot enter them into a meta-analysis; the study report failed to include results for a key outcome that we would expect to have been reported for such a study (ORBIT classification).

(Continued)

Other bias

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

Appendix 6. Selection bias decisions

Selection bias decisions for trials reporting 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	Risk of bias using baseline information and methods reporting
Unclear methods	Unclear risk	Baseline imbalances present in important prognostic variable(s)	**High risk**
		Groups appear similar at baseline in 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 in important prognostic variable(s)	**Unclear risk[b]**
		Groups appear similar at baseline in 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 random, or allocation concealment is inadequate	High risk	Baseline imbalances present in important prognostic variable(s)	High risk
		Groups appear similar at baseline in 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 which appears likely to be due to chance.
[c]Details for the remaining important prognostic variables not reported.

Appendix 7. Description of interventions

Trial ID	Intervention(s) (route, frequency, total dose/day)	Intervention(s) appropriate as applied in a clinical practice setting[a] (description)	Comparator(s) (route, frequency, total dose/day)	Comparator(s) appropriate as applied in a clinical practice setting[a] (description)
Berard 2015	Insulin glargine once daily in the evening ± OAD or short-acting insulins (or both).	Target BG levels unclear.	NPH insulin once (in the evening) or twice daily (in the morning and evening) ± OAD or short-acting insulins (or both).	Target BG levels unclear.
Eliaschewitz 2006	Glimepiride 4 mg/day, oral, once in the morning + subcutaneous insulin glargine 100 IU once at bedtime. The glimepiride dose was kept stable throughout the study and insulin doses were titrated during the first 6 weeks of treatment using a predefined titration regimen or the investigator's own regimen to achieve a target FBG concentration of ≤ 100 mg/dL.	Target BG levels were low and not adjusted individually,	Glimepiride 4 mg/day, oral, once in the morning + subcutaneous NPH insulin once at bedtime. The glimepiride dose was kept stable throughout the study and insulin doses were titrated during the first 6 weeks of treatment using a predefined titration regimen or the investigator's own regimen to achieve a target FBG concentration of ≤ 100 mg/dL.	According to the summary of product characteristics and to common clinical practice, the frequency of daily NPH injections should be adapted as needed to achieve targeted BG levels. Thus, limiting NPH administration to a single daily injection does not seem to be appropriate. Targeted BG levels were low and not adjusted individually.
Fajardo Montañana 2008	Insulin detemir at bedtime + insulin aspart at mealtimes ± metformin 1000–2250 g (unchanged dose throughout the trial). Starting doses insulin detemir/aspart: 40/60% of total daily doses before trial start. Titration targets insulin detemir: prebreakfast PG ≤ 6.1 mmol/L (110 mg/dL) without levels of hypoglycaemia unacceptable to the participant. Titration target insulin aspart: 90-minute PPG ≤ 10.0 mmol/L (180 mg/dL).	Target BG levels were low and not adjusted individually. According to the summary of product characteristics, the frequency of insulin detemir injections should be adopted to twice daily if necessary when given with rapid-acting insulins at mealtime.	NPH insulin at bedtime + insulin aspart at mealtimes ± metformin 1000–2250 g (unchanged dose throughout the trial). Starting doses NPH insulin/aspart: 40/60% of total daily doses before trial start. Titration targets NPH insulin: prebreakfast PG ≤ 6.1 mmol/L (110 mg/dL) without levels of hypoglycaemia unacceptable to the participant. Titration target insulin aspart: 90-minute PPG ≤ 10.0 mmol/L (180 mg/dL).	According to the summary of product characteristics and to common clinical practice, the frequency of daily NPH injections should be adapted as needed to achieve targeted BG levels. Thus, limiting NPH administration to a single daily injection does not seem to be appropriate. Target BG levels were low and not adjusted individually.
Fritsche 2003	I1: insulin glargine once daily subcutaneously in the morning + glimepiride 3 mg.	Target BG levels were low and not adjusted individually.	NPH insulin once daily subcutaneously at bedtime + glimepiride 3 mg.	According to the summary of product characteristics and to common clin-

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	I2: insulin glargine once daily subcutaneously at bedtime + glimepiride 3 mg. The insulin dose for the first day of the treatment phase was calculated according to the formula of Holman and Turner. During the treatment phase, the insulin dose was titrated every visit by using a predefined regimen (target FBG concentration ≤ 100 mg/dL). Doses of glimepiride remained unchanged throughout the study.		The insulin dose for the first day of the treatment phase was calculated according to the formula of Holman and Turner. During the treatment phase, the insulin dose was titrated every visit by using a predefined regimen (target FBG concentration ≤ 100 mg/dL). Doses of glimepiride remained unchanged throughout the study.	ical practice, the frequency of daily NPH injections should be adapted as needed to achieve targeted BG levels. Thus, limiting NPH administration to a single daily injection does not seem to be appropriate. Targeted BG levels were low and not adjusted individually.
Haak 2005	Detemir once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart. Titration targets: prebreakfast < 4–7 mmol/L (72–126 mg/dL), nocturnal < 4–7 mmol/L (72–126 mg/dL), 90 minutes postprandial < 10 mmol/L (180 mg/dL).	Target BG levels were low and not adjusted individually.	NPH insulin once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart. Titration targets: prebreakfast < 4–7 mmol/L (72–126 mg/dL), nocturnal < 4–7 mmol/L (72–126 mg/dL), 90 minutes postprandial < 10 mmol/L (180 mg/dL).	Target BG levels were low and not adjusted individually.
Hermanns 2015	(Sequence A, period 1; sequence B, period 2): insulin glargine by subcutaneous injection once daily (at any time, but each day at the same time); maximum of 2 OHAs (metformin, sulphonylurea or DPP-IV inhibitors), dosage remained stable during the study period; prandial short-acting insulin if PPG > 11.1 mmol/L on 2 consecutive visits.	Target BG levels unclear.	(Sequence A, period 2; sequence B, period 1): NPH basal insulin once-daily at bedtime (21:00–23:00) or if the NPH dose was exceeding 30 IU or nocturnal hypoglycaemia occurred (or both), the NPH dose was split into 2 doses with the second dose applied in the morning (07:00–09:00); maximum of 2 OHAs (metformin, sulphonylurea, or DPP-IV inhibitors), dosage remained stable during the study period. prandial short-acting insulin if PPG > 11.1 mmol/L on 2 consecutive visits.	Target BG levels unclear.
Hermansen 2006	Insulin detemir twice daily in the morning and evening + pre-existing OAD-treatment (metformin, insulin secretagogues, alpha-glucosidase inhibitors) in unchanged dosage. Titration BG target: prebreakfast and predinner BG ≤ 6.0 mmol/L (≤ 108 mg/dL) throughout the trial; titration was done according to a prespecified algorithm.	Target BG levels were low and not adjusted individually.	NPH insulin twice daily in the morning and evening + pre-existing OAD treatment (metformin, insulin secretagogues, alpha-glucosidase inhibitors) in unchanged dosage. Titration BG-target: prebreakfast and predinner BG ≤ 6.0 mmol/L (≤ 108 mg/dL) throughout the trial; titration was done according to a prespecified algorithm.	Target BG levels were low and not adjusted individually.
Home 2015	Insulin glargine, to be given once daily in the evening between	Target BG levels were low and not	NPH insulin, to be given once daily in the evening between	According to the summary of prod-

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	20:00 and 22:00 hours; the recommended starting insulin dose was 0.2 U/kg; systematic dose-titration regimen based on both prebreakfast (FPG) and nocturnal SMPG levels, with a goal of 4.4–5.5 mmol/L at both times; insulin dose was to be adjusted weekly during weeks 1–4, twice weekly during weeks 5–12, and then weekly up to week 36; the median of the last 3 prebreakfast glucose measurements (unless 1 value was ≤ 4.4 mmol/L) was used for dose titration, together with the last nocturnal glucose measurement; a measurement < 4.4 mmol/L at either time called for reduction of insulin by 2 U; additionally if prebreakfast glucose was < 2.8 mmol/L the dose was to be decreased by 2 U and remain at the lower dose for 1, 2 or 3 weeks, depending if this was the first, second or third such occurrence; in the event of severe hypoglycaemia or HbA1c ≤ 6.0% (42 mmol/mol), no insulin dose increase was allowed for the remainder of the study; an international dose-titration committee reviewed SMPG values and insulin doses on an ongoing basis via a website and the study investigators were contacted by e-mail if titration was inadequate; additional glimepiride 2 mg once daily, or less if this was not tolerated; same metformin dose as before trial.	adjusted individually.	20:00 and 22:00 hours; the recommended starting insulin dose was 0.2 U/kg; systematic dose-titration regimen based on both prebreakfast (FPG) and nocturnal SMPG levels, with a goal of 4.4–5.5 mmol/L at both times; insulin dose was to be adjusted weekly during weeks 1–4, twice weekly during weeks 5–12, and then weekly up to week 36; the median of the last 3 prebreakfast glucose measurements (unless 1 value was ≤ 4.4 mmol/L) was used for dose titration, together with the last nocturnal glucose measurement; a measurement < 4.4 mmol/L at either time called for reduction of insulin by 2 U; additionally if prebreakfast glucose was < 2.8 mmol/L the dose was to be decreased by 2 U and remain at the lower dose for 1, 2 or 3 weeks, depending if this was the first, second or third such occurrence; in the event of severe hypoglycaemia or HbA1c ≤ 6.0% (42 mmol/mol) no insulin dose increase was allowed for the remainder of the study; an international dose-titration committee reviewed SMPG values and insulin doses on an ongoing basis via a website and the study investigators were contacted by e-mail if titration was inadequate; additional glimepiride 2 mg once daily, or less if this was not tolerated; same metformin dose as before trial.	uct characteristics and to common clinical practice, the frequency of daily NPH injections should be adapted as needed to achieve targeted BG levels. Thus, limiting NPH administration to a single daily injection does not seem to be appropriate. Targeted BG levels were low and not adjusted individually.
Hsia 2011	I1: insulin glargine at bedtime + OAD (maintained at constant dosages throughout the entire 26-week trial). Titration: 8-week dose titration phase; 50% of fasting glucose readings < 120 mg/dL. I2: insulin glargine in the morning + OAD (maintained at constant dosages throughout the entire 26-week trial). Titration: 8-week dose titration phase; 50% of fasting glucose readings < 120 mg/dL.	Target BG levels were low and not adjusted individually.	NPH insulin at bedtime + OAD (maintained at constant dosages throughout the entire 26-week trial). Titration: 8-week dose titration phase; 50% of fasting glucose readings < 120 mg/dL.	According to the summary of product characteristics and to common clinical practice, the frequency of daily NPH injections should be adapted as needed to achieve targeted BG levels. Thus, limiting NPH administration to a single daily injection does not seem to be appropriate. Targeted BG levels were low

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				and not adjusted individually.
Kawamori 2003	Insulin glargine once daily subcutaneously in the morning before breakfast + pre-existing OAD treatment (sulphonylurea monotherapy or in combination with α-glucosidase inhibitors, metformin or both), type of medication was unchanged, but change of dosage was possible during the study; training in dietary- and exercise-therapy. Titration BG target: prebreakfast 80–140 mg/dL throughout the trial; titration was done by a prespecified algorithm.	Yes	NPH insulin once daily subcutaneously in the morning before breakfast + pre-existing OAD-treatment (sulphonylurea monotherapy or in combination with α-glucosidase inhibitors, metformin or both), type of medication was unchanged, but change of dosage was possible during the study; training in dietary- and exercise-therapy. Titration BG target: prebreakfast 80–140 mg/dL throughout the trial; titration was done by a prespecified algorithm.	According to the summary of product characteristics and to common clinical practice, the frequency of daily NPH injections should be adapted as needed to achieve targeted BG levels. Thus, limiting NPH administration to a single daily injection does not seem to be appropriate.
Kobayashi 2007 A	Insulin detemir subcutaneously once daily at bedtime or twice daily at breakfast and at bedtime + insulin aspart as bolus insulin subcutaneously 3 times a day before every meal, by the same method and at the same dose as in the previous therapy. Initial detemir dose was approximately 70% of the basal insulin dose of the previous therapy. After starting administration, the dose was regulated for each individual participant on considering the blood sugar control including hypoglycaemia, and adverse event onset, with an HbA1c < 5.8%, a fasting blood sugar level < 100 mg/dL, and a blood sugar level < 120 mg/dL 2 hours after a meal as the therapy goal; 4 weeks after starting administration, the dose was optimised, mainly by adjusting the basal insulin dose, keeping the bolus insulin dose unaltered as a rule.	Target BG levels were low and not adjusted individually.	NPH insulin subcutaneously once daily at bedtime or twice daily at breakfast and at bedtime + insulin aspart as bolus insulin subcutaneously 3 times a day before every meal, by the same method and at the same dose as in the previous therapy. Initial NPH dose was the same as the basal insulin dose of the previous therapy. After starting administration, the dose was regulated for each individual participant on considering the blood sugar control including hypoglycaemia, and adverse event onset, with an HbA1c < 5.8%, a fasting blood sugar level < 100 mg/dL, and a blood sugar level of < 120 mg/dL 2 hours after a meal as the therapy goal; 4 weeks after starting administration, the dose was optimised, mainly by adjusting the basal insulin dose, keeping the bolus insulin dose unaltered as a rule.	Target BG levels were low and not adjusted individually.
Kobayashi 2007 B	Insulin detemir at bedtime + OAD (stable dose throughout trial). Titration target: FPG ≤ 119 mg/dL and 2-hour PPG ≤ 169 mg/dL (HbA1c ≤ 6.4%).	Target BG levels were low and not adjusted individually.	NPH insulin at bedtime + OAD (stable dose throughout the trial). Titration target: FPG ≤ 119 mg/dL and 2-hour PPG ≤ 169 mg/dL (HbA1c ≤ 6.4%).	According to the summary of product characteristics and to common clinical practice, the frequency of daily NPH injections should be adapted as needed to achieve targeted BG levels. Thus, lim-

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				iting NPH administration to a single daily injection does not seem to be appropriate. Target BG levels were low and not adjusted individually.
Massi 2003	Insulin glargine once daily subcutaneously at bedtime + previous oral antihyperglycaemic agents continued. The insulin dose was titrated according to self-monitored FBG. The optimal dose was defined by a target FBG level of 6.66 mmol/L over ≥ 2 – 4 days in absence of nocturnal hypoglycaemia. The starting insulin dose was calculated by the investigator based on bodyweight and FBG concentrations.	Target BG levels were low and not adjusted individually.	NPH insulin once daily subcutaneously at bedtime + previous oral antihyperglycaemic agents continued. The insulin dose was titrated according to self-monitored FBG. The optimal dose was defined by a target FBG level of 6.66 mmol/L over ≥ 2 – 4 days in absence of nocturnal hypoglycaemia. The starting insulin dose was calculated by the investigator based on bodyweight and FBG concentrations.	According to the summary of product characteristics and to common clinical practice, the frequency of daily NPH injections should be adapted as needed to achieve targeted BG levels. Thus, limiting NPH administration to a single daily injection does not seem to be appropriate. Target BG levels were low and not adjusted individually.
NCT00687453	Insulin glargine at bedtime titrated to morning fasting glucose readings + OAD.	Target BG levels unclear.	NPH insulin in the morning and at bedtime titrated to pre-supper and fasting glucose readings, respectively + OAD.	Target BG levels unclear.
NN304-1337	Insulin detemir once daily at bedtime + metformin in maximum clinical effective or maximum tolerated dose titration target FBG ≤ 72–126 mg/dL.	Target BG levels were low and not adjusted individually.	NPH insulin once daily at bedtime + metformin in maximum clinical effective or maximum tolerated dose titration target FBG ≤ 72–126 mg/dL.	According to the summary of product characteristics and to common clinical practice, the frequency of daily NPH injections should be adapted as needed to achieve targeted BG levels. Thus, limiting NPH administration to a single daily injection does not seem to be appropriate. Target BG levels were low and not adjusted individually.
NN304-1808	Insulin detemir at individually adjusted dose subcutaneously once daily before breakfast; continuation of pre-existing metformin at optimal dose possible. Other OADs were discontinued at or before randomisation.	Target BG levels unclear.	NPH insulin at individually adjusted dose subcutaneously once daily before breakfast; continuation of pre-existing metformin at optimal dose possible. Other OADs were discontinued at or before randomisation.	According to the summary of product characteristics and to common clinical practice, the frequency of daily NPH injections should be adapted as needed

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	1-month intensive titration phase; titration according to PG levels (titration target not reported).		1-month intensive titration phase; titration according to PG levels (titration target not reported).	to achieve targeted BG levels. Thus, limiting NPH administration to a single daily injection does not seem to be appropriate. Target BG levels unclear.
NN304-3614	Insulin detemir subcutaneously in the evening in combination with insulin aspart subcutaneously as mealtime insulin. Titration target not reported.	Target BG levels unclear. According to the summary of product characteristics, the frequency of insulin detemir injections should be adopted to twice daily if necessary when given with rapid-acting insulins at mealtime.	NPH insulin subcutaneously in the evening in combination with insulin aspart subcutaneously as mealtime insulin. Titration target not reported.	According to the summary of product characteristics and to common clinical practice, the frequency of daily NPH injections should be adapted as needed to achieve targeted BG levels. Thus, limiting NPH administration to a single daily injection does not seem to be appropriate. Target BG levels unclear.
Pan 2007	Insulin glargine subcutaneously once daily in the evening + glimepiride 3 mg orally in the morning; titration target: FPG ≤ 6.7 mmol/L (120 mg/dL); insulin starting doses: 0.15 IU/kg/day; upward titration: 2 IU every 3 days.	Target BG levels were low and not adjusted individually.	NPH insulin subcutaneously once daily in the evening + glimepiride 3 mg orally in the morning; titration target: FPG ≤ 6.7 mmol/L (120 mg/dL); insulin starting doses: 0.15 IU/kg/day; upward titration: 2 IU every 3 days.	According to the summary of product characteristics and to common clinical practice, the frequency of daily NPH injections should be adapted as needed to achieve targeted BG levels. Thus, limiting NPH administration to a single daily injection does not seem to be appropriate. Target BG levels were low and not adjusted individually.
Betônico 2019	Insulin glargine subcutaneously in the morning + insulin lispro subcutaneously at mealtime. Glargine: initially 80% of the total daily dose of NPH before study begin; dose titration: nocturnal and prebreakfast SMBG < 6.6 mmol/L (120 mg/dL) Lispro dose titration: postmeal (breakfast, lunch, dinner) SMBG < 10.0 mmol/L (180 mg/dL).	Target BG levels were low and not adjusted individually.	NPH insulin subcutaneously 1–3 times daily + insulin lispro subcutaneously at mealtime. NPH insulin: initially participants received the same dose as before study begin; dose titration: premeal (breakfast, lunch, dinner) SMBG < 6.6 mmol/L (120 mg/dL). Lispro dose titration: meal (breakfast, lunch, dinner) SMBG < 10.0 mmol/L (180 mg/dL).	Target BG levels were low and not adjusted individually.

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Riddle 2003	Insulin glargine once daily subcutaneously at bedtime + OAD (sulphonylureas, metformin, glitazones) continued at prestudy dosages. No dietary advice. The starting dose was 10 IU, and dosage was titrated weekly according to daily self-monitored capillary FBG measurements using meters (Accu-Chek Advantage; Roche Diagnostics) that provide values corresponding closely to laboratory measurements of PG. A forced titration schedule was used, seeking a target FPG of ≤ 100 mg/dL (≤ 5.6 mmol/L).	Target BG levels were low and not adjusted individually.	NPH insulin once daily subcutaneously at bedtime + OAD (sulphonylureas, metformin, glitazones) continued at prestudy dosages. No dietary advice. The starting dose was 10 IU, and dosage was titrated weekly according to daily self-monitored capillary FBG measurements using meters (Accu-Chek Advantage; Roche Diagnostics) that provide values corresponding closely to laboratory measurements of PG. A forced titration schedule was used, seeking a target FPG of ≤ 100 mg/dL (≤ 5.6 mmol/L).	According to the summary of product characteristics and to common clinical practice, the frequency of daily NPH injections should be adapted as needed to achieve targeted BG levels. Thus, limiting NPH administration to a single daily injection does not seem to be appropriate. Target BG levels were low and not adjusted individually.
Rosenstock 2001	Insulin glargine once daily subcutaneously at bedtime + continuation of premeal regular insulin as indicated. Participants previously using twice-daily NPH were advised to reduce insulin glargine dosage 10% compared with total NPH dosage. Thereafter, insulin doses were individually titrated based on a target FPG of 4.4–7.8 mmol/L. Evening doses were increased if FPG was ≥ 10.0 mmol/L on 3 consecutive measurements unless nocturnal hypoglycaemia had occurred.	Target BG levels were low.	NPH once at bedtime or twice daily in the morning or at bedtime subcutaneously, depending on prior treatment + continuation of premeal regular insulin as indicated. Insulin doses were individually titrated based on a target FPG of 4.4–7.8 mmol/L. Evening doses were increased if FPG was ≥ 10.0 mmol/L on 3 consecutive measurements unless nocturnal. hypoglycaemia had occurred. Targets for use of regular insulin were premeal BG 4.4–7.8 mmol/L and bedtime BG 6.7–10.0 mmol/L.	Target BG levels were low.
Rosenstock 2009	Open-label insulin glargine once daily, generally at bedtime; insulin doses were titrated over the first 3 years of the study with the aim of achieving FPG levels of ≤ 6.7 mmol/L (120 mg/dL) and the aim of ≤ 5.5 mmol/L (100 mg/dL) for the last 2 years of the study; OHAs or prandial insulin doses (or both) taken at baseline could be continued or modified during the trial and human regular insulin could be added with meals even if not used at baseline at the investigator's discretion.	Target BG levels were low and not adjusted individually.	Open-label NPH insulin twice daily, generally in the morning and at bedtime; insulin doses were titrated over the first 3 years of the study with the aim of achieving FPG levels of ≤ 6.7 mmol/L (120 mg/dL) and the aim of ≤ 5.5 mmol/L (100 mg/dL) for the last 2 years of the study; OHAs or prandial insulin (or both) doses taken at baseline could be continued or modified during the trial and human regular insulin could be added with meals even if not used at baseline at the investigator's discretion.	Target BG levels were low and not adjusted individually.

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Yki-Järvinen 2006	Insulin glargine (subcutaneous, individually titrated, once at bedtime) + metformin (oral, dose unclear (abstract 2 g), frequency unclear). The initial bedtime insulin dose was 10 IU for all participants who were using metformin alone, and 20 IU if the participants had used both sulphonylurea and metformin and sulphonylurea was stopped as was mandated by the study design. The goal was to achieve an FPG of 4.0–5.5 mmol/L (72–100 mg/dL) in both groups. The participants were taught to increase their insulin dose by 2 IU if FPG > 5.5 mmol/L (100 mg/dL), and by 4 IU if FPG > 10 mmol/L (180 mg/dL) on 3 consecutive mornings.	Target BG levels were low and not adjusted individually.	NPH insulin (subcutaneous, individually titrated, once at bedtime) + metformin (oral, dose unclear (abstract 2 g), frequency unclear). The initial bedtime insulin dose was 10 IU for all participants who were using metformin alone, and 20 IU if the participants had used both sulphonylurea and metformin and sulphonylurea was stopped as was mandated by the study design. The goal was to achieve an FPG of 4.0–5.5 mmol/L (72–100 mg/dL) in both groups. The participants were taught to increase their insulin dose by 2 IU if FPG > 5.5 mmol/L (100 mg/dL), and by 4 IU if FPG > 10 mmol/L (180 mg/dL) on 3 consecutive mornings.	According to the summary of product characteristics and to common clinical practice, the frequency of daily NPH injections should be adapted as needed to achieve targeted BG levels. Thus, limiting NPH administration to a single daily injection does not seem to be appropriate. Target BG levels were low and not adjusted individually.
Yokoyama 2006	Insulin glargine at breakfast, subcutaneous (total dose should be 50% of the total daily insulin dose, once) + mealtime aspart/lispro subcutaneous (individually titrated, at each meal); additional treatment with oral antihyperglycaemic agents was possible (oral, dose unclear, frequency unclear). The dose of insulin glargine was increased by 2–4 U, if necessary, to meet the target FBG. When the dose was increased, mealtime rapid-acting insulin analogue was recommended to be reduced by 1–2 U to avoid postprandial hypoglycaemia. The total daily dose of insulin was principally unchanged.	Target BG levels unclear.	NPH insulin at bedtime, subcutaneous + mealtime aspart/lispro, subcutaneous, (individually titrated, at each meal); additional treatment with oral antihyperglycaemic agents was possible (oral, dose unclear, frequency unclear). The dose of NPH insulin was principally left unchanged.	According to the summary of product characteristics and to common clinical practice, the frequency of daily NPH injections should be adapted as needed to achieve targeted BG levels. Thus, limiting NPH administration to a single daily injection does not seem to be appropriate. Target BG levels unclear. No adjustment of NPH dosage allowed.

— denotes not reported.

[a]The term 'clinical practice setting' refers to the specification of the intervention/comparator as used in the course of a standard medical treatment (such as dose, dose escalation, dosing scheme, provision for contraindications and other important features).

BG: blood glucose; **C:** comparator; **DPP:** dipeptidyl peptidase; **FBG:** fasting blood glucose; **HbA1c:** glycosylated haemoglobin A1c; **I:** intervention; **IU:** international unit; **NPH:** neutral protamine Hagedorn; **OAD:** oral antihyperglycaemic drug; **PG:** plasma(-referenced) glucose; **PPG:** postprandial blood glucose; **SMBG:** self-monitoring of blood glucose; **SMPG:** self-monitored plasma glucose.

Appendix 8. Baseline characteristics (I)

Trial ID	Intervention(s) and comparator(s)	Duration of intervention/duration of follow-up	Description of participants	Trial period	Country	Setting	Ethnic groups (%)	Duration of type 2 diabetes (mean/range years (SD))	Pharmaco-naive participants (%)
Berard 2015	I: insulin glargine once daily	6 months	Type 2 diabetes mellitus; participants in the ACCORD trial who were receiving basal insulin therapy with a long-acting insulin analogue	—	Canada	Winnipeg ACCORD trial centre	—	—	0
	C: NPH insulin once or twice daily						—	—	0
Eliaschewitz 2006	I: insulin glargine at bedtime + glimepiride 4 mg/day in the morning	24 weeks/24 weeks	People with type 2 diabetes poorly controlled on OADs	—	10 Central and South American countries	—	White: 43.7 Black: 5.2 Asian/Oriental: 1.3 Multiracial: 43.3 Hispanic: 6.5 Other: 0	10.3 (6.4)	0
	C: NPH insulin at bedtime + glimepiride 4 mg/day in the morning						White: 48.4 Black: 2.8 Asian/Oriental: 0 Multiracial: 43.2	10.8 (6.4)	0

(Continued)

							Hispanic: 5.2 Other: 0.4		
Fajardo Montañana 2008	I: insulin detemir at bedtime	26 weeks	Type 2 diabetes mellitus; overweight or obese	2005–2006	Spain	—	White: 99 Hispanic: 1 Asian/Pacific Islander: 0	16.2 (8.7)	0
	C: NPH insulin at bedtime						White: 99 Hispanic: 0 Asian/Pacific Islander: 1	16.4 (7.4)	0
Fritsche 2003	I1: insulin glargine in the morning + glimepiride 3 mg	24 weeks/24 weeks	People with type 2 diabetes mellitus, who did not achieve good metabolic control while receiving oral antidiabetic drugs	2000–2001	Europe	—	—	11 (7)	0
	I2: insulin glargine at bedtime + glimepiride 3 mg						—	10 (7)	0
	C: NPH insulin at bedtime + glimepiride 3 mg						—	10 (6)	0
Haak 2005	I: detemir once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart	26 weeks/26 weeks	Type 2 diabetes mellitus; pre-existing insulin therapy	—	Europe	Unclear	White: 99.1 Asian: 0.9	13 (7.4)	0
	C: detemir once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart						White: 98.8 Asian: 1.2	14 (8.0)	0
Hermanns 2015	I: insulin glargine	48 weeks (period 1: 24 weeks, period 2: 24	Insulin-naive people with type 2 diabetes mellitus uncontrolled on OHA treatment	2009–2012	Germany	Outpatients (internists and dia-	—	9.6 (5.9)	0
	C: NPH basal insulin							9.6 (5.9)	0

(Continued)

		weeks)/48 weeks (efficacy); 49 weeks (safety)				betologists)			
Hermansen 2006	I: detemir in the morning and evening	24 weeks/24 weeks	Type 2 diabetes mellitus; insulin-naive; treatment with OAD	2003–2004	10 European countries	—	Asian: 100	10.3 (6.3)	0
	C: NPH insulin in the morning and evening						Asian: 100	10 (5.4)	0
Home 2015	I: insulin glargine	36 weeks/36 weeks (efficacy); 37 weeks (safety)	Insulin-naive people with type 2 diabetes diagnosed for > 1 year	2009–2012	16 countries in Europe (9), Asia (3), the Middle East (2) and South America (2)	—	—	9.1 (5.5)	—
	C: NPH insulin							9.4 (5.7)	—
Hsia 2011	I1: insulin glargine at bedtime	24 weeks/24 weeks (+2 weeks run-in)	Insulin-naive US inner city, ethnic minorities with type 2 diabetes diagnosed for > 1 year suboptimally controlled on maximally tolerated doses of combination oral agents	2002–2009	USA	Diabetes Specialty Clinic at the Martin Luther King Jr. Multi-Service Ambulatory Clinic located in South Los Angeles	Hispanic: 80 African-American: 17 Other: 3	9.0 (5.9)	0
	I2: insulin glargine in the morning						Hispanic: 84 African-American: 12 Other: 4	9.5 (5.2)	0
	C: NPH insulin at bedtime						Hispanic: 83 African-American: 13	7.8 (4.2)	0

(Continued)

							Other: 3		
Kawamori 2003	I: insulin glargine once in the morning + OAD	28 weeks/28 weeks	People with type 2 diabetes poorly controlled on OADs	—	Japan	Inpatient and outpatient care	—	12 (7)	0
	C: NPH insulin once in the morning + OAD						—	12 (6)	0
Kobayashi 2007 A	I: insulin detemir once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart	48 weeks	Type 2 diabetes mellitus with ≥ 12 weeks basal-bolus insulin therapy	2003–2005	Japan	—	—	14.1 (7.5)	0
	C: NPH insulin once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart						—	15.3 (8.6)	0
Kobayashi 2007 B	I: detemir at bedtime + OAD	36 weeks	Type 2 diabetes; insulin-naive; OAD treatment	2003–2005	Japan	—	—	11.9 (7.1)	0
	C: NPH at bedtime + OAD						—	12.1 (6.5)	0
Massi 2003	I: insulin glargine once daily subcutaneously at bedtime + OAD	52 weeks/52 weeks	People with type 2 diabetes mellitus treated with OAD	1997–1999	Europe, South Africa	—	—	10.2 (6.2)	total: 0.2
	C: NPH insulin once daily subcutaneously at bedtime + OAD						—	10.5 (6.0)	
NCT00687453	I: insulin glargine at bedtime	6 months	People with inadequately controlled type 2 diabetes mellitus on once-daily NPH insulin and stable maximum-tolerated doses of a sulphonylurea, metformin or thiazolidinedione; low-income ethnic minorities	2002–2009	USA	Diabetes specialty referral clinic, primary care clinics	African American: 18 White: 82	9.4 (3.5)	0
	C: NPH insulin in the morning and at bedtime						African American: 31 White: 69	11.5 (4.0)	0
NN304-1337	I: insulin detemir once daily at bedtime + metformin	24 weeks/24 weeks	People with type 2 diabetes mellitus treated with metformin alone	—	USA and Puerto Rico	—	—	9 (6)	0

(Continued)

	C: NPH insulin once daily at bedtime + metformin		or in combination with other OADs				—	10 (8)	0
NN304-1808	I: insulin detemir once daily before breakfast ± metformin at optimal dose	7 months	Insulin-naive people with type 2 diabetes aged ≥ 70 years treated with OAD at maximum tolerated dose	2007–2008	France and UK	—	—	13.3 (10.3)	0
	C: NPH insulin once daily before breakfast ± metformin at optimal dose no bolus insulin						—	15.2 (9.4)	0
NN304-3614	I: insulin detemir in the evening + insulin aspart each meal	26 weeks/26 weeks	Overweight or obese people with type 2 diabetes mellitus treated with insulin	2009–2010	Spain	—	White: 100	13.6 (6.7)	0
	C: NPH insulin in the evening + insulin aspart each meal						White: 100	17.4 (9.0)	0
Pan 2007	I: insulin glargine in the evening + glimepiride 3 mg in the morning	24 weeks/24 weeks	Insulin-naive people with type 2 diabetes mellitus poorly controlled on OADs	—	10 countries in Asia	—	Asian: 100	10.3 (6.3)	0
	C: NPH insulin in the evening + glimepiride 3 mg in the morning						Asian: 100	10 (5.4)	0
Betônico 2019	I: insulin glargine in the morning + insulin lispro at mealtime	6 month per period, crossover	Type 2 diabetes mellitus with chronic kidney disease	2014–2016	Brazil	University hospital	—	19 (11.6)	0
	C: NPH insulin 3 times daily + insulin lispro at mealtime						—	19 (7.0)	0
Riddle 2003	I: insulin glargine once at bedtime + OAD	24 weeks/24 weeks	People with type 2 diabetes mellitus inadequate controlled with OAD	2000–2001	USA, Canada	—	White: 84 Black: 11 Asian: 3 Multiracial: 1 Hispanic heritage: 10	8.4 (5.6)	0
	C: NPH insulin once at bedtime + OAD						White: 83 Black: 13	9.0 (5.6)	0

(Continued)

							Asian: 3 Multiracial: 1 Hispanic heritage: 6		
Rosenstock 2001	I: insulin glargine once daily at bedtime + premeal regular insulin	28 weeks/28 weeks	People with type 2 diabetes mellitus with insulin treatment	—	North America	—	White: 81 Black: 16 Hispanic: 9	13.4 (8.3)	0
	C: NPH insulin once at bedtime or twice daily in the morning and at bedtime + premeal regular insulin						White: 81 Black: 14 Hispanic: 9	14.1 (9.0)	0
Rosenstock 2009	I: insulin glargine once daily, generally at bedtime	5 years/5 years	People with type 2 diabetes mellitus, aged 30–70 years, treated with oral hypoglycaemic agents or insulin alone or in combination	2001–2007	Canada and USA	—	—	10.7 (6.9)	0
	C: NPH insulin twice daily, generally in the morning and at bedtime						—	10.8 (6.7)	0
Yki-Järvinen 2006	I: insulin glargine once at bedtime + metformin	36 weeks/36 weeks	People with poorly controlled type 2 diabetes on metformin alone or sulphonylurea and metformin	—	6 sites in Finland, 1 in UK	—	—	9 (1)[a]	0
	C: NPH insulin once at bedtime + metformin						—	9 (1)[a]	0
Yokoyama 2006	I: insulin glargine once at breakfast + aspart/lispro at each meal with or without OADs	6 months/6 months	People who were intensively treated with type 2 diabetes	—	Japan	Outpatient clinic	—	14 (10)	0
	C: NPH insulin daily at bedtime + aspart/lispro at each meal with or without OADs						—	12 (9)	0

— denotes not reported

(Continued)

[a]Standard error.

ACCORD: Action to Control Cardiovascular Disease; **C:** comparator; **I:** intervention; **NPH:** neutral protamine Hagedorn; **OAD:** oral antihyperglycaemic drug; **SD:** standard deviation.

Appendix 9. Baseline characteristics (II)

Trial ID	Intervention(s) and comparator(s)	Sex (% women)	Age (mean years (SD))	HbA1c (mean % (SD))	BMI (mean kg/m² (SD))	Comedications/cointerventions (% of participants)	Comorbidities (% of participants)
Berard 2015	I: insulin glargine once daily	—	—	8.2 (1.3)	—	—	—
	C: NPH insulin once or twice daily	—	—	8.0 (1.1)	—	—	—
Eliaschewitz 2006	I: insulin glargine at bedtime + glimepiride 4 mg/day in the morning	57	56.1 (9.9)	9.1 (1.0)	27.3 (3.7)	—	—
	C: NPH insulin at bedtime + glimepiride 4 mg/day in the morning	62	57.1 (9.6)	9.2 (0.9)	27.2 (4.0)	—	—
Fajardo Montañana 2008	I: insulin detemir at bedtime	62	62.1 (9.3)	8.9 (0.9)	31.6 (4.3)	Metformin: 50	Retinopathy: 35.2 Neuropathy: 12.8 Nephropathy: 13.6 Macroangiopathy: 14.4
	C: NPH insulin at bedtime	57	61.8 (8.3)	8.8 (1.0)	32.0 (4.2)	Metformin: 58	Retinopathy: 43.1 Neuropathy: 13.7 Nephropathy: 8.9 Macroangiopathy: 17.1
Fritsche 2003	I1: insulin glargine in the morning + glimepiride 3 mg	48	61 (9)	9.1 (1.0)	28.6 (4.5)	ACE inhibitors: 48 Lipid-lowering drugs: 36 Antithrombotic agents: 34 β-blockers: 23	CVD: 64 Diabetic retinopathy: 19 Neuropathy: 24 Nephropathy: 6
	I2: insulin glargine at bedtime + glimepiride 3 mg	41	60 (9)	9.1 (1.0)	28.7 (3.9)		
	C: NPH insulin at bedtime + glimepiride 3 mg	48	62 (9)	9.1 (1.1)	28.9 (3.9)		

(Continued)

							Peripheral macroangiopathy: 13
Haak 2005	I: detemir once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart	52	61 (9)	7.9 (1.3)	30.1 (5)	Basal bolus insulin: 86 Premix insulin: 14	—
	C: detemir once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart	43	60 (8)	7.8 (1.3)	31.1 (5.8)	Basal bolus insulin: 88	

Trial ID	Intervention(s) and comparator(s)	Sex (% women)	Age (mean years (SD))	HbA1c (mean% (SD))	BMI (mean kg/m² (SD))	Comedications/cointerventions (% of participants)	Comorbidities (% of participants)
Berard 2015	I: insulin glargine once daily	—	—	8.2 (1.3)	—	—	—
	C: NPH insulin once or twice daily	—	—	8.0 (1.1)	—	—	—
Eliaschewitz 2006	I: insulin glargine at bedtime + glimepiride 4 mg/day in the morning	57	56.1 (9.9)	9.1 (1.0)	27.3 (3.7)	—	—
	C: NPH insulin at bedtime + glimepiride 4 mg/day in the morning	62	57.1 (9.6)	9.2 (0.9)	27.2 (4.0)	—	—
Fajardo Montañana 2008	I: insulin detemir at bedtime	62	62.1 (9.3)	8.9 (0.9)	31.6 (4.3)	Metformin: 50	Retinopathy: 35.2 Neuropathy: 12.8 Nephropathy: 13.6 Macroangiopathy: 14.4
	C: NPH insulin at bedtime	57	61.8 (8.3)	8.8 (1.0)	32.0 (4.2)	Metformin: 58	Retinopathy: 43.1 Neuropathy: 13.7

(Continued)

							Nephropathy: 8.9 Macroangiopathy: 17.1
Fritsche 2003	I1: insulin glargine in the morning + glimepiride 3 mg	48	61 (9)	9.1 (1.0)	28.6 (4.5)	ACE inhibitors: 48 Lipid-lowering drugs: 36 Antithrombotic agents: 34 β-blockers: 23	CVD: 64 Diabetic retinopathy: 19 Neuropathy: 24 Nephropathy: 6 Peripheral macroangiopathy: 13
	I2: insulin glargine at bedtime + glimepiride 3 mg	41	60 (9)	9.1 (1.0)	28.7 (3.9)		
	C: NPH insulin at bedtime + glimepiride 3 mg	48	62 (9)	9.1 (1.1)	28.9 (3.9)		
Haak 2005	I: detemir once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart	52	61 (9)	7.9 (1.3)	30.1 (5)	Basal bolus insulin: 86 Premix insulin: 14	—
	C: detemir once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart	43	60 (8)	7.8 (1.3)	31.1 (5.8)	Basal bolus insulin: 88 Premix insulin: 12	—
Hermanns 2015	I: insulin glargine	38	61.9 (8.8)	8.2 (0.73)	30.9 (4.5)	Metformin: 90.9 SU: 57.7 DPP-IV inhibitors: 22.3	Cardiac disorders: 28 Vascular disorders: 86.3 Renal and urinary disorders: 24.6
	C: NPH basal insulin	41	62.7 (9.2)	8.1 (0.72)	31.2 (4.7)	Metformin: 89.6 SU: 54.9 DPP-IV inhibitors: 26.2	Cardiac disorders: 23.8 Vascular disorders: 88.4 Renal and urinary disorders: 18.3
Hermansen 2006	I: detemir in the morning and evening	51	61 (9)	8.6 (0.8)	28.9 (3.6)	Metformin: 6 Secretagogue: 29	Retinopathy: 10 Neuropathy: 17

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						Acarbose: 0 Combination therapy: 65	Nephropathy: 5 Macroangiopathy: 27
	C: NPH insulin in the morning and evening	43	60 (9)	8.5 (0.8)	29.0 (3.6)	Metformin: 8 Secretagogue: 27 Acarbose: 0 Combination therapy: 65	Retinopathy: 9 Neuropathy: 16 Nephropathy: 7 Macroangiopathy: 22
Home 2015	I: insulin glargine	56	57.3 (8.3)	8.2 (0.8)	29.7 (4.5)	Metformin: 96[a] SU: 91.2[a] Repaglinide: 1.4[a] α-GI: 1.4[a] TZD: 8.2[a]	Retinopathy: 15.9 Nephropathy: 6.8 Neuropathy: 27.6
	C: NPH insulin	56	57.2 (7.8)	8.2 (0.9)	30.1 (4.5)	Metformin: 94.8[a] SU: 90.5[a] Repaglinide: 1.4[a] α-GI: 2[a] TZD: 8[a]	Retinopathy: 12.9 Nephropathy: 7.2 Neuropathy: 23.8
Hsia 2011	I1: insulin glargine at bedtime	50	50.3 (11.2)	9.2 (1.3)	31.6 (5.0)	Metformin: 97 SU: 100 TZDs: 90	—
	I2: insulin glargine in the morning	52	53.0 (8.6)	9.6 (1.2)	31.1 (5.2)	Metformin: 96 SU: 100 TZDs: 80	—
	C: NPH insulin at bedtime	70	53.2 (7.7)	9.3 (1.6)	32.1 (6.0)	Metformin: 100 SU: 97 TZDs: 60	—
Kawamori 2003	I: insulin glargine once in the morning + OAD	38	55 (9)	9.1 (1.1)	24 (3)	SU only: 38.3	Diabetic retinopathy: 45

(Continued)

						SU + BG: 18.4 SU + α-Gl: 31.9 SU + BG + α-Gl: 12.3	Neuropathy: 36 Nephropathy: 18 Other diabetic complications: 15
	C: NPH insulin once in the morning + OAD	38	57 (8)	9.1 (1.0)	23 (3)	SU only: 34. SU + BG: 23.9 SU + α-Gl: 32.8 SU + BG + α-Gl: 9	Diabetic retinopathy: 46 Neuropathy: 34 Nephropathy: 19 Other diabetic complications: 9
Kobayashi 2007 A	I: insulin detemir once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart	46	55.2 (13.3)	7.7 (1.1)	24 (3)	—	—
	C: NPH insulin once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart	29	58.1 (12.2)	7.6 (1.1)	24 (3)	—	—
Kobayashi 2007 B	I: detemir at bedtime + OAD	44	60 (9)	8.3 (0.6)	23.8 2.9)	SU only: 18.9 SU + BG: 37.2 SU + α-Gl: 24.4 SU + BG + α-Gl: 19.4	—
	C: NPH at bedtime + OAD	37	61 (9)	8.3 (0.7)	23.2 (3.0)	SU only: 19.1 SU + BG: 36.6 SU + α-Gl: 20.8 SU + BG + α-Gl: 23.5	—
Massi 2003 [b]	I: insulin glargine once daily subcutaneously at bedtime + OAD	47	59.6 (9.3)	9.0 (1.2)	29.3 (4.3)	SU only: 19.8 SU + metformin: 40.9 SU + acarbose: 7.5	Diabetic retinopathy: 18 Neuropathy: 18

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						Metformin only: 2.5 Metformin + acarbose: 0.2 Metformin + other OAD: 0.2 Other OADs alone: 0.2 Insulin + OAD: 25.3	Nephropathy: 8 Macroangiopathy: 10
	C: NPH insulin once daily subcutaneously at bedtime + OAD	46	59.4 (9.1)	8.9 (1.1)	28.8 (4.3)		Diabetic retinopathy: 16 Neuropathy: 16 Nephropathy: 6 Macroangiopathy: 10
NCT00687453	I: insulin glargine at bedtime	73	55.6 (7.0)	9.1 (1.4)	29.9 (4.1)	Metformin, SUs or TZDs: 100	—
	C: NPH insulin in the morning and at bedtime	77	54.6 (7.6)	9.5 (1.2)	33.5 (6.6)	Metformin, SUs or TZDs: 100	—
NN304-1337	I: insulin detemir once daily at bedtime + metformin	49	56 (10)	9.5 (1.2)	32 (6)	—	—
	C: NPH insulin once daily at bedtime + metformin	41	56 (11)	9.4 (1.1)	31 (5)	—	—
NN304-1808	I: insulin detemir once daily before breakfast ± metformin at optimal dose	55	77.6 (5.5)	9.3 (0.9)	29.1 (4.6)	—	—
	C: NPH insulin once daily before breakfast ± metformin at optimal dose no bolus insulin	40	76.1 (4.9)	9.1 (0.8)	29.8 (5.5)	—	—
NN304-3614	I: insulin detemir in the evening + insulin aspart each meal	46	60.6 (8.8)	—	32.2 (4.1)	—	Retinopathy: 45.8 Nephropathy: 16.7 Neuropathy: 20.8 Macroangiopathy: 16.7

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	C: NPH insulin in the evening + insulin aspart each meal	54	63.7 (9.4)	—	34.0 (4.0)	—	Retinopathy: 45.7 Nephropathy: 14.3 Neuropathy: 20 Macroangiopathy: 34.3
Pan 2007	I: insulin glargine in the evening + glimepiride 3 mg in the morning	61	56 (8)	9.0 (0.9)	25 (3)	—	—
	C: NPH insulin in the evening + glimepiride 3 mg in the morning	56	57 (8)	9.1 (0.9)	25 (3)	—	—
Betônico 2019	I: insulin glargine in the morning + insulin lispro at mealtime	Period 1: 25 Period 2: 33	Period 1: 63 (7.0) Period 2: 60 (—)	Period 1: 8.9 (1.3) Period 2: 8.8 (1.6)	Period 1: 28.6 (4.8) Period 2: 30.8 (4.6)	0	Chronic kidney disease: 100
	C: NPH insulin 3 times daily + insulin lispro at mealtime	Period 1: 39 Period 2: 21	Period 1: 60 (8.7) Period 2: 63 (—)	Period 1: 8.6 (1.1) Period 2: 7.7 (0.9)	Period 1: 30.4 (4.3) Period 2: 29.4 (4.6)	0	Chronic kidney disease: 100
Riddle 2003 [c]	I: insulin glargine once at bedtime + OAD	45	55 (9.5)	8.6 (0.9)	32.5 (4.6)	SU only: 11 Metformin only: 8 SU + metformin: 71 TZD only: < 1 SU + TZD: 6 Metformin + TZD: 3	—
	C: NPH insulin once at bedtime + OAD	44	56 (8.9)	8.6 (0.9)	32.2 (4.8)	SU only: 10 Metformin only: 7 SU + metformin: 74 TZD only: < 1	—

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						SU + TZD: 5 Metformin + TZD: 3	
Rosenstock 2001	I: insulin glargine once daily at bedtime + premeal regular insulin	42	59.5 (9.7)	8.6 (1.2)	30.7 (5.0)	—	Retinopathy: 48
	C: NPH insulin once at bedtime or twice daily in the morning and at bedtime + premeal regular insulin	38	59.2 (9.9)	8.5 (1.2)	30.4 (5.1)	—	Retinopathy: 57
Rosenstock 2009	I: insulin glargine once daily, generally at bedtime	46	55 (9)	8.4 (1.4)	34.5 (7.2)	OHA: 96 or insulin (or both): 67[d]	—
	C: NPH insulin twice daily, generally in the morning and at bedtime	46	55 (9)	8.3 (1.4)	34.1 (7.2)	OHA: 94 or insulin (or both): 70[d]	—
Yki-Järvinen 2006	I: insulin glargine once at bedtime + metformin	38	56 (9)	9.5 (0.1)[e]	31.3 (5)	Metformin: 100	—
	C: NPH insulin once at bedtime + metformin	35	57 (9)	9.6 (0.1)[e]	32.0 (5)	Metformin: 100	—
Yokoyama 2006	I: insulin glargine once at breakfast + aspart/lispro at each meal with or without OADs	52	61 (13)	7.2 (0.9)	26.4 (4.5)	Aspart: 83.9 Lispro: 16.1 Glimepiride: 38.7 Metformin: 64.5	—
	C: NPH insulin daily at bedtime + aspart/lispro at each meal with or without OADs	39	62 (10)	6.9 (0.7)	26.1 (3.2)	Aspart: 87.1 Lispro: 12.9 Glimepiride: 45.2 Metformin: 61.3	—

— denotes not reported

[a]OGLD treatment at study entry.

[b]Even though it was required that eligible people for this trial be on oral antihyperglycaemic therapy with or without insulin, the authors reported that 0.2% of included participants were not undergoing antihyperglycaemic therapy at baseline. The reported baseline values referred to 289 participants in the glargine group and 281 in the NPH group, i.e. compared with the number of randomised participants, there were 4 fewer participants in each group. Age range of included participants was 34–80 years, even though inclusion criteria required participants to be 40–80 years of age.

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[c]Baseline characteristics are given for I1: 367 and C1: 389 participants.

[d]Treatment prior to the study which could be continued or modified at the investigator's discretion.

[e]Standard error.

ACE: angiotensin-converting enzyme; **BG:** blood glucose; **BMI:** body mass index; **C:** comparator; **CVD:** coronary vascular disease; **DPP:** dipeptidyl peptidase; **GI:** glucosidase inhibitor; **HbA1c:** glycosylated haemoglobin A1c; **I:** intervention; **NPH:** neutral protamine Hagedorn; **OAD:** oral antihyperglycaemic drug; **OHA:** oral hypoglycaemic agent(s); **SD:** standard deviation; **SU:** sulphonylurea; **TZD:** thiazolidinedione.

Appendix 10. Matrix of trial endpoints (publications and trial documents)

Trial ID	Endpoints quoted in trial document(s) (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a]	Endpoints quoted in publication(s)[b,c]	Endpoints quoted in abstract of publication(s)[b,c]
Berard 2015	**Source**: NT	**Primary outcome measures**: —	**Primary outcome measures**: —
		Secondary outcome measures: —	**Secondary outcome measures**: —
		Other outcome measures: HbA1c, FPG, BG profiles, hypoglycaemia symptomatic severe and nocturnal; DTSQ, insulin dosage, weight, resource utilisation (number of strips, visit with healthcare professional, emergency department visits, number of medical assistance visits, work)	**Other outcome measures**: hypoglycaemia symptomatic and severe, HbA1c, FPG, BG profile, DTSQ, weight, insulin dosage adjustment
Eliaschewitz 2006	**Source**: IQWiG report A05-03 [d] **Primary outcome measure**: change in HbA1c	**Primary outcome measures**: change in HbA1c from baseline to the end of the study	**Primary outcome measure**: equivalence of 24-week mean changes in HbA1c
	Secondary outcome measures: —	**Secondary outcome measures**: percentage of participants who responded to treatment; change in FBG between baseline and the end of the study	**Secondary outcome measures**: —
	Source: IQWiG report A05-03 [d] **Other outcome measures**: treatment satisfaction; hypoglycaemic events (overall, severe, serious, nocturnal); AEs; bodyweight	**Other outcome measures**: percentage of participants achieving FBG ≤ 100 mg/dL; treatment satisfaction (DTSQc); pharmacoeconomics; symptomatic (nocturnal) hypoglycaemic events; treatment-emerged AEs	**Other outcome measures**: nocturnal hypoglycaemia; HbA1c levels ≤ 7.0% without hypoglycaemia; treatment satisfaction; lost time from work or normal activities due to diabetes
Fajardo Montañana 2008	**Source**: NCT00504673 **Primary outcome measure**: bodyweight loss after 26 weeks of treatment **Source**: NN304-1659 study report **Primary outcome measure**: bodyweight change during 26 weeks of treatment	**Primary outcome measure**: weight change	**Primary outcome measures**: —
	Source: NCT00504673 **Secondary outcome measures**: HbA1c; incidence of hypoglycaemia	**Secondary outcome measures**: HbA1c; FPG; proportion of participants achieving HbA1c ≤ 7.0% without hypoglycaemia; intrap-	**Secondary outcome measures**: —

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	Source: NN304-1659 study report **Secondary outcome measures**: HbA1c; FPG; within-subject variation of self-measured FPG; 7-point PG profile; percentage of participants reaching titration BG targets; participants achieving HbA1c ≤ 7.0%; treatment satisfaction and QoL, AEs; AESs; death; hypoglycaemic episodes (all, nocturnal), lipids, laboratory tests; physical examination; vital signs; HOMA-IR	erson variability in FPG; hypoglycaemia	
	Other outcome measures: —	**Other outcome measures**: AEs; standard laboratory safety analyses; physical examination	**Other outcome measures**: weight change (kg and BMI), HbA1c, hypoglycaemia (all and nocturnal)
	History of changes: 6 documented changes; last change 20 November 2014		
Fritsche 2003	**Source**: IQWiG report A05-03 [d] **Primary outcome measure**: change in HbA1c	**Primary outcome measures**: change in HbA1c level from baseline to endpoint; frequency of participants who experienced hypoglycaemic episodes	**Primary outcome measures**: —
	Secondary outcome measures: —	**Secondary outcome measures**: HbA1c (≤ 7.5%); FBG (≤ 5.6 mmol/L); response rates; mean 24-hour BG values	**Secondary outcome measures**: —
	Source: IQWiG report A05-03 [d] **Other outcome measures**: hypoglycaemic events (symptomatic, severe, serious, nocturnal); treatment satisfaction; AEs; bodyweight	**Other outcome measures**: insulin dose; bodyweight; AEs	**Other outcome measures**: HbA1c; FBG; nocturnal hypoglycaemia
Haak 2005	**Source**: IQWiG report A05-03 [d] **Primary outcome measure**: HbA1c at study end	**Primary outcome measure**: HbA1c	**Primary outcome measures**: —
	Secondary outcome measures: —	**Secondary outcome measures**: —	**Secondary outcome measures**: —
	Source: IQWiG report A05-03 [d] **Other outcome measures**: treatment satisfaction; hypoglycaemic events (overall, severe, serious, nocturnal, severe nocturnal); AEs	**Other outcome measures**: hypoglycaemia (major, symptoms only, nocturnal); SMBG; FPG; physical examinations; standard laboratory parameters; insulin doses; weight; AEs; SAE; death; funduscopy	**Other outcome measures**: HbA1c, number of insulin injections, 9-point BG profile, FPG, weight, AEs, hypoglycaemia
Hermanns 2015	**Source**: NCT00941369 **Primary outcome measures**: health assessment, participant treatment satisfaction and QoL **Source**: LANTU_L_04079 study report	**Primary outcome measures**: composite DRQoL score, which consisted of a standardised and unweighted ITEQ score (Cronbach's α = 0.93), a PAID questionnaire score (Cronbach's α = 0.86), and the mental health score of the SF-12 Health Survey	**Primary outcome measures**: composite DRQoL score based on an unweighted ITEQ score, PAID questionnaire score, and the mental health

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	Primary outcome measures: mean score of DRQoL		score in the SF-12 Health Survey
	Source: NCT00941369 **Secondary outcome measures**: glycaemic parameters assessment; anthropometric data (weight, waist circumference) assessment; lipid assessment; hypoglycaemia assessment **Source**: LANTU_L_04079 study report **Secondary outcome measures**: mean scores of patient questionnaires (ITEQ, DTSQ, PAID, SF-12; EQ-5D; treatment preference; laboratory parameters (HbA1c, FBG, TC, HDL, LDL, triglycerides); 7-point BG profile; hypoglycaemia episodes; anthropometric data (weight, waist circumference); insulin dose	**Secondary outcome measures**: ITEQ score; PAID questionnaire score; mental health score of the SF-12 Health Survey; EQ-5D questionnaire; DTSQs; HbA1c; FBG; 7-point BG profiles; bodyweight; waist circumference; BP; lipids; hypoglycaemic events (symptomatic or severe (or both)); total daily insulin doses; participants' treatment preference	**Secondary outcome measures**: —
	Other outcome measures: —	**Other outcome measures**: total number of serious adverse; total number of AEs; pain, redness or inflammation at the injection site	**Other outcome measures**: —
	History of changes: 6 documented changes; last change 21 November 2012		
Hermansen 2006	**Source**: NCT00604396 **Primary outcome measure**: HbA1c **Source**: IQWiG report A05-03 [d] **Primary outcome measure**: HbA1c at study end	**Primary outcome measure**: HbA1c	**Primary outcome measures**: —
	Source: NCT00604396 **Secondary outcome measures**: FPG; total hypoglycaemic episodes; bodyweight; AEs; insulin antibodies	**Secondary outcome measures**:—	**Secondary outcome measures**:—
	Source: IQWiG report A05-03 [d] **Other outcome measures**: hypoglycaemic events (overall, severe, serious, nocturnal, severe nocturnal); AEs; bodyweight; funduscopy	**Other outcome measures**: FPG; proportion of participants achieving HbA1c ≤ 7.0%; proportion of participants achieving HbA1c ≤ 7.0% without hypoglycaemia; hypoglycaemia (major, minor, symptoms only and nocturnal); within-participant variation in self-measured prebreakfast and predinner PG; 10-point PG profile; AEs; standard laboratory analyses; physical examination	**Other outcome measures**: HbA1c; proportion of participants achieving HbA1c ≤ 7.0%; proportion of participants achieving HbA1c ≤ 7.0% without hypoglycaemia; hypoglycaemia (overall and nocturnal); weight
Home 2015	**Source**: NCT00949442 **Primary outcome measure**: HbA1c **Source**: LANTU_C_02762 study report **Primary outcome measure**: change in HbA1c	**Primary outcome measure**: change in HbA1c from baseline to the end of the treatment period	**Primary outcome measure**: HbA1c

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	Source: NCT00949442 **Secondary outcome measures**: self-monitored FPG; 8-points profiles; episodes of hypoglycaemia; daily doses of insulin; need of additional prandial insulin **Source**: LANTU_C_02762 study report **Secondary outcome measures**: FPG; 8-points PG profiles; percentage of participants reaching the target of HbA1c < 7% and < 6.5%; use of prandial insulin as rescue medication at month 6; rates of hypoglycaemia; daily doses of insulin; overall safety; treatment satisfaction	**Secondary outcome measures**: time profile of HbA1c; FPG; nocturnal SMPG and 8-point SMPG profiles; percentage of participants achieving HbA1c < 7.0 or < 6.5%; daily dose of insulin; prandial insulin use at 6 months as rescue medication; change in bodyweight; incidence and rate of hypoglycaemia	**Secondary outcome measures**: —
	Other outcome measures: —	**Other outcome measures**: —	**Other outcome measures**: —
	History of changes: 38 documented changes; last change 20 August 2012		
Hsia 2011	**Source**: NCT00686712 **Primary outcome measure**: HbA1c change from baseline	**Primary outcome measure**: between-group difference in the change of HbA1c from baseline	**Primary outcome measures**: —
	Secondary outcome measures: frequency of glucose readings < 130 mg/dL; frequency of total hypoglycaemic reactions; frequency of severe hypoglycaemic reactions; BMI change from baseline; total daily insulin dose; any AE other than hypoglycaemia	**Secondary outcome measures**: between-group differences in the proportion of participants achieving HbA1c ≤ 7.0% by week 26; change in fasting SMBG readings; percentage of readings that achieved the ADA-recommended target of < 130 mg/dL between the run-in phase and the study's end; change in presupper SMBG readings and the percentage of readings that achieved < 130 mg/dL between the run-in phase and the study end; incidence of hypoglycaemic events at each diurnal monitoring	**Secondary outcome measures**: —
	Other outcome measures: —	**Other outcome measures**: —	**Other outcome measures**: —
	History of changes: 4 documented changes, last changed 28 March 2016		
Kawamori 2003	**Source**: IQWiG report A05-03 [d] **Primary outcome measure**: change in HbA1c	**Primary outcome measure**: change in HbA1c level from baseline to study end	**Primary outcome measures**: —
	Secondary outcome measures: —	**Secondary outcome measures**: FPG; insulin dose; hypoglycaemic events	**Secondary outcome measures**: —
	Source: IQWiG report A05-03 [d]	**Other outcome measures**: AEs; SAEs	**Other outcome measures**: —

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	Other outcome measures: hypoglycaemic events (overall, severe, serious, nocturnal, severe nocturnal); AEs		
Kobayashi 2007 A	**Source**: NCT00604344 **Primary outcome measure**: HbA1c after 48 weeks of treatment **Source**: NN304-1476 study report **Primary outcome measure**: HbA1c after 48 weeks of treatment	**Primary outcome measure**: HbA1c	**Primary outcome measures**:—
	Source: NCT00604344 **Secondary outcome measures**: BG profiles; hypoglycaemic episodes; AEs; bodyweight; insulin antibodies **Source**: NN304-1476 study report **Secondary outcome measures**: BG profiles; hypoglycaemic episodes; AEs; clinical laboratory; ECG; funduscopy/fundus photography; bodyweight; BP; insulin antibodies; insulin doses; therapy related QoL at night; treatment satisfaction	**Secondary outcome measures**: —	**Secondary outcome measures**:—
	Other outcome measures: —	**Other outcome measures**: SMBG level over 7 days; intraindividual variation in FPG over 7 days; 7-point measurement blood sugar profile; hypoglycaemia, AEs, laboratory tests, ECG, fundus examination/fundus photograph, bodyweight; BP; satisfaction with the insulin therapy method; nocturnal QoL associated with the insulin therapy	**Other outcome measures**:—
	History of changes: 4 documented changes; last change 26 January 2017		
Kobayashi 2007 B	**Source**: NCT00604253 **Primary outcome measure**: HbA1c **Source**: NN304-1477 study report **Primary outcome measure**: HbA1c after 36 weeks	**Primary outcome measure**: HbA1c	**Primary outcome measure**: HbA1c
	Source: NCT00604253 **Secondary outcome measures**: PG profiles; incidence of hypoglycaemic episodes; AEs; insulin antibodies **Source**: NN304-1477 study report **Secondary outcome measures**: PG profiles; incidence of hypoglycaemic episodes; AEs; insulin	**Secondary outcome measures**: FPG, 7-point BG profile,	**Secondary outcome measures**: —

(Continued)

	antibodies; laboratory parameters; ECG; funduscopy/fundus photography; bodyweight; BP		
	Other outcome measures: —	**Other outcome measures**: hypoglycaemia, AEs, laboratory tests, ECG, fundus examinations/photographs, BP, bodyweight	**Other outcome measures**: FPG, insulin dose, hypoglycaemia (overall and nocturnal), bodyweight increase, AEs, laboratory tests, antibodies
	History of changes: 6 documented changes; last change 26 January 2017		
Massi 2003	**Source**: IQWiG report A05-03 [d] **Primary outcome measure**: change in HbA1c	**Primary outcome measure**: change in HbA1c level from baseline to study end	**Primary outcome measures**: —
	Secondary outcome measures: —	**Secondary outcome measures**: FPG; FBG; FBG variability	**Secondary outcome measures**: —
	Source: IQWiG report A05-03 [d] **Other outcome measures**: hypoglycaemic events (overall, severe, serious, nocturnal, severe nocturnal); AEs; QoL; treatment satisfaction; retinopathy	**Other outcome measures**: hypoglycaemia; bodyweight; AEs	**Other outcome measures**: HbA1c; symptomatic hypoglycaemia; nocturnal hypoglycaemia; AEs
NCT00687453	**Source**: NCT00687453 **Primary outcome measures**: change in HbA1c	**Primary outcome measures**: no publication available	**Primary outcome measures**: no publication available
	Secondary outcome measures: frequency of presupper glucose readings ≤ 120 mg/dL; hypoglycaemic reactions; severe hypoglycaemic reactions; change of BMI from baseline; total daily insulin dose; AEs	**Secondary outcome measures**: no publication available	**Secondary outcome measures**: no publication available
	Other outcome measures: —	**Other outcome measures**: no publication available	**Other outcome measures**: no publication available
	History of changes: 4 documented changes, last change 10 February 2014		
NN304-1337	**Source**: IQWiG report A05-03 [d] **Primary outcome measure**: HbA1c at study end	**Primary outcome measures**: no publication available	**Primary outcome measures**: no publication available
	Secondary outcome measures: —	**Secondary outcome measures**: no publication available	**Secondary outcome measures**: no publication available
	Source: IQWiG report A05-03 [d] **Other outcome measures**: hypoglycaemia (overall, severe, nocturnal, severe nocturnal); AEs; bodyweight; funduscopy	**Other outcome measures**: no publication available	**Other outcome measures**: no publication available

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NN304-1808	**Source**: NCT00506662 **Primary outcome measure**: change in HbA1c at month 7 **Source**: NN304-1808 study report **Primary outcome measure**: HbA1c after 7 months of treatment	**Primary outcome measures**: no publication available	**Primary outcome measures**: no publication available
	Source: NCT00506662 **Secondary outcome measures**: change in HbA1c at month 4; change in mean FPG; change in mean prelunch PG; change in mean predinner PG; change in bodyweight; number of total hypoglycaemic episodes **Source**: NN304-1808 study report **Secondary outcome measures**: QoL (treatment satisfaction, health status, behavioural and psychosocial scoring); percentage of participants with HbA1c ≤ 8.0%; glycaemic control as measured by 3-point SMPG; within-participant variation of bodyweight; percentage of participants achieving FPG ≤ 8.8 mmol/L; within-participant variation of PG; incidence of hyperglycaemic episodes; incidence of hypoglycaemic control; occurrence of AEs; insulin dose requirements	**Secondary outcome measures**: no publication available	**Secondary outcome measures**: no publication available
	Other outcome measures: —	**Other outcome measures**: no publication available	**Other outcome measures**: no publication available
	History of changes: 11 documented changes; last change 15 June 2016		
NN304-3614	**Source**: NCT00795600 **Primary outcome measures**: percentage change in trunk fat mass (defined as peripheral fat ratio); absolute change in trunk fat mass assessed by DEXA **Source**: NN304-3614 study synopsis **Primary outcome measures**: change in trunk fat mass, assessed by DEXA after 26 weeks	**Primary outcome measures**: no publication available	**Primary outcome measures**: no publication available
	Source: NCT00795600 **Secondary outcome measures**: absolute change in whole body fat; percentage change in whole body fat mass; absolute change in whole body lean mass; percentage change in whole body lean mass; absolute change in trunk lean mass; percentage change in trunk lean; absolute change in calculated whole body fat percentage; percent change in calculated whole body fat; absolute change in calculated trunk fat percentage; perceptual change in calculated trunk fat percentage; absolute change in visceral adi-	**Secondary outcome measures**: no publication available	**Secondary outcome measures**: no publication available

(Continued)

pose tissue; percentage change in visceral adipose tissue; absolute change in subcutaneous adipose tissue area; percentage change in subcutaneous adipose tissue area; absolute change in calculated visceral/subcutaneous adipose tissue ratio; percentage change in calculated visceral/subcutaneous adipose tissue ratio; absolute change in liver/spleen attenuation ratio; percentage change in liver/spleen attenuation ratio; absolute change in HbA1c; absolute change in FPG; absolute change in adiponectin; absolute change in TC; absolute change in HDL cholesterol; absolute change in LDL; absolute change in VLDL; absolute change in triglycerides; absolute change in free fatty acids; absolute change in haemoglobin; absolute change in blood volume; absolute change in thrombocytes; absolute change in erythrocytes; absolute change in leucocytes; absolute change in lymphocytes; absolute change in monocytes; absolute change in neutrophils; absolute change in eosinophils; absolute change in basophils; absolute change in creatinine; absolute change in creatine phosphokinase; absolute change in urea; absolute change in albumin; absolute change in bilirubin total; absolute change in ALT/AST; absolute change in alkaline phosphatase; absolute change in sodium; absolute change in potassium; absolute change in bodyweight; absolute change in waist circumference; absolute change in hip circumference; absolute change in hsCRP; absolute change in PAI-1; number of hypoglycaemic episodes; number of non-serious AEs

Source: NN304-3614 study synopsis

Secondary outcome measures: whole body fat mass; whole body lean mass; trunk lean mass; calculated whole body fat percentage and calculated trunk fat percentage; visceral adipose tissue area; subcutaneous adipose tissue area; calculated visceral/subcutaneous adipose tissue ratio and liver/spleen attenuation ratio; change in HbA1c; change in FPG; to quantify the relationship between BMI and required daily dose of insulin detemir; change in cytokine in the adipose tissue; change of inflammatory parameters (hsCRP and PAI-1); change of weight; change in waist and hip circumference; incidence of hypoglycaemia; change of lipid profile; incidence of AEs during the trial; safety profile as measured by laboratory safety parameters (haematology, biochemistry) and physical examination/vital signs

Other outcome measures: —	**Other outcome measures**: no publication available	**Other outcome measures**: no publication available

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	History of changes: 11 documented changes, last changed 15 March 2016		
Pan 2007	**Source**: IQWiG report A05-03 [d] **Primary outcome measure**: change of HbA1c levels from baseline to study end	**Primary outcome measure**: change of HbA1c levels from baseline to study end	**Primary outcome measure**: HbA1c
	Secondary outcome measures: —	**Secondary outcome measures**: FBG levels, proportion of participants with FBG ≤ 6.7 mmol/L (120 mg/dL), mean daily BG, nocturnal BG profiles, proportion of participants with HbA1c < 7.5% (58 mmol/mol), insulin dose, proportion of participants with hypoglycaemia (severe, serious, nocturnal, all), change in BMI, AEs; proportion of participants of combined responders (HbA1c < 7.5% (58 mmol/mol) and FPG ≤ 6.7 mmol/L, proportion of participants HbA1c levels < 7.5% (58 mmol/mol) and without hypoglycaemia (post hoc analysis)	**Secondary outcome measures**: hypoglycaemia (all, severe, nocturnal); insulin dose
	Other outcome measures: hypoglycaemia (severe, serious, all, nocturnal), AE, SAE, weight, BMI	**Other outcome measure**: 8-point BG profiles	**Other outcome measures**:
Betônico 2019	**Source**: NCT02451917 **Primary outcome measure**: change in HbA1c	**Primary outcome measures**: change in HbA1c, number of hypoglycaemic events (severe, overall, nocturnal) between weeks 1 and 24 of each treatment arm	**Primary outcome measures**: change in HbA1c, incidence of nocturnal hypoglycaemia
	Secondary outcome measure: number of hypoglycaemic events	**Secondary outcome measures**: within-day glycaemic variability, change in BMI, total daily insulin dose	**Secondary outcome measures**: —
	Other outcome measures: glycaemic variability; total daily insulin dose; ESRD; creatinine; GFR	**Other outcome measures**: GFR, serum creatinine, blood urea nitrogen, calcium, parathormone, plasma lipids, blood cell count	**Other outcome measures**: —
	History of changes: 3 documented changes; last change 4 August 2016		
Riddle 2003	**Source**: NCT00653341 **Primary outcome measure**: percentage of participants reaching target HbA1c ≤ 7% at endpoint and not experiencing symptomatic nocturnal hypoglycaemia **Source**: IQWiG report A05-03 [d] **Primary outcome measure**: % of participants achieving HbA1c ≤ 7% without hypoglycaemic events	**Primary outcome measure**: percentage of participants achieving HbA1c ≤ 7% without a single instance of confirmed symptomatic nocturnal hypoglycaemia or severe hypoglycaemia, or both	**Primary outcome measures**: —

(Continued)

	Source: NCT00653341 **Secondary outcome measures**: AEs; vital signs; laboratory values	**Secondary outcome measures**: —	**Secondary outcome measures**: —
	Source: IQWiG report A05-03 [d] **Other outcome measures**: change in HbA1c; hypoglycaemic events (overall, severe, serious, nocturnal); AEs; bodyweight; BMI; treatment satisfaction	**Other outcome measures**: changes from baseline for HbA1c, FPG and weight; percentage of participants achieving HbA1c ≤ 7.0% or FPG ≤ 5.6 mmol/L independent of occurrence of hypoglycaemia; participants achieving FPG ≤ 5.6 mmol/L without confirmed hypoglycaemia; within-subject variability between 7 sequential fasting glucose measures; rates of symptomatic hypoglycaemia including unconfirmed, confirmed and severe hypoglycaemia	**Other outcome measures**: FPG; HbA1c; hypoglycaemia;% of participants reaching HbA1c ≤ 7% without documented nocturnal hypoglycaemia
Rosenstock 2001	**Source**: IQWiG report A05-03 [d] **Primary outcome measure**: change in HbA1c	**Primary outcome measure**: change in HbA1c level from baseline to study end	**Primary outcome measures**: —
	Secondary outcome measures: —	**Secondary outcome measures**: —	**Secondary outcome measures**: —
	Other outcome measures: hypoglycaemia (overall, severe, serious, nocturnal, severe nocturnal); QoL; treatment satisfaction; retinopathy; AEs	**Other outcome measures**: FBG; frequency and severity of hypoglycaemia; insulin dose; bodyweight; AEs	**Other outcome measures**: HbA1c; symptomatic hypoglycaemia; nocturnal hypoglycaemia; weight gain
Rosenstock 2009	**Source**: NCT00174824 **Primary outcome measure**: percentage of participants with a 3-step or greater progression in the patient-level recorded integer ETDRS retinopathy scale **Source**: IQWiG report A05-03 [d] **Primary outcome measure**: percentage of participants with a 3-step or greater progression in the patient-level recorded integer ETDRS retinopathy scale	**Primary outcome measure**: percentage of participants with ≥ 3 step progression in ETDRS score after 5 years of treatment	**Primary outcome measure**: percentage of participants with 3 or more step progression in the ETDRS retinopathy patient-level severity scale
	Source: NCT00174824 **Secondary outcome measures**: percentage of participants who develop proliferative retinopathy or develop clinically significant macular oedema; the distribution of participants on the patient-level recorded integer ETDRS retinopathy scale; the change from baseline in HbA1c and fasting PG; incidence of hypoglycaemia	**Secondary outcome measures**: percentage of participants with ≥ 3 step progression in ETDRS score after 3, 6, 12, 24, 36, 48 and 60 months of treatment; the percentage of participants who developed proliferative diabetic retinopathy; the distribution of change on the ETDRS scale; the percentage of participants who developed clinically significant macular oedema; the change from baseline in over-	**Secondary outcome measures**: —

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		all HbA1c and FPG levels; the overall incidence and rate of symptomatic hypoglycaemia (all episodes of symptomatic hypoglycaemia), symptomatic nocturnal hypoglycaemia and severe hypoglycaemia; insulin doses.	
	Source: IQWiG report A05-03 [d] **Other outcome measures**: hypoglycaemic events (overall, severe, nocturnal, severe nocturnal); AEs; bodyweight; BMI; retinopathy	**Other outcome measures**: weight, BP	**Other outcome measures**: development of proliferative retinopathy, progression to clinically significant macular oedema, severe hypoglycaemia
	History of changes: 6 documented changes; last change 26 March 2009		
Yki-Järvinen 2006	**Source**: IQWiG report A05-03 [d] **Primary outcome measure**: change in HbA1c	**Primary outcome measure**: change in HbA1c from baseline to end of study	**Primary outcome measure**: changes in HbA1c
	Secondary outcome measures: —	**Secondary outcome measures**: diurnal glucose concentrations; symptomatic hypoglycaemia	**Secondary outcome measures**: diurnal glucose profiles; symptomatic hypoglycaemia
	Other outcome measures: hypoglycaemic events (overall, severe, nocturnal, severe nocturnal); AEs; bodyweight; BMI; retinopathy	**Other outcome measures**: bodyweight; S-ALT; triglycerides; insulin doses; AEs	**Other outcome measures**: —
Yokoyama 2006	**Source**: NT	**Primary outcome measures**: —	**Primary outcome measures**: —
		Secondary outcome measures: —	**Secondary outcome measures**: —
		Other outcome measures: HbA1c; hypoglycaemia; total daily insulin dose; % of basal insulin dose; BMI; FBG; PPG	**Other outcome measures**: HbA1c; percentage of basal insulin dose; hypoglycaemia

—: denotes not reported.

[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.

ADA: American Diabetes Association; **AE:** adverse event; **ALT:** alanine aminotransferase; **AST:** aspartate transaminase; **BG:** blood glucose; **BMI:** body mass index; **BP:** blood pressure; **DEXA:** double energy X-ray absorptiometry; **DRQoL:** diabetes-related quality of life; **DTSQ(s/c):** Diabetes Treatment Satisfaction Questionnaire (status/change); **ECG:** electrocardiogram; **EMA:** European Medicines Agency; **EQ-5(D):** EuroQol 5 (Dimension); **ESRD:** end-stage renal disease; **ETDRS:** Early Treatment of Diabetic Retinopathy

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Study; **FBG:** fasting blood glucose; **FDA:** Food and Drug Administration; **FPG:** fasting plasma glucose; **GFR:** glomerular filtration rate; **HbA1c:** glycosylated haemoglobin A1c; **HDL:** high-density lipoprotein; **HOMA-IR:** homeostatic model assessment for insulin resistance; **hsCRP:** high-sensitivity C-reactive protein; **IQWiG:** Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care); **ITEQ:** insulin therapy experience questionnaire; **ITR-QOLN:** insulin therapy related quality of life at night; **LDL:** low-density lipoprotein; **LEAD:** lantus evaluation in Asian diabetics; **NT:** no trial document available; **PAI-1:** plasminogen activator inhibitor-1; **PAID:** problem areas in diabetes; **PG:** plasma(-referenced) glucose; **PPG:** postprandial blood glucose; **QoL:** quality of life; **SAE:** serious adverse event; **S-ALT:** serum alanine aminotransferase; **SF-12:** 12-item Short Form Health Survey; **SF-36:** 36-item Short Form Health Survey; **SMBG:** self-monitoring of blood glucose; **SMPG:** self-monitored plasma glucose; **TC:** total cholesterol; **VLDL:** very-low-density lipoprotein.

Appendix 11. 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]
Berard 2015	All-cause mortality	No	No	Yes	No
	Hypoglycaemia	No			
	Adverse events	No	No	Yes	No
	HbA1c	No			
Eliaschewitz 2006	All-cause mortality	No			
	Hypoglycaemia	No			
	Adverse events	No			
	HbA1c	No			
Fajardo Montañana 2008	All-cause mortality	No			
	Hypoglycaemia	No			
	Adverse events	No			
	HbA1c	No			
	QoL	No			
Fritsche 2003	All-cause mortality	No			
	Hypoglycaemia	No			
	Adverse events	No			
	HbA1c	No			
Haak 2005	Diabetic complications	No			
	All-cause mortality	No			

(Continued)

	Hypoglycaemia	No			
	Adverse events	No			
	HbA1c	No			
	QoL	No			
Hermanns 2015	All-cause mortality	No			
	Hypoglycaemia	No			
	Adverse events (skin reactions)	No	Yes	No	No
	HbA1c	No			
	QoL	No			
Hermansen 2006	All-cause mortality	No			
	Hypoglycaemia	No			
	Adverse events	No			
	HbA1c	No			
Home 2015	All-cause mortality	No			
	Hypoglycaemia	No			
	Adverse events	No			
	Serious adverse events	No	Yes	No	No
	HbA1c	No			
Hsia 2011	All-cause mortality	No			
	Hypoglycaemia	No			
	Adverse events	No			
	HbA1c	No			
Kawamori 2003	All-cause mortality	No			
	Hypoglycaemia	No			
	Adverse events	No			
	HbA1c	No			
Kobayashi 2007 A	Diabetic complications (retinopathy)	No	Yes	No	No
	All-cause mortality	No			

(Continued)

	Severe hypoglycaemia	No	Yes	No	No
	Confirmed hypoglycaemia	No	Yes	No	No
	Adverse events	No			
	HbA1c	No			
Kobayashi 2007 B	All-cause mortality	No			
	Hypoglycaemia	No			
	Adverse events	No			
	HbA1c	No			
Massi 2003	Diabetic complications	No			
	All-cause mortality	No			
	Hypoglycaemia	No			
	Adverse events	No			
	HbA1c	No			
	QoL	No			
NCT00687453	—[e]				
NN304-1337	*[e]				
NN304-1808	*[e]				
NN304-3614	*[e]				
Pan 2007	Diabetic complications (myocardial infarction)	Yes	No	No	No
	Diabetic complications (stroke)	Yes	No	No	No
	Diabetic complications (ESRD)	Yes	No	No	No
	All-cause mortality	No			
	Hypoglycaemia	No			
	Adverse events	No			
	HbA1c	No			
Betônico 2019	Hypoglycaemia	No			
	HbA1c	No			
Riddle 2003	All-cause mortality	No			

(Continued)

	Hypoglycaemia	No			
	Adverse events	No			
	HbA1c	No			
Rosenstock 2001	Diabetic complications	No			
	All-cause mortality	No			
	Hypoglycaemia	No			
	Adverse events	No			
	HbA1c	No			
	QoL	No			
Rosenstock 2009	Diabetic complications	No			
	All-cause mortality	No			
	Hypoglycaemia	No			
	Adverse events	No			
	HbA1c	No			
Yki-Järvinen 2006	All-cause mortality	No			
	Hypoglycaemia	No			
	Adverse events	No			
	HbA1c	No			
Yokoyama 2006	All-cause mortality	No	No	No	Yes
	Hypoglycaemia	No			
	Serious adverse event	No	No	No	Yes
	Adverse events all	No	No	No	Yes
	HbA1c	No			

[a]Clear that outcome was measured and analysed; trial report stated that outcome was analysed but reported only that result was not significant (Classification 'A', table 2, Kirkham 2010).
[b]Clear that outcome was measured and analysed; trial report stated that outcome was analysed but reported no results (Classification 'D', table 2, Kirkham 2010).
[c]Clear that outcome was measured but not necessarily analysed; clinical assessment implied 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 assessment implied 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 has been published, so assessment of risk of outcome reporting bias was not possible.

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ESRD: end-stage renal disease; **HbA1c:** glycosylated haemoglobin A1c; **ORBIT:** Outcome Reporting Bias In Trials; **QoL:** quality of life.

Appendix 12. Definition of endpoint measurement (I)[a]

Trial ID	Diabetes-related complications	Health-related quality of life	All-cause mortality	Adverse events other than hypoglycaemia	Socioeconomic effects	HbA1c
Berard 2015	NR	NR	NR	NR	NR	ND (IO)
Eliaschewitz 2006	NR	NR	ND	Treatment-emergent adverse events: any event that was present before and worsened after the first dose of study medication; not present before the first dose of study medication; considered possibly related to the study medication; led to permanent discontinuation of the study medication; or led to death.	Pharmacoeconomics: time lost from work or from normal activities due to diabetes illness throughout the treatment phase.	Centrally measured
Fajardo Montañana 2008	Weight change measured in kg and BMI; Myocardial infarction (ND)	SF-36v2; 10 subscales reaching from 0 to 100	ND	**All**: undesirable medical event occurring to a subject in a clinical trial, whether or not related to the trial product, any clinical laboratory abnormality regarded as clinically significant, i.e. an abnormality that suggests a disease or organ toxicity (or both) and is of a severity, which requires active management; eye disorders: retinal detachment (SO/IO) **Serious**: death, life-threatening* experience; hospitalisation or prolongation of existing hospitalisation, persistent or significant disability/incapacity, congenital anomaly/birth defect, might jeopardise the subject and might require medical or surgical intervention to prevent 1 of the outcomes listed in this definition (SO/IO)	NR	HbA1c and FPG were measured in a central laboratory using standard methods
Fritsche 2003	ND	NR	ND	ND	NR	Centrally measured
Haak 2005	ND	DHP-2 SO	ND	ND (SO/IO)	NR	Centrally measured
Hermanns 2015	NR	DRQoL (SO) calculated as mean of	ND	**All**: reported by participant or noted by investigator, as well as abnor-	NR	ND

(Continued)

		3 subscores (ITEQ, PAID, and SF-12); EQ-5D (SO)		mal standard haematology and blood chemistry and vital signs **Serious**: ND		
Hermansen 2006	ND	NR	ND	ND (SO)	NR	Centrally measured
Home 2015	NR	NR	ND	ND	NR	Measured in a central laboratory (AO)
Hsia 2011	NR	NR	ND	ND	NR	Performed by the MLK-MACC clinical chemistry laboratory, utilising an HPLC method that conforms to the DCCT standard (AO)
Kawamori 2003	ND	NR	ND	**All**: SO/IO **Serious**: results in death; is life-threatening; requires inpatient hospitalisation or causes prolongation of existing hospitalisation; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; or requires intervention to prevent permanent impairment or damage	NR	ND
Kobayashi 2007 A	Blood pressure (ND), ECG (ND), fundus examination or fundus photograph (ND), bodyweight on completion of administration in kilograms	ITR-QOLN (insulin therapy related quality of life at night)	ND	Adverse events were classified according to Medical Dictionary for Regulatory Activities (MedDRA) organ classification, basic terminology, severity and causal relationship with the study drug.	NR	ND
Kobayashi 2007 B	ND	NR	ND	Adverse events were classified according to Medical Dictionary for Regulatory Activities (MedDRA) organ classification, basic terminology, severity and causal relationship with the study drug.	NR	ND
Massi 2003	ND	W-BQ22	ND	**All**: SO/IO	NR	Centrally measured
NCT00687453	NR	NR	ND	ND	NR	ND

(Continued)

NN304-1337	Retinal disorder, retinal oedema, abnormal visual acuity (assessed with fundus examination or funduscopy)	NR	ND	ND	NR	Centrally measured
NN304-1808	NR	Treatment satisfaction, health status, behavioural and psychosocial scoring (SO)	ND	**All**: any undesirable medical event occurring in a participant in a clinical trial, whether or not related to the trial product(s). This included events from the first trial-related activity after the participant had signed the informed consent. **Serious**: death, life-threatening experience, inpatient hospitalisation or prolongation of existing hospitalisation, persistent or significant disability/incapacity, important medical events that may not have resulted in death, or been life-threatening, or required hospitalisation were considered to be SAEs, when, based upon appropriate medical judgement, they may have jeopardised the participant and may have required medical or surgical intervention to prevent 1 of the outcomes listed in this definition	NR	Determined centrally by HPLC
NN304-3614	ND	NR	ND	ND	NR	ND
Pan 2007	ND	NR	ND	**All**: ND **Severe/serious**: ND	NR	ND
Betônico 2019	ND (IO)	NR	Investigator assessed	**All**: ND **Severe/serious**: death, ESRD, myocardial infarction (SO/IO) **Discontinuation because of adverse event**: death, ESRD, myocardial infarction (SO/IO) **Hospitalisation**: ND **Adverse event in association with retinopathy**: ND (IO) **Necessity of outpatient treatment**: ND (IO) **Skin reactions**: ND (IO) **Change in BMI**: ND (IO)	NR	Not centrally measured

(Continued)

Riddle 2003	ND	NR	ND	ND	NR	Centrally measured
Rosenstock 2001	ND	W-BQ22	ND	ND	NR	Centrally measured
Rosenstock 2009	Diabetic retinopathy status assessed in 7-field stereoscopic fundus photographs obtained at screening and after 3, 6, 12, 24, 36, 48 and 60 months of treatment. Photographs underwent treatment-group-masked grading, without comparison with other photographs, at the University of Wisconsin Fundus Photograph Reading Centre (FPRC). To verify progression status, a side-by-side comparison of baseline and follow-up photographs masked to treatment was conducted by a senior grader for any participant whose ETDRS score demonstrated a 3 step or greater progression over baseline at any time point during the study (AO); clinically significant macular oedema	NR	Treatment-emergent adverse event leading to death	Evaluation of reported adverse events using the Medical Dictionary for Regulatory Activities (MedDRA) coding (Version 10.0; MSSO, Chantilly, VA, USA) (SO/IO)	NR	Performed by the Diabetes Diagnostic Laboratories, Columbia, MO, USA, using the National Glycohemoglobin Standardization Programme (level 1)) (AO)

(Continued)

	(AO); proliferative diabetic retinopathy (AO)					
Yki-Järvinen 2006	NR	NR	ND	ND (SO)	NR	HbA1c was measured by HPLC using the fully automated Glycosylated Hemoglobin Analyzer System (Bio-Rad, Richmond, CA, USA) traceable to the DCCT reference method, with a reference range of 4.0–6.0%.
Yokoyama 2006	NR	NR	NR	NR	NR	Measured by HPLC; method standardised by the Japan Diabetes Society aligned with the 1 used at the DCCT, and calibrated every 2 weeks using glyco-HB as a control.

[a]In addition to definition of endpoint measurement, description of who measured the outcome.

AO: adjudicated outcome measurement; **BMI:** body mass index; **DCCT:** Diabetes Control and Complications Trial; **DHP-2:** Diabetes Health Profile 2; **DRQoL:** diabetes-related quality of life; **ECG:** electrocardiogram; **EQ-5(D):** EuroQol 5 (Dimension); **ESRD: e**nd-stage renal disease; **ETDRS:** Early Treatment of Diabetic Retinopathy Study; **FPG:** fasting plasma glucose; **FPRC:** Fundus Photograph Reading Centre; **glyco-HB:** glycated haemoglobin; **HbA1c:** glycosylated haemoglobin A1c; **HPLC:** high-pressure liquid chromatography; **IO:** investigator-assessed outcome measurement; **IQWiG:** Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care); **ITEQ: I**nsulin Therapy Experience Questionnaire; **ITR-QOLN:** insulin therapy-related quality of life at night; **MedDRA: M**edical Dictionary for Regulatory Activities; **MSSO:** maintenance and support services organisation; **ND:** not defined; **NR:** not reported; **PAID:** problem areas in diabetes; **SAE:** serious adverse event; **SF-12:** 12-item Short Form Health Survey; **SF-36:** 36-item Short Form Health Survey; **SO:** self-reported outcome measurement; **W-BQ22:** Well-Being Questionnaire (22 items).

Appendix 13. Definition of endpoint measurement (II)[a]

Trial ID	Severe hypoglycaemia	Serious hypoglycaemia	Overall confirmed hypoglycaemia	Nocturnal confirmed hypoglycaemia

(Continued)

Berard 2015	BG < 2.8 mmol/L (50 mg/dL) (SO)	ND	BG < 4.0 mmol/L (72 mg/dL) (SO)	ND
Eliaschewitz 2006	Symptoms consistent with hypoglycaemia requiring assistance from another person and BG < 2.8 mmol/L (50 mg/dL) or prompt recovery after oral carbohydrate, IV glucose or glucagon administration (SO)	Hypoglycaemic event fulfilling ≥ 1 criterion for an SAE (SO/IO)	Symptoms + BG ≤ 4.2 mmol/L (75 mg/dL) (SO)	Symptoms + BG ≤ 4.2 mmol/L (75 mg/dL), while asleep between bedtime and getting up in the morning (SO)
Fajardo Montañana 2008	Third-party assistance required, IV glucose or glucagon because of severe CNS symptoms associated with hypoglycaemic episodes (SO)	Hypoglycaemic episode also fulfilling ≥ 1 SAE criteria (IO)	SMBG ≤ 3.0 mmol/L (56 mg/dL) (SO)	Between bedtime and measurement of prebreakfast BG; SMBG ≤ 3.0 mmol/L (56 mg/dL) (SO)
Fritsche 2003	Symptoms consistent with hypoglycaemia and requirement of assistance from another person and BG < 2.8 mmol/L (50 mg/dL) or prompt recovery after oral carbohydrate, IV glucose or glucagon administration (SO)	Hypoglycaemic event fulfilling ≥ 1 criterion for an SAE (SO/IO)	ND	ND
Haak 2005	Requirement of assistance from another person + severe CNS symptoms and BG < 2.8 mmol/L (50 mg/dL) + prompt recovery after glucose IV/glucagon or carbohydrates orally (SO)	Hypoglycaemic event fulfilling ≥ 1 criterion for an SAE (SO/IO)	BG < 2.8 mmol/L (50 mg/dL) + symptoms (SO)	BG < 2.8 mmol/L (50 mg/dL) + symptoms; between 23:00 and 06:00 (SO)
Hermanns 2015	ND	ND	BG < 3.9 mmol/L (70.2 mg/dL) or < 3.1 mmol/L (55.8 mg/dL) (SO)	ND
Hermansen 2006	Requirement of assistance from another person + severe CNS symptoms + glucose IV/glucagon (SO)	Hypoglycaemic event fulfilling ≥ 1 criterion for an SAE (SO/IO)	PG ≤ 3.0 mmol/L (54 mg/dL) but no third-party help required (SO)	PG ≤ 3.0 mmol/L (54 mg/dL) + no third-party help required; between 23:00 and 06:00 (SO)
Home 2015	Symptoms consistent with hypoglycaemia requiring assistance from another person + BG < 2.0 mmol/L (36 mg/dL) or prompt recovery after oral carbohydrate, IV glucose or glucagon (SO)	ND	BG < 3.9 mmol/L (70.2 mg/dL) or < 3.1 mmol/L (55.8 mg/dL) + symptoms (SO)	After bedtime and before getting up in the morning; BG < 3.9 mmol/L (70.2 mg/dL) or < 3.1 mmol/L (55.8 mg/dL) + symptoms (SO)
Hsia 2011	ND	ND	ND	ND
Kawamori 2003	Symptoms and requirement of assistance from another person and BG < 2.8 mmol/L (50 mg/dL) or prompt recovery after oral carbohydrate, IV glucose or glucagon administration (SO)	Hypoglycaemic event fulfilling ≥ 1 criterion for an SAE (SO/IO)	ND	ND
Kobayashi 2007 A	Hypoglycaemia was accompanied by subjective symptoms, and treatment by a third party was required (SO)	ND	BG ≤ 3.1 mmol/L (55 mg/dL) ± symptoms (SO)	ND
Kobayashi 2007 B	Symptoms + treatment by a third party was required (SO)	ND	BG ≤ 3.1 mmol/L (55 mg/dL) ±	ND

(Continued)

			symptoms but no third-party help was required (SO)	
Massi 2003	According to DCCT as an event with symptoms and requirement of assistance from another person and BG < 2.8 mmol/L (50 mg/dL) or prompt recovery after oral carbohydrate, IV glucose or glucagon administration (SO)	Hypoglycaemic event fulfilling ≥ 1 criterion for an SAE (SO/IO)	BG < 2.8 mmol/L (50 mg/dL) ± symptoms (SO)	While asleep, between the insulin injection in the evening and before the insulin injection in the morning or before BG measurement in the morning; BG < 2.8 mmol/L (50 mg/dL) ± symptoms (SO)
NCT00687453	ND	ND	ND	ND
NN304-1337	Symptomatic hypoglycaemia that required third-party assistance and BG < 2.8 mmol/L (50 mg/dL) or with prompt recovery after oral carbohydrate, IV glucose or glucagon administration (SO)	Hypoglycaemic event fulfilling ≥ 1 criterion for an SAE (SO/IO)	Symptoms + BG < 70 mg/dL (SO)	Confirmed hypoglycaemia that occurred between 11pm and 6am (SO)
NN304-1808	When assistance to treat was required (SO)	ND	PG < 3.1 mmol/L (< 56 mg/dL) (SO)	Confirmed hypoglycaemia (PG < 3.1 mmol/L) that occurred between bedtime and before getting up in the morning (SO)
NN304-3614	ND	Hypoglycaemic episode reported as SAE (IO)	ND	ND
Pan 2007	Symptoms consistent with hypoglycaemia + BG < 2.8 mmol/L (50 mg/dL) or with prompt recovery after oral carbohydrate, IV glucose or glucagon administration + the requirement of third-party assistance (SO)	Hypoglycaemic event fulfilling ≥ 1 criterion for an SAE (IO)	Symptoms + BG ≤ 75 mg/dL (SO)	Symptoms + BG ≤ 75 mg/dL, after evening insulin injection and before getting up in the morning (SO)
Betônico 2019	SMBG < 50 mg/dL (2.8 mmol/L) or when it resulted in stupor, seizure, or unconsciousness that precluded self-treatment, thus requiring the assistance of another individual (SO)	ND	SMBG or CGM < 3.9 mmol/L (70 mg/dL) even if it was not accompanied by typical symptoms (SO)	Hypoglycaemia (SMBG < 3.9 mmol/L (70 mg/dL) occurring after midnight and before wake-up in the morning (before 7:00 am); values of CGM were not used (SO)
Riddle 2003	Symptoms and requirement of assistance from another person and BG < 3.1 mmol/L (55 mg/dL) or prompt recovery after oral carbohydrate, IV glucose or glucagon administration (SO)	Hypoglycaemic event fulfilling ≥ 1 criterion for an SAE (SO/IO)	PG ≤ 4 mmol/L (72 mg/dL) ± symptoms (SO)	Confirmed hypoglycaemia between the insulin injection in the evening and breakfast or OAD in the morning (SO)
Rosenstock 2001	Symptoms and requirement of assistance from another person and BG < 2.0 mmol/L (36 mg/dL) or prompt recovery after oral carbohydrate, IV glucose or glucagon administration (SO)	Hypoglycaemic event fulfilling ≥ 1 criterion for an SAE (SO/IO)	BG < 2.8 mmol/L (50 mg/dL) ± symptoms (SO)	While asleep, between the insulin injection in the evening and the insulin injection or BG measurement in the morning; BG <

(Continued)

				2.8 mmol/L (50 mg/dL) ± symptoms (SO)
Rosenstock 2009	symptomatic hypoglycaemia requiring assistance and either with BG ≤ 3.1 mmol/L (56 mg/dL) or treated with oral or injectable carbohydrate or glucagon injection (SO)	Hypoglycaemic episode also fulfilling ≥ 1 SAE criteria (SO/IO)	Symptoms + SMBG < 3.9 mmol/L (70 mg/dL) or SMBG < 2.0 mmol/L (36 mg/dL) (SO)	Hypoglycaemia that occurs while asleep, between bedtime after the evening injection and before getting up in the morning, with SMBG < 3.9 mmol/L (70 mg/dL) or SMBG < 2.0 mmol/L (< 36 mg/dL) (SO)
Yki-Järvinen 2006	Symptoms consistent with hypoglycaemia with requirement of assistance from another person and BG < 3.1 mmol/L (56 mg/dL) or prompt recovery after oral carbohydrate, IV glucose or glucagon administration (SO)	ND	Symptoms consistent with hypoglycaemia + BG ≤ 2.8 mmol/L (50 mg/dL) (SO)	BG < 3.5 mmol/L (63 mg/dL) measured in an 8-point 24-hour glucose-profile between bedtime and getting up (before FPG measurement in the morning) (SO)
Yokoyama 2006	Hypoglycaemia requiring any type of external help (SO)	ND	ND	ND

[a]In addition to definition of endpoint measurement, description of who measured the outcome (AO: adjudicated outcome measurement; IO: investigator-assessed outcome measurement; SO: self-reported outcome measurement).

BG: blood glucose; **CGM: c**ontinuous glucose monitoring; **CNS:** central nervous system; **DCCT:** Diabetes Control and Complications Trial; **FPG:** fasting plasma glucose; **IO:** investigator-assessed outcome measurement; **IV:** intravenous; **ND:** not defined; **OAD:** oral antihyperglycaemic drug; **PG:** plasma(-referenced) glucose; **SAE:** serious adverse event; **SMBG:** self-monitoring of blood glucose; **SO:** self-reported outcome measurement.

Appendix 14. Adverse events (I)

Trial ID	Intervention(s) and comparator(s)	Participants included in analysis (n)	Deaths (n)	Deaths (% of participants)	Participants with ≥ 1 adverse event (n)	Participants with ≥ 1 adverse event (%)	Participants with ≥ 1 severe/serious adverse event (n)	Participants with ≥ 1 severe/serious adverse event (%)
Berard 2015	I: insulin glargine once daily	32	—	—	—	—	—	—
	C: NPH insulin once or twice daily	34	—	—	—	—	—	—
Eliaschewitz 2006 [a]	I: insulin glargine at bedtime + glimepiride 4 mg/day in the morning	231	0	0	137	59.3	10	4.3
	C: NPH insulin at bedtime + glimepiride 4 mg/day in the morning	250	0	0	150	60.0	10	4.0
Fajardo Montañana 2008	I: insulin detemir at bedtime	125	0	0	58	46.4	4	3.2
	C: NPH insulin at bedtime	146	0	0	45	30.9	4	2.7
Fritsche 2003	I1: insulin glargine in the morning + glimepiride 3 mg	236	0	0	153	64	19	8.0
	I2: insulin glargine at bedtime + glimepiride 3 mg	227	2	0.9	149	65.6	21	9.3
	C: NPH insulin at bedtime + glimepiride 3 mg	232	1	0.4	152	65.2	22	9.4
Haak 2005	I: detemir once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart	341	2	0.6	213	63	22	6.5
	C: detemir once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart	164	0	0	103	63	16	9.8
Hermanns 2015	I: insulin glargine	340	3[b]	0.9	157[b]	46.2	25[b]	7.3
	C: NPH basal insulin	340	1[b]	0.3	147[b]	43.2	18[b]	5.2

(Continued)

Hermansen 2006 [c]	I: detemir in the morning and evening	237	0	0	119	50.2	15	6.3
	C: NPH insulin in the morning and evening	238	2	0.8	114	47.9	16	6.7
Home 2015	I: insulin glargine	354	5	1.4	113	31.9	—	—
	C: NPH insulin	350	2	0.6	107	30.6	—	—
Hsia 2011	I1: insulin glargine at bedtime	30	0	0	23	76.7	0	0
	I2: insulin glargine in the morning	25	0	0	24	96.0	1	4.0
	C: NPH insulin at bedtime	30	0	0	23	76.7	0	0
Kawamori 2003	I: insulin glargine once in the morning + OAD	158	0	0	110	69.6	4	2.5
	C: NPH insulin once in the morning + OAD	159	0	0	113	71.1	5	3.1
Kobayashi 2007 A	I: insulin detemir once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart	67	0	0	61	91.0	4	6.0
	C: NPH insulin once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart	35	0	0	29	82.9	4	11.4
Kobayashi 2007 B	I: detemir at bedtime + OAD	180	0	0	157	87.2	11	6.1
	C: NPH at bedtime + OAD	183	1	0.5	162	88.5	8	4.4
Massi 2003 [d]	I: insulin glargine once daily subcutaneously at bedtime + OAD	289	1	0.3	185	64.0	46	15.9
	C: NPH insulin once daily subcutaneously at bedtime + OAD	281	7	2.1	193	68.7	41	14.6
NCT00687453	I: insulin glargine at bedtime	11	0	0	8	72.7	0	0
	C: NPH insulin in the morning and at bedtime	13	0	0	5	38.5	0	0
NN304-1337	I: insulin detemir once daily at bedtime + metformin	309	3	1.0	214	69.3	21	6.8

(Continued)

	C: NPH insulin once daily at bedtime + metformin	158	0	0	102	64.6	10	6.3
NN304-1808	I: insulin detemir once daily before breakfast ± metformin at optimal dose	38	0	0	20	52.6	4	10.5
	C: NPH insulin once daily before breakfast ± metformin at optimal dose no bolus insulin	48	2	4.2	28	58.3	10	20.8
NN304-3614	I: insulin detemir in the evening + insulin aspart each meal	24	0	0	21	87.5	3	12.5
	C: NPH insulin in the evening + insulin aspart each meal	35	0	0	32	91.4	3	8.6
Pan 2007	I: insulin glargine in the evening + glimepiride 3 mg in the morning	221	1	0.5	120	54.3	10	4.5
	C: NPH insulin in the evening + glimepiride 3 mg in the morning	223	0	0	130	58.3	12	5.4
Betônico 2019	I: insulin glargine in the morning + insulin lispro at mealtime	Period 1:16 Period 2: 15	Period 1: 0 Period 2: 0	Period 1: 0 Period 2: 0	Period 1: 0 Period 2: 0	Period 1: 0 Period 2: 0	Period 1: 0 Period 2: 0	Period 1: 0 Period 2: 0
	C: NPH insulin 3 times daily + insulin lispro at mealtime	Period 1: 18 Period 2: 14	Period 1: 1 Period 2: 0	Period 1: 5.6 Period 2: 0	Period 1: 3 Period 2: 0	Period 1: 16.7 Period 2: 0	Period 1: 3 Period 2: 0	Period 1: 16.7 Period 2: 0
Riddle 2003	I: insulin glargine once at bedtime + OAD	367	0	0	304	82.8	25	6.8
	C: NPH insulin once at bedtime + OAD	389	0	0	294	75.6	27	6.9
Rosenstock 2001	I: insulin glargine once daily at bedtime + premeal regular insulin	259	2	0.8	218	84.2	35	13.5
	C: NPH insulin once at bedtime or twice daily in the morning and at bedtime + premeal regular insulin	259	3	1.2	218	84.2	36	13.9
Rosenstock 2009	I: insulin glargine once daily, generally at bedtime	514	14	2.7	490	95.3	211	41.1

(Continued)

	C: NPH insulin twice daily, generally in the morning and at bedtime	503	11	2.2	479	95.2	215	42.7
Yki-Järvinen 2006 [e]	I: insulin glargine once at bedtime + metformin	61	0	0	33	54.0	3	4.9
	C: NPH insulin once at bedtime + metformin	49	0	0	24	49.0	4	8.2
Yokoyama 2006	I: insulin glargine once at breakfast + aspart/lispro at each meal with or without OADs	31	—	—	—	—	—	—
	C: NPH insulin daily at bedtime + aspart/lispro at each meal with or without OADs	31	—	—	—	—	—	—

— denotes not reported

[a]Conflicting statements are made in this paper concerning the participants who died during the study. In the paragraph describing the patient flow, it was noted that one participant in the glargine group and five participants in the NPH group died and an additional two participants in the NPH group after discontinuing the study medication. In the results section in the safety paragraph, the authors stated that seven deaths, one in the glargine group and six in the NPH group occurred.
[b]Cross-over trial; number of participants with events only reported combined for both cross-over periods.
[c]The safety analysis population included all randomised participants who received at least one dose of study medication.
[d]Adverse event profiles were similar between the groups. The only between treatment difference with a probable relation to trial medication concerned injection site reports: I1: 13 (participants), 14 (events); C1: 6 (participants), 6 (events).
[e]98% for I1 and 93% for C1 of confirmed symptomatic hypoglycaemia.

C: comparator; **I:** intervention; **n:** number of participants;**NPH:** neutral protamine Hagedorn;**OAD:** oral antihyperglycaemic drug.

Appendix 15. Adverse events (II)

Trial ID	Intervention(s) and comparator(s)	Participants included in analysis (n)	Participants discontinuing trial due to an adverse event (n)	Participants discontinuing trial due to an adverse event (%)	Participants with ≥ 1 hospitalisation (n)	Participants with ≥ 1 hospitalisation (%)	Participants with ≥ 1 outpatient treatment (n)	Participants with ≥ 1 outpatient treatment (%)
Berard 2015	I: insulin glargine once daily	32	—	—	—	—	—	—
	C: NPH insulin once or twice daily	34	—	—	—	—	—	—
Eliaschewitz 2006	I: insulin glargine at bedtime + glimepiride 4 mg/day in the morning	231	2	0.9	—	—	—	—
	C: NPH insulin at bedtime + glimepiride 4 mg/day in the morning	250	0	0	—	—	—	—
Fajardo Montañana 2008	I: insulin detemir at bedtime	125	1	0.8	—	—	—	—
	C: NPH insulin at bedtime	146	0	0	—	—	—	—
Fritsche 2003	I1: insulin glargine in the morning + glimepiride 3 mg	236	5	2.1	—	—	—	—
	I2: insulin glargine at bedtime + glimepiride 3 mg	227	4	1.8	—	—	—	—
	C: NPH insulin at bedtime + glimepiride 3 mg	232	7	3.0	—	—	—	—
Haak 2005	I: detemir once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart	341	8	2.3	—	—	—	—
	C: detemir once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart	164	1	0.6	—	—	—	—
Hermanns 2015	I: insulin glargine	340	6[a]	1.8	—	—	—	—
	C: NPH basal insulin	340	5[a]	1.5	—	—	—	—

(Continued)

Hermansen 2006	I: detemir in the morning and evening	237	3	1.3	—	—	—	—
	C: NPH insulin in the morning and evening	238	4	1.7	—	—	—	—
Home 2015	I: insulin glargine	354	6	1.7	—	—	—	—
	C: NPH insulin	350	4	1.1	—	—	—	—
Hsia 2011	I1: insulin glargine at bedtime	30	1	3.3	—	—	—	—
	I2: insulin glargine in the morning	25	1	4	—	—	—	—
	C: NPH insulin at bedtime	30	0	0	—	—	—	—
Kawamori 2003	I: insulin glargine once in the morning + OAD	158	2	1.3	—	—	—	—
	C: NPH insulin once in the morning + OAD	159	1	0.6	—	—	—	—
Kobayashi 2007 A	I: insulin detemir once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart	67	0	0	—	—	—	—
	C: NPH insulin once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart	35	1	2.9	—	—	—	—
Kobayashi 2007 B	I: detemir at bedtime + OAD	180	8	4.4	—	—	—	—
	C: NPH at bedtime + OAD	183	5	2.7	—	—	—	—
Massi 2003	I: insulin glargine once daily subcutaneously at bedtime + OAD	289	5	1.7	32	11.1	—	—
	C: NPH insulin once daily subcutaneously at bedtime + OAD	281	7	2.5	32	11.4	—	—
NCT00687453	I: insulin glargine at bedtime	11	—	—	—	—	—	—
	C: NPH insulin in the morning and at bedtime	13	—	—	—	—	—	—
NN304-1337	I: insulin detemir once daily at bedtime + metformin	309	9	2.9	—	—	—	—

(Continued)

	C: NPH insulin once daily at bedtime + metformin	158	4	2.5	—	—	—	—
NN304-1808	I: insulin detemir once daily before breakfast ± metformin at optimal dose	38	0	0	—	—	—	—
	C: NPH insulin once daily before breakfast ± metformin at optimal dose no bolus insulin	48	2	4.2	—	—	—	—
NN304-3614	I: insulin detemir in the evening + insulin aspart each meal	24	1	4.2	—	—	—	—
	C: NPH insulin in the evening + insulin aspart each meal	35	1	2.9	—	—	—	—
Pan 2007	I: insulin glargine in the evening + glimepiride 3 mg in the morning	221	5	2.3	—	—	—	—
	C: NPH insulin in the evening + glimepiride 3 mg in the morning	223	2	0.9	—	—	—	—
Betônico 2019	I: insulin glargine in the morning + insulin lispro at mealtime	Period 1:16 Period 2: 15	Period 1: 0 Period 2: 0	Period 1: 0 Period 2: 0	Period 1: 0 Period 2: 0	Period 1: 0 Period 2: 0	Period 1: 0 Period 2: 0	Period 1: 0 Period 2: 0
	C: NPH insulin 3 times daily + insulin lispro at mealtime	Period 1: 18 Period 2: 14	Period 1: 3 Period 2: 0	Period 1: 16.7 Period 2: 0	Period 1: 4 Period 2: 0	Period 1: 22.2 Period 2: 0	Period 1: 0 Period 2: 0	Period 1: 0 Period 2: 0
Riddle 2003	I: insulin glargine once at bedtime + OAD	367	6	1.6	14	3.8	—	—
	C: NPH insulin once at bedtime + OAD	389	4	1.0	18	4.6	—	—
Rosenstock 2001	I: insulin glargine once daily at bedtime + premeal regular insulin	259	9	3.5	24	9.3	—	—
	C: NPH insulin once at bedtime or twice daily in the morning and at bedtime + premeal regular insulin	259	7	2.7	23	8.9	—	—
Rosenstock 2009	I: insulin glargine once daily, generally at bedtime	514	16	3.1	—	—	—	—

(Continued)

	C: NPH insulin twice daily, generally in the morning and at bedtime	503	11	2.2	—	—	—	—
Yki-Järvinen 2006	I: insulin glargine once at bedtime + metformin	61	1	1.6	—	—	—	—
	C: NPH insulin once at bedtime + metformin	49	1	2.0	—	—	—	—
Yokoyama 2006	I: insulin glargine once at breakfast + aspart/lispro at each meal with or without OADs	31	—	—	—	—	—	—
	C: NPH insulin daily at bedtime + aspart/lispro at each meal with or without OADs	31	—	—	—	—	—	—

— denotes not reported.

[a]Cross-over trial; number of participants with events only reported combined for both cross-over periods.

C: comparator; **I:** intervention; **n:** number of participants;**NPH:** neutral protamine Hagedorn;**OAD:** oral antihyperglycaemic drug.

Appendix 16. Adverse events (III)

Trial ID	Intervention(s) and comparator(s)	Participants included in analysis (n)	Participants with ≥ 1 hypoglycaemic episode (n)	Participants with ≥ 1 hypoglycaemic episode (%)	Participants with ≥ 1 nocturnal hypoglycaemic episode (n)	Participants with ≥ 1 nocturnal hypoglycaemic episode (% participants)
Berard 2015	I: insulin glargine once daily	32	—	—	—	—
	C: NPH insulin once or twice daily	34	—	—	—	—
Eliaschewitz 2006	I: insulin glargine + glimepiride	231	BG ≤ 75 mg/dL: 122	BG ≤ 75 mg/dL: 52.8	BG ≤ 75 mg/dL: 39 BG ≤ 50 mg/dL: 19	BG ≤ 75 mg/dL: 16.9 BG ≤ 50 mg/dL: 8.3
	C: NPH insulin at bedtime + glimepiride 4 mg/day in the morning	250	BG ≤ 75 mg/dL: 157	BG ≤ 75 mg/dL: 62.8	BG ≤ 75 mg/dL: 75 BG ≤ 50 mg/dL: 37	BG ≤ 75 mg/dL: 30.0 BG ≤ 50 mg/dL: 14.8
Fajardo Montañana 2008	I: insulin detemir at bedtime	125	BG < 70 mg/dL: 45 BG < 36 mg/dL: 7	BG < 70 mg/dL: 36.0 BG < 36 mg/dL: 5.6	BG < 70 mg/dL: 20 BG < 36 mg/dL: 4	BG < 70 mg/dL: 16.0 BG < 36 mg/dL: 3.2
	C: NPH insulin at bedtime	146	BG < 70 mg/dL: 76 BG < 36 mg/dL: 19	BG < 70 mg/dL: 52.1 BG < 36 mg/dL: 13.0	BG < 70 mg/dL: 44 BG < 36 mg/dL: 10	BG < 70 mg/dL: 30.0 BG < 36 mg/dL: 6.8
Fritsche 2003	I1: insulin glargine in the morning + glimepiride 3 mg	236	—	—	—	—
	I2: insulin glargine at bedtime + glimepiride 3 mg	227	—	—	—	—
	C: NPH insulin at bedtime + glimepiride 3 mg	232	—	—	—	—
Haak 2005	I: detemir once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart	341	BG < 36 mg/dL: 24 BG < 70 mg/dL: 162	BG < 36 mg/dL: 7.0 BG < 70 mg/dL: 47.5	BG < 36 mg/dL: 5 BG < 70 mg/dL: 55	BG < 36 mg/dL: 1.5 BG < 70 mg/dL: 16.1
	C: detemir once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart	164	BG < 36 mg/dL: 18 BG < 70 mg/dL: 88	BG < 36 mg/dL: 11.0 BG < 70 mg/dL: 53.7	BG < 36 mg/dL: 9 BG < 70 mg/dL: 44	BG < 36 mg/dL: 5.5 BG < 70 mg/dL: 26.8

(Continued)

Hermanns 2015	I: insulin glargine	**Period 1**: 175 **Period 2**: 152 **Complete study period**: 327	**Period 1**: BG < 3.9 mmol/L: 44 BG < 3.1 mmol/L: 32 **Period 2**: BG < 3.9 mmol/L: 38 BG < 3.1 mmol/L: 26 **Complete study period**: BG < 3.9 mmol/L: 82 BG < 3.1 mmol/L: 58	**Period 1**: BG < 3.9 mmol/L: 25.1 BG < 3.1 mmol/L: 18.3 **Period 2**: BG < 3.9 mmol/L: 25.0 BG < 3.1 mmol/L: 17.1 **Complete study period**: BG < 3.9 mmol/L: 25.1 BG < 3.1 mmol/L: 17.7	**Period 1**: BG < 3.9 mmol/L: 16 BG < 3.1 mmol/L: 14 **Period 2**: BG < 3.9 mmol/L: 9 BG < 3.1 mmol/L: 7 **Complete study period**: BG < 3.9 mmol/L: 25 BG < 3.1 mmol/L: 21	**Period 1**: BG < 3.9 mmol/L: 9.1 BG < 3.1 mmol/L: 8.0 **Period 2**: BG < 3.9 mmol/L: 5.9 BG < 3.1 mmol/L: 4.6 **Complete study period**: BG < 3.9 mmol/L: 7.6 BG < 3.1 mmol/L: 6.4
	C: NPH basal insulin	**Period 1**: 164 **Period 2**: 159 **Complete study period**: 323	**Period 1**: BG < 3.9 mmol/L: 37 BG < 3.1 mmol/L: 25 **Period 2**: BG < 3.9 mmol/L: 38 BG < 3.1 mmol/L: 26 **Complete study period**: BG < 3.9 mmol/L: 75 BG < 3.1 mmol/L: 51	**Period 1**: BG < 3.9 mmol/L: 22.6 BG < 3.1 mmol/L: 15.2 **Period 2**: BG < 3.9 mmol/L: 23.9 BG < 3.1 mmol/L: 16.4 **Complete study period**: BG < 3.9 mmol/L: 23.2 BG < 3.1 mmol/L: 15.8	**Period 1**: BG < 3.9 mmol/L: 20 BG < 3.1 mmol/L: 14 **Period 2**: BG < 3.9 mmol/L: 15 BG < 3.1 mmol/L: 10 **Complete study period**: BG < 3.9 mmol/L: 35 BG < 3.1 mmol/L: 24	**Period 1**: BG < 3.9 mmol/L: 12.2 BG < 3.1 mmol/L: 8.5 **Period 2**: BG < 3.9 mmol/L: 9.4 BG < 3.1 mmol/L: 6.3 **Complete study period**: BG < 3.9 mmol/L: 10.8 BG < 3.1 mmol/L: 7.4
Hermansen 2006	I: detemir in the morning and evening	237	BG < 36 mg/dL: 5 BG < 70 mg/dL: 135	BG < 36 mg/dL: 2.1 BG < 70 mg/dL: 57	BG < 36 mg/dL: 2 BG < 70 mg/dL: 62	BG < 36 mg/dL: 0.8 BG < 70 mg/dL: 26.2
	C: NPH insulin in the morning and evening	238	BG < 36 mg/dL: 15 BG < 70 mg/dL: 186	BG < 36 mg/dL: 6.3 BG < 70 mg/dL: 78.2	BG < 36 mg/dL: 6 BG < 70 mg/dL: 105	BG < 36 mg/dL: 2.5 BG < 70 mg/dL: 44.1

(Continued)

Home 2015	I: insulin glargine	354	BG < 3.9 mmol/L: 229 BG < 3.1 mmol/L: 129	BG < 3.9 mmol/L: 64.7 BG < 3.1 mmol/L: 36.4	BG < 3.9 mmol/L: 123 BG < 3.1 mmol/L: 57	BG < 3.9 mmol/L: 34.7 BG < 3.1 mmol/L: 16.1
	C: NPH insulin	350	BG < 3.9 mmol/L: 214 BG < 3.1 mmol/L: 126	BG < 3.9 mmol/L: 61.1 BG < 3.1 mmol/L: 36.0	BG < 3.9 mmol/L: 133 BG < 3.1 mmol/L: 69	BG < 3.9 mmol/L: 38.0 BG < 3.1 mmol/L: 19.7
Hsia 2011	I1: insulin glargine at bedtime	30	—	—	—	—
	I2: insulin glargine in the morning	25	—	—	—	—
	C: NPH insulin at bedtime	30	—	—	—	—
Kawamori 2003	I: insulin glargine once in the morning + OAD	158	—	—	—	—
	C: NPH insulin once in the morning + OAD	159	—	—	—	—
Kobayashi 2007 A	I: insulin detemir once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart	67	—	—	—	—
	C: NPH insulin once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart	35	—	—	—	—
Kobayashi 2007 B	I: detemir at bedtime + OAD	180	—	—	—	—
	C: NPH at bedtime + OAD	183	—	—	—	—
Massi 2003	I: insulin glargine once daily subcutaneously at bedtime + OAD	289	BG < 36 mg/dL: 6 BG < 50 mg/dL: 39	BG < 36 mg/dL: 2.1 BG < 50 mg/dL: 13.5	BG < 36 mg/dL: 2 BG < 50 mg/dL: 14	BG < 36 mg/dL: 0.7 BG < 50 mg/dL: 4.8
	C: NPH insulin once daily subcutaneously at bedtime + OAD	281	BG < 36 mg/dL: 8 BG < 50 mg/dL: 46	BG < 36 mg/dL: 2.8 BG < 50 mg/dL: 16.4	BG < 36 mg/dL: 3 BG < 50 mg/dL: 27	BG < 36 mg/dL: 1.1 BG < 50 mg/dL: 9.6
NCT00687453	I: insulin glargine at bedtime	11	—	—	—	—
	C: NPH insulin in the morning and at bedtime	13	—	—	—	—
NN304-1337	I: insulin detemir once daily at bedtime + metformin	309	PG < 36 mg/dL: 6	PG < 36 mg/dL: 1.9	PG < 36 mg/dL: 0	PG < 36 mg/dL: 0

(Continued)

			PG < 70 mg/dL: 48	PG < 70 mg/dL: 15.5	PG < 70 mg/dL: 21	PG < 70 mg/dL: 6.8
	C: NPH insulin once daily at bedtime + metformin	158	PG < 36 mg/dL: 9 PG < 70 mg/dL: 47	PG < 36 mg/dL: 5.7 PG < 70 mg/dL: 29.7	PG < 36 mg/dL: 3 PG < 70 mg/dL: 25	PG < 36 mg/dL: 1.9 PG < 70 mg/dL: 15.8
NN304-1808	I: insulin detemir once daily before breakfast ± metformin at optimal dose	38	—	—	—	—
	C: NPH insulin once daily before breakfast ± metformin at optimal dose	48	—	—	—	—
NN304-3614	I: insulin detemir in the evening + insulin aspart each meal	24	—	—	—	—
	C: NPH insulin in the evening + insulin aspart each meal	35	—	—	—	—
Pan 2007	I: insulin glargine in the evening + glimepiride 3 mg in the morning	221	BG ≤ 75 mg/dL: 85	BG ≤ 75 mg/dL: 38.5	BG ≤ 75 mg/dL: 54	BG ≤ 75 mg/dL: 24.4
	C: NPH insulin in the evening + glimepiride 3 mg in the morning	223	BG ≤ 75 mg/dL: 125	BG ≤ 75 mg/dL: 56.1	BG ≤ 75 mg/dL: 90	BG ≤ 75 mg/dL: 40.4
Betônico 2019	I: insulin glargine in the morning + insulin lispro at mealtime	**Period 1**: 16 **Period 2**: 15	**Period 1**: BG < 3.9 mmol/L: 13 BG < 2.8 mmol/L: 5 **Period 2**: BG < 3.9 mmol/L: 11 BG < 2.8 mmol/L: 1	**Period 1**: BG < 3.9 mmol/L: 81.3 BG < 2.8 mmol/L: 31.3 **Period 2**: BG < 3.9 mmol/L: 73.3 BG < 2.8 mmol/L: 6.7	**Period 1**: BG < 3.9 mmol/L: 4 BG < 2.8 mmol/L: 3 **Period 2**: BG < 3.9 mmol/L: 4 BG < 2.8 mmol/L: 0	**Period 1**: BG < 3.9 mmol/L: 25.0 BG < 2.8 mmol/L: 18.8 **Period 2**: BG < 3.9 mmol/L: 26.7 BG < 2.8 mmol/L: 0
	C: NPH insulin 3 times daily + insulin lispro at mealtime	**Period 1**: 18 **Period 2**: 14	**Period 1**: BG < 3.9 mmol/L: 14 BG < 2.8 mmol/L: 3 **Period 2**: BG < 3.9 mmol/L: 12	**Period 1**: BG < 3.9 mmol/L: 77.8 BG < 2.8 mmol/L: 16.7 **Period 2**: BG < 3.9 mmol/L: 85.7	**Period 1**: BG < 3.9 mmol/L: 10 BG < 2.8 mmol/L: 4 **Period 2**: BG < 3.9 mmol/L: 2	**Period 1**: BG < 3.9 mmol/L: 55.6 BG < 2.8 mmol/L: 22.2 **Period 2**: BG < 3.9 mmol/L: 14.3

(Continued)

			BG < 2.8 mmol/L: 5	BG < 2.8 mmol/L: 35.7	BG < 2.8 mmol/L: 4	BG < 2.8 mmol/L: 28.6
Riddle 2003	I: insulin glargine once at bedtime + OAD	367	PG < 36 mg/dL: 18 PG < 72 mg/dL: 248	PG < 36 mg/dL: 4.9 PG < 72 mg/dL: 67.6	PG < 36 mg/dL: 6 PG < 72 mg/dL: 146	PG < 36 mg/dL: 1.6 PG < 72 mg/dL: 39.8
	C: NPH insulin once at bedtime + OAD	389	PG < 36 mg/dL: 30 PG < 72 mg/dL: 282	PG < 36 mg/dL: 7.7 PG < 72 mg/dL: 72.5	PG < 36 mg/dL: 11 PG < 72 mg/dL: 192	PG < 36 mg/dL: 2.8 PG < 72 mg/dL: 49.4
Rosenstock 2001	I: insulin glargine once daily at bedtime + premeal regular insulin	259	BG < 36 mg/dL: 17 BG < 50 mg/dL: 76	BG < 36 mg/dL: 6.6 BG < 50 mg/dL: 29.3	BG < 36 mg/dL: 13 BG < 50 mg/dL: 45	BG < 36 mg/dL: 5.0 BG < 50 mg/dL: 17.4
	C: NPH insulin once at bedtime or twice daily in the morning and at bedtime + premeal regular insulin	259	BG < 36 mg/dL: 27 BG < 50 mg/dL: 95	BG < 36 mg/dL: 10.4 BG < 50 mg/dL: 36.7	BG < 36 mg/dL: 12 BG < 50 mg/dL: 50	BG < 36 mg/dL: 4.6 BG < 50 mg/dL: 19.3
Rosenstock 2009	I: insulin glargine once daily, generally at bedtime	513	BG < 3.9 mmol/L: 381 BG < 2.0 mmol/L: 185	BG < 3.9 mmol/L: 74.3 BG < 2.0 mmol/L: 36.1	BG < 3.9 mmol/L: 275 BG < 2.0 mmol/L: 93	BG < 3.9 mmol/L: 53.6 BG < 2.0 mmol/L: 18.1
	C: NPH insulin twice daily, generally in the morning and at bedtime	504	BG < 3.9 mmol/L: 394 BG < 2.0 mmol/L: 222	BG < 3.9 mmol/L: 78.2 BG < 2.0 mmol/L: 44.0	BG < 3.9 mmol/L: 295 BG < 2.0 mmol/L: 126	BG < 3.9 mmol/L: 58.5 BG < 2.0 mmol/L: 25.0
Yki-Järvinen 2006	I: insulin glargine once at bedtime + metformin	61	BG ≤ 50 mg/dL: 45	BG ≤ 50 mg/dL: 73.8	BG ≤ 63 mg/dL: 19	BG ≤ 63 mg/dL: 32.2
	C: NPH insulin once at bedtime + metformin	49	BG ≤ 50 mg/dL: 40	BG ≤ 50 mg/dL: 81.6	BG ≤ 63 mg/dL: 20	BG ≤ 63 mg/dL: 42.6
Yokoyama 2006	I: insulin glargine once at breakfast + aspart/lispro at each meal with or without OADs	31	—	—	—	—
	C: NPH insulin daily at bedtime + aspart/lispro at each meal with or without OADs	31	—	—	—	—

(Continued)

— denotes not reported

[a]Different numbers of participants with severe hypoglycaemic events given in the official study report: 1 vs. 1.

BG: blood glucose;**C:** comparator; **I:** intervention; **n:** number of participants;**NPH:** neutral protamine Hagedorn; **OAD:** oral antihyperglycaemic drug; **PG:** plasma(-referenced) glucose.

Appendix 17. Adverse events (IV)

Trial ID	Intervention(s) and comparator(s)	Participants included in analysis (n)	Participants with ≥ 1 severe hypoglycaemic episode (n)	Participants with ≥ 1 severe hypoglycaemic episode (%)	Participants with ≥ 1 serious hypoglycaemic episode (n)	Participants with ≥ 1 serious hypoglycaemic episode (%)
Berard 2015	I: insulin glargine once daily	32	—	—	—	—
	C: NPH insulin once or twice daily	34	—	—	—	—
Eliasche-witz 2006	I: insulin glargine + glimepiride	231	6	2.6	0	0
	C: NPH insulin at bedtime + glimepiride 4 mg/day in the morning	250	11	4.4	0	0
Fajardo Montañana 2008	I: insulin detemir at bedtime	125	0	0	0	0
	C: NPH insulin at bedtime	146	2	1.4	0	0
Fritsche 2003	I1: insulin glargine in the morning + glimepiride 3 mg	236	5	2.1	3	1.3
	I2: insulin glargine at bedtime + glimepiride 3 mg	227	4	1.8	1	0.4
	C: NPH insulin at bedtime + glimepiride 3 mg	232	6	2.6	0	0
Haak 2005	I: detemir once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart	341	6	1.8	0	0
	C: detemir once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart	164	3	1.9	2	1.2
Hermanns 2015	I: insulin glargine	**Period 1**: 175 **Period 2**: 152	**Period 1**: — **Period 2**: — **Complete study period**: 0[a]	**Period 1**: — **Period 2**: — **Complete study period**: 0.0	—	—

(Continued)

		Complete study period: 327				
	C: NPH basal insulin	**Period 1**: 164 **Period 2**: 159 **Complete study period**: 323	**Period 1**: — **Period 2**: — **Complete study period**: 2[a]	**Period 1**: — **Period 2**: — **Complete study period**: 0.6	—	—
Hermansen 2006	I: detemir in the morning and evening	237	1	0.4	0	0
	C: NPH insulin in the morning and evening	238	6	2.5	5	2.1
Home 2015	I: insulin glargine	354	3	0.8	—	—
	C: NPH insulin	350	1	0.3	—	—
Hsia 2011	I1: insulin glargine at bedtime	30	0	0	0	0
	I2: insulin glargine in the morning	25	0	0	0	0
	C: NPH insulin at bedtime	30	0	0	0	0
Kawamori 2003	I: insulin glargine once in the morning + OAD	158	2	1.4	0	0
	C: NPH insulin once in the morning + OAD	159	0	0	0	0
Kobayashi 2007 A	I: insulin detemir once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart	67	—	—	—	—
	C: NPH insulin once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart	35	—	—	—	—
Kobayashi 2007 B	I: detemir at bedtime + OAD	180	—	—	—	—
	C: NPH at bedtime + OAD	183	—	—	—	—
Massi 2003	I: insulin glargine once daily subcutaneously at bedtime + OAD	289	5	1.7	2	0.9
	C: NPH insulin once daily subcutaneously at bedtime + OAD	281	3	1.1	2	1.0
NCT00687453	I: insulin glargine at bedtime	11	—	—	—	—
	C: NPH insulin in the morning and at bedtime	13	—	—	—	—
NN304-1337	I: insulin detemir once daily at bedtime + metformin	309	0	0	0	0

(Continued)

	C: NPH insulin once daily at bedtime + metformin	158	1	0.6	1	0.6
NN304-1808	I: insulin detemir once daily before breakfast ± metformin at optimal dose	38	0	0	—	—
	C: NPH insulin once daily before breakfast ± metformin at optimal dose	48	1	2.1	—	—
NN304-3614	I: insulin detemir in the evening + insulin aspart each meal	24	—	—	1	4.2
	C: NPH insulin in the evening + insulin aspart each meal	35	—	—	0	0
Pan 2007	I: insulin glargine in the evening + glimepiride 3 mg in the morning	221	5	2.3	0	0
	C: NPH insulin in the evening + glimepiride 3 mg in the morning	223	16	7.2	2	0.9
Betônico 2019	I: insulin glargine in the morning + insulin lispro at mealtime	**Period 1**:16 **Period 2**: 15	**Period 1**: 0 **Period 2**: 0	**Period 1**: 0 **Period 2**: 0	—	—
	C: NPH insulin 3 times daily + insulin lispro at mealtime	**Period 1**: 18 **Period 2**: 14	**Period 1**: 2 **Period 2**: 0	**Period 1**: 11.1 **Period 2**: 0	—	—
Riddle 2003	I: insulin glargine once at bedtime + OAD	367	9	2.5	9	2.5
	C: NPH insulin once at bedtime + OAD	389	7	1.8	7	1.8
Rosenstock 2001	I: insulin glargine once daily at bedtime + premeal regular insulin	259	1	0.4	2	0.8
	C: NPH insulin once at bedtime or twice daily in the morning and at bedtime + premeal regular insulin	259	6	2.3	6	2.3
Rosenstock 2009	I: insulin glargine once daily, generally at bedtime	513	40	7.8	33	6.4
	C: NPH insulin twice daily, generally in the morning and at bedtime	504	60	11.9	46	9.1
Yki-Järvinen 2006	I: insulin glargine once at bedtime + metformin	61	0	0	0	0
	C: NPH insulin once at bedtime + metformin	49	0	0	0	0
Yokoyama 2006	I: insulin glargine once at breakfast + aspart/lispro at each meal with or without OADs	31	0	0	—	—

(Continued)

C: NPH insulin daily at bedtime + aspart/lispro at each meal with or without OADs	31	0	0	—	—

— denotes not reported.

[a]Different numbers of participants with severe hypoglycaemic events given in the official study report

BG: blood glucose;**C:** comparator; **I:** intervention; **N:** number of participants;**NPH:** neutral protamine Hagedorn; **OAD:** oral antihyperglycaemic drug; **PG:** plasma(-referenced) glucose.

Appendix 18. Adverse events (V)

Trial ID	Interventions(s) and comparator(s)	Participants included in analysis (n)	Participants with a specific AE (description)	Participants with ≥ 1 specific AEs (n)	Participants with ≥ 1 specific AE (%)
Berard 2015	I: insulin glargine once daily	—	(1) Skin reaction	(1) —	(1) —
			(2) Weight gain (BMI)	(2) —	(2) —
			(3) AE associated with the eye	(3) —	(3) —
	C: NPH insulin once or twice daily	—	(1) Skin reaction	(1) —	(1) —
			(2) Weight gain (BMI)	(2) —	(2) —
			(3) AE associated with the eye	(3) —	(3) —
Eliaschewitz 2006	I: insulin glargine in the evening + glimepiride 4 mg in the morning	231	(1) Skin reaction	(1) 23	(1) 10.0
			(2) Weight gain (BMI)	(2) 1.5 (1.4)[a]	(2) NA
			(3) AE associated with the eye	(3) —	(3) —
	C: NPH insulin in the evening + glimepiride 4 mg in the morning	250	(1) Skin reaction	(1) 29	(1) 11.6
			(2) Weight gain (BMI)	(2) 1.3 (1.3)[a]	(2) NA
			(3) AE associated with the eye	(3) —	(3) —
Fajardo Montañana 2008	I: insulin detemir at bedtime	125	(1) Skin reaction	(1) 2	(1) 1.6
			(2) Weight gain (BMI)	(2) 0.17 (1.11)[a]	(2) NA
			(3) AE associated with the eye	(3) 0	(3) 0
	C: NPH insulin at bedtime	146	(1) Skin reaction	(1) 0	(1) 0
			(2) Weight gain (BMI)	(2) 0.77 (1.21)[a]	(2) NA
			(3) AE associated with the eye	(3) 1	(3) 0.7
Fritsche 2003	I1: insulin glargine in the morning + glimepiride 3 mg	236	(1) Skin reaction	(1) 17	(1) 7.2
			(2) Weight gain (BMI)	(2) 1.4 (1.6)[a]	(2) NA

(Continued)

			(3) AE associated with the eye	(3) 6	(3) 2.5
	I2: insulin glargine at bedtime + glimepiride 3 mg	227	(1) Skin reaction	(1) 17	(1) 7.5
			(2) Weight gain (BMI)	(2) 1.3 (1.3)[a]	(2) NA
			(3) AE associated with the eye	(3) 1	(3) 0.4
	C: NPH insulin at bedtime + glimepiride 3 mg	232	(1) Skin reaction	(1) 21	(1) 9.0
			(2) Weight gain (BMI)	(2) 1.1 (1.6)[a]	(2) NA
			(3) AE associated with the eye	(3) 3	(3) 1.3
Haak 2005	I: detemir once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart	341	(1) Skin reaction	(1) 5	(1) 1.5
			(2) Weight gain (BMI)	(2) —	(2) —
			(3) AE associated with the eye	(3) 20	(3) 5.9
	C: detemir once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart	164	(1) Skin reaction	(1) 0	(1) 0
			(2) Weight gain (BMI)	(2) —	(2) —
			(3) AE associated with the eye	(3) 10	(3) 6.1
Hermanns 2015	I: insulin glargine	—	(1) Skin reaction	(1) —	(1) —
			(2) Weight gain (BMI)	(2) —	(2) —
			(3) AE associated with the eye	(3) —	(3) —
	C: NPH basal insulin	—	(1) Skin reaction	(1) —	(1) —
			(2) Weight gain (BMI)	(2) —	(2) —
			(3) AE associated with the eye	(3) —	(3) —
Hermansen 2006	I: detemir in the morning and evening	237	(1) Skin reaction	(1)15	(1) 6.3
			(2) Weight gain (BMI)	(2) —	(2) —
			(3) AE associated with the eye – retina disorders	(3) 0	(3) 0
			(4) AE associated with the eye – abnormal visual acuity	(4) 1	(4) 0.4
	C: NPH insulin in the morning and evening	238	(1) Skin reaction	(1) 8	(1) 3.4
			(2) Weight gain	(2) —	(2) —
			(3) AE associated with the eye– retina disorders	(3) 1	(3) 0.4
			(4) AE associated with the eye – abnormal visual acuity	(4) 1	(4) 0.4
Home 2015	I: insulin glargine	—	(1) Skin reaction	(1) —	(1) —
			(2) Weight gain (BMI)	(2) —	(2) —

(Continued)

			(3) AE associated with the eye	(3) —	(3) —
	C: NPH insulin	—	(1) Skin reaction	(1) —	(1) —
			(2) Weight gain (BMI)	(2) —	(2) —
			(3) AE associated with the eye	(3) —	(3) —
Hsia 2011	I1: insulin glargine at bedtime	30	(1) Skin reaction	(1) —	(1) —
			(2) Weight gain (BMI)	(2) 0.7 (1.6)[a]	(2) NA
			(3) AE associated with the eye	(3) 1	(3) 3.3
	I2: insulin glargine in the morning	25	(1) Skin reaction	(1) —	(1) —
			(2) Weight gain (BMI)	(2) 1.1 (1.4)[a]	(2) NA
			(3) AE associated with the eye	(3) 0	(3) 0
	C: NPH insulin at bedtime	30	(1) Skin reaction	(1) —	(1) —
			(2) Weight gain (BMI)	(2) 0 (1.5)[a]	(2) NA
			(3) AE associated with the eye	(3) 0	(3) 0
Kawamori 2003	I: insulin glargine once in the morning + OAD	158	(1) Skin reaction	(1) 1	(1) 0.6
			(2) Weight gain (BMI)	(2) —	(2) —
			(3) AE associated with the eye	(3) 1	(3) 0.2
	C: NPH insulin once in the morning + OAD	159	(1) Skin reaction	(1) 1	(1) 0.6
			(2) Weight gain (BMI)	(2) —	(2) —
			(3) AE associated with the eye	(3) 2	(3) 1.2
Kobayashi 2007 A	I: insulin detemir once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart	67	(1) Skin reaction	(1) —	(1) —
			(2) Weight gain (BMI)	(2) —	(2) —
			(3) AE associated with the eye	(3) 1	(3) 1.5
	C: NPH insulin once daily at bedtime or twice daily in the morning and at bedtime + mealtime insulin aspart	35	(1) Skin reaction	(1) —	(1) —
			(2) Weight gain (BMI)	(2) —	(2) —
			(3) AE associated with the eye	(3) 1	(3) 2.9
Kobayashi 2007 B	I: detemir at bedtime + OAD	180	(1) Skin reaction	(1) —	(1) —
			(2) Weight gain (BMI)	(2) —	(2) —
			(3) AE associated with the eye	(3) 3	(3) 1.7
	CI: NPH at bedtime + OAD	183	(1) Skin reaction	(1) —	(1) —
			(2) Weight gain (BMI)	(2) —	(2) —
			(3) AE associated with the eye	(3) 17	(3) 9.3

(Continued)

Massi 2003	I: insulin glargine once daily subcutaneously at bedtime + OAD	289	(1) Skin reaction	(1) 9	(1) 3.1
			(2) Weight gain (BMI)	(2) —	(2) —
			(3) AE associated with the eye	(3) 9	(3) 3.1
	C: NPH insulin once daily subcutaneously at bedtime + OAD	281	(1) Skin reaction	(1) 11	(1) 3.9
			(2) Weight gain (BMI)	(2) —	(2) —
			(3) AE associated with the eye	(3) 7	(3) 2.5
NCT00687453	I: insulin glargine at bedtime	11	(1) Skin reaction	(1) —	(1) —
			(2) Weight gain (BMI)	(2) —	(2) —
			(3) AE associated with the eye	(3) —	(3) —
	C: NPH insulin in the morning and at bedtime	13	(1) Skin reaction	(1) —	(1) —
			(2) Weight gain (BMI)	(2) —	(2) —
			(3) AE associated with the eye	(3) —	(3) —
NN304-1337	I: insulin detemir once daily at bedtime + metformin	309	(1) Skin reaction	(1) 29	(1) 9.4
			(2) Weight gain (BMI)	(2) —	(2) —
			(3) AE associated with the eye – retina disorders	(3) 5	(3) 1.6
				(4) 0	(4) 0
			(4) AE associated with the eye – retina oedema	(5) 6	(5) 1.9
			(5) AE associated with the eye – abnormal visual acuity		
	C: NPH insulin once daily at bedtime + metformin	158	(1) Skin reaction	(1) 18	(1) 11.4
			(2) Weight gain (BMI)	(2) —	(2) —
			(3) AE associated with the eye – retina disorders	(3) 1	(3) 0.6
				(4) 1	(4) 0.6
			(4) AE associated with the eye – retina oedema	(5) 4	(5) 2.5
			(5) AE associated with the eye – abnormal visual acuity		
NN304-1808	I: insulin detemir once daily before breakfast ± metformin at optimal dose	38	(1) Skin reaction	(1) 3	(1) 7.9
			(2) Weight gain (BMI)	(2) —	(2) —
			(3) AE associated with the eye	(3) 0	(3) 0
	C: NPH insulin once daily before breakfast ± metformin at optimal dose	48	(1) Skin reaction	(1) 2	(1) 4.2
			(2) Weight gain (BMI)	(2) —	(2) —
			(3) AE associated with the eye	(3) 1	(3) 2.1

(Continued)

NN304-3614	I: insulin detemir in the evening + insulin aspart each meal	24	(1) Skin reaction (2) Weight gain (BMI) (3) AE associated with the eye	(1) 0 (2) — (3) 0	(1) 0 (2) — (3) 0
	C: NPH insulin in the evening + insulin aspart each meal	35	(1) Skin reaction (2) Weight gain (BMI) (3) AE associated with the eye	(1) 2 (2) — (3) 0	(1) 5.7 (2) — (3) 0
Pan 2007	I: insulin glargine in the evening + glimepiride 3 mg in the morning	221	(1) Skin reaction (2) Weight gain (BMI) (3) AE associated with the eye	(1) 19 (2) 1.18 (0.99)[a] (3) 5	(1) 8.6 (2) NA (3) 2.3
	C: NPH insulin in the evening + glimepiride 3 mg in the morning	223	(1) Skin reaction (2) Weight gain (BMI) (3) AE associated with the eye	(1) 19 (2) 1.08 (1.08)[a] (3) 2	(1) 8.5 (2) NA (3) 0.9
Betônico 2019	I: insulin glargine in the morning + insulin lispro at mealtime	Period 1: 16 Period 2: 15	(1) Skin reaction (2) Weight gain (BMI) (3) AE associated with the eye	(1) Period 1: 0 Period 2: 0 (2) Period 1: 1.0 (—)[a] Period 2: −0.3 (—)[a] (3) Period 1: 0 Period 2: 0	(1) Period 1: 0 Period 2: 0 (2) Period 1: NA Period 2: NA (3) Period 1: 0 Period 2: 0
	C: NPH insulin 3 times daily + insulin lispro at mealtime	Period 1: 18 Period 2: 14	(1) Skin reaction (2) Weight gain (BMI) (3) AE associated with the eye	(1) Period 1: 0 Period 2: 0 (2) Period 1: 0.4 (—)[a] Period 2: 0.5 (—)[a] (3) Period 1: 0 Period 2: 0	(1) Period 1: 0 Period 2: 0 (2) Period 1: NA Period 2: NA (3) Period 1: 0 Period 2: 0
Riddle 2003	I: insulin glargine once at bedtime + OAD	367	(1) Skin reaction (2) Weight gain (BMI) (3) AE associated with the eye	(1) 15 (2) 1.01 (1.14)[a] (3) 5	(1) 4.1 (2) NA (3) 1.4
	C: NPH insulin once at bedtime + OAD	389	(1) Skin reaction (2) Weight gain (BMI) (3) AE associated with the eye	(1) 11 (2) 0.94 (1.04)[a] (3) 3	(1) 2.8 (2) NA (3) 0.8

(Continued)

Rosenstock 2001	I: insulin glargine once daily at bedtime + pre-meal regular insulin	259	(1) Skin reaction	(1) 31	(1) 12.0
			(2) Weight gain (BMI)	(2) —	(2) —
			(3) AE associated with the eye	(3) 57	(3) 22.0
	C: NPH insulin once at bedtime or twice daily in the morning and at bedtime + premeal regular insulin	259	(1) Skin reaction	(1) 22	(1) 8.5
			(2) Weight gain (BMI)	(2) —	(2) —
			(3) AE associated with the eye	(3) 64	(3) 24.7
Rosenstock 2009	I: insulin glargine once daily, generally at bedtime	514	(1) Skin reaction	(1) 12	(1) 2.3
			(2) Weight gain (BMI)	(2) —	(2) —
			(3) AE associated with the eye	(3) —	(3) —
	C: NPH insulin twice daily, generally in the morning and at bedtime	503	(1) Skin reaction	(1) 7	(1) 1.4
			(2) Weight gain (BMI)	(2) —	(2) —
			(3) AE associated with the eye	(3) —	(3) —
Yki-Järvinen 2006	I: insulin glargine once at bedtime + metformin	61	(1) Skin reaction	(1) 0	(1) 0
			(2) Weight gain (BMI)	(2) 0.9 (1.5)[a]	(2) NA
			(3) AE associated with the eye	(3) —	(3) —
	C: NPH insulin once at bedtime + metformin	49	(1) Skin reaction	(1) 1	(1) 2.0
			(2) Weight gain (BMI)	(2) 1.2 (1.6)[a]	(2) NA
			(3) AE associated with the eye	(3) —	(3) —
Yokoyama 2006	I: insulin glargine once at breakfast + aspart/lispro at each meal with or without OADs	31	(1) Skin reaction	(1) —	(1) —
			(2) Weight gain (BMI)	(2) 0.5 (4.24)[a]	(2) NA
			(3) AE associated with the eye	(3) —	(3) —
	C: NPH insulin daily at bedtime + aspart/lispro at each meal with or without OADs	31	(1) Skin reaction	(1) —	(1) —
			(2) Weight gain (BMI)	(2) −0.6 (2.86)[a]	(2) NA
			(3) AE associated with the eye	(3) —	(3) —

— denotes not reported

[a]Mean (SD) change in BMI from baseline and study end.

AE: adverse event; **BMI:** body mass index; **C:** comparator; **I:** intervention; **n:** number of participants;**NA:** not applicable;**NPH:** neutral protamine Hagedorn; **OAD:** oral antihyperglycaemic drug; **SD:** standard deviation.

Appendix 19. Survey of trial investigators providing information on included trials

Trial ID	Date trial author contacted	Date trial author replied	Date trial author was asked for additional information (short summary)	Date trial author provided data (short summary)
Berard 2015	3 March 2017	3 March 2017	9 May 2017 (information on study design, characteristics and results).	No additional information provided.
Eliaschewitz 2006	2006[a]	—	—	Additional information was derived from the IQWiG report.
Fajardo Montañana 2008	—	—	—	Additional information was derived from the IQWiG report.
Fritsche 2003	2006[a]	—	—	Additional information was derived from the IQWiG report.
Haak 2005	2006[a]	2006	2006 (information on study design, characteristics and results).	2006 (information on study design, characteristics and results) Additional information was derived from the IQWiG report.
Hermanns 2015	3 March 2017	8 March 2017	9 May 2017 (information on study design, characteristics and results).	6 June 2017 (information on study design and characteristics)
Hermansen 2006	2006[a]	—	—	Additional information was derived from the IQWiG report.
Home 2015	3 March 2017	3 March 2017	9 May 2017 (information on study design, characteristics and results).	No additional information provided.
Hsia 2011	3 March 2017	3 March 2017	9 May 2017 (information on study design, characteristics and results).	No additional information provided.
ISRCTN76123473	5 March 2017	16 March 2020	—	16 March 2020 (not conducted as a separate trial but integrated in the trial Yki-Järvinen 2006).
Kawamori 2003	—	—	—	Additional information was derived from the IQWiG report.
Kobayashi 2007 A	3 March 2017	No answer	—	Additional information was derived from the IQWiG report.
Kobayashi 2007 B	3 March 2017	No answer	—	Additional information was derived from the IQWiG report.
Massi 2003	2006[a]	No answer	—	Additional information was derived from the IQWiG report.
NCT00687453	3 March 2017	3 March 2017	9 May 2017 (information on study design, characteristics and results).	No additional information provided.

(Continued)

NN304-1337	7 March 2017	9 March 2017	—	—
NN304-1808	7 March 2017	9 March 2017	—	—
NN304-3614	7 March 2017	9 March 2017	—	—
NCT00788840	3 March 2017	No answer	—	—
NCT01310452	3 March 2017	No answer	—	—
NCT01500850	3 March 2017	No answer	—	—
NCT01854723	5 March 2020	No answer	—	Status of trial on ClinicalTrials.gov was changed to "withdrawn" on 10 March 2020.
Pan 2007	—	—	—	Additional information was derived from the IQWiG report.
Betônico 2019	3 March 2017	8 March 2017	9 May 2017 and 3 July 2017 (information on study design, characteristics and results).	22 May 2017 and 18 July 2017 (information on study design, characteristics and results).
Riddle 2003	2006[a]	2006	2006 (information on study design, characteristics and results).	2006 (information on study design, characteristics and results). Additional information was derived from the IQWiG report.
Rosenstock 2001	2006[a]	No answer	—	Additional information was derived from the IQWiG report.
Rosenstock 2009	—	—	—	Additional information was derived from the IQWiG report.
Yki-Järvinen 2006	2006[a]	2006	2006 (information on study design, characteristics and results).	2006 (information on study design, characteristics and results). Additional information was derived from the IQWiG report.
Yokoyama 2006	2006[a] 3 March 2017	2006 2017 No answer	2006 (information on study design, characteristics and results).	2006 (information on study design, characteristics and results). Additional information was derived from the IQWiG report.

[a]Trial authors were contacted during the preparation of the original version of this review.

IQWiG: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care).

Appendix 20. 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	Minimal important difference
Problem Areas in Diabetes Questionnaire (PAID) (S) Used in: Hermanns 2015	Overall 20 items no dimensions	Yes	5-point Likert scale	Overall score	Minimum score: 0 Maximum score: 100	No	Lower values mean better assessment	Not evaluated
SF-12 (G) Used in: Hermanns 2015	Physical functioning (PF) (2) Role-physical (RP) (2) Bodily pain (BP) (1) General health (GH) (1) Vitality (VT) (1) Social functioning (SF) (1) Role-emotional (RE) (2) Mental health (MH) (2)	Yes	2-, 3-, 5- and 6-point Likert scale	Scores for dimensions; PCS; MCS	Minimum scores: scores for dimensions/PCS/MCS: norm-based scale Maximum scores: scores for dimensions/PCS/MCS: norm-based scale	No	Higher values mean better assessment	Not evaluated
EQ-5D (G) Used in: Hermanns 2015	Mobility (3) Self-care Usual activities (3) Pain/discomfort (3) Anxiety/depression (3)	Yes	3-point scale and 100-point VAS	Overall score	Single weighted summary index score calculated from the individual scores for the 5 dimensions Minimum index: 0 Maximum index: 1	Yes	Higher index score means better assessment	—
W-BQ22 Used in: Massi 2003; Rosenstock 2001	Depression (6) Anxiety (6) Energy (4) Positive well-being (6)	Yes	4-point Likert scale	Scores for dimensions; overall score	Minimum scores: scores for dimensions: 0 Overall score: 0 Maximum scores: Depression, anxiety, positive well-being: 18; energy: 12 Overall score: 66	No	General well-being; energy; positive well-being: higher values mean better assessment Depression; anxiety: lower values mean	Not evaluated

(Continued)

							better assessment	
Insulin Therapy Related Quality Of Life at Night (ITR-QOLN) (S) Used in: Kobayashi 2007 A	Overall 21 items; Anxiety before sleep (—) Disturbances during sleep (—) Glycaemic control before breakfast (—) Overall well-being (—)	Yes	7-point Likert scale	Scores for dimensions; overall score	—	No	—	—

EQ-5D: EuroQol 5 Dimension; **G:** generic; **MCS:** mental component summary; **PCS:** physical component summary; **S:** specific; **SF-12:** 12-item Short Form Health Survey; **VAS:** visual analogue scale; **W-BQ22:** Well-being Questionnaire (22 items).

FEEDBACK

Comment to the protocol by Horvath,

Summary

Page 1: The general statement "evidence for the beneficial effect of antihyperglycaemic therapy is conflicting" is out of date. It is generally accepted that microvascular complications are reduced by effective glycaemic control in diabetes type 2, and there is increasing evidence for reduction of macrovascular complications if glycaemic control is established early in the course of the disease (published type 1 diabetes, ongoing large clinical studies in type 2 diabetes). There is no evidence "that different interventions carry different substance specific beneficial or adverse effects". Establishing glycaemic control in diabetes type 2 is the essential element of preventing microvascular and macrovascular complications [by early insulin therapy, in suitable clinical conditions by oral antihyperglycaemic agents, and by combination treatment]. The substance specific beneficial or adverse effects of the two classes of compounds (insulins versus oral antidiabetic drugs, OAD) are entirely different. Within the pharmacological group of insulins, differences are related more to the dosage form (immediate acting insulin or intermediate acting insulin) than to the specific substances (animal insulins, human insulin or insulin analogues).

The statement "firm conclusions on the effect of interventions on patient relevant outcomes cannot be drawn from the effect…. on blood glucose concentrations alone" is ambiguous because treatment to glycaemic targets is the primary objective in type 2 diabetes, the effect of achieving glycaemic control on microvascular complications is firmly established.

The statement "insulin in itself is a group of heterogeneous preparations" needs to be changed to "the insulin drug substance is used in a number of presentations of different duration of action".

Page 2: It is useful to extend the definition of insulin analogues "changing the amino acid sequence, and the physicochemical properties", because the essential element is delayed absorption due to the physicochemical change.

The definition of insulin glargine needs to include "which is less soluble at the injection site, and forms an amorphous precipitate in the subcutaneous tissue which is gradually absorbed (Sandow et al 2003)". Glargine does not form crystals or micro-precipitates as quoted in outdated reviews.

The statement in the last paragraph refers to human insulin as well as insulin analogues and can be worded "structural homology of human insulin to insulin like growth factor (IGF-I) has caused concern…" because the findings with high (supra-physiological) doses of human insulin in experimental preclinical studies indicate that human insulin has mitogenic activity which is dose-related, when animals are treated with excessive doses of human insulin may cause effects similar to those of IGF-I [EPAR].

The references that "IGF-I may affect the progression of retinopathy" need to be updated in view of the clinical consensus that progression of retinopathy is related to the rapid normalisation of glycaemic control, whereas the systemic and local factors involved in progression of retinopathy are not completely resolved. The specific effect of IGF-I in clinical studies (Thrailkill et al 1999) on formation of macular edema is not found with insulin analogues.

The statement "modified insulin analogues have shown a carcinogenic effect in the mammary gland of female rats" is not correct, there is only one fast acting insulin analogue [B10-Asp]-insulin which has shown such an effect and was subsequently used as the comparator for all new insulin analogues. > From the publication of Kurtzhals 2000 it is evident that all clinically used insulin analogues differ from [B10-Asp]-insulin (which has markedly prolonged residence time on the insulin receptor) by a (rate of dissociation which is similar to human insulin or even shorter. It cannot be justified to quote the evidence for the current insulin analogues in this rudimentary form. No preclinical evidence has been brought forward for the "potentially adverse properties of insulin analogues", on the contrary extensive clinical testing and post-marketing surveillance reporting has shown no evidence for either increased mitogenic efficacy in patients, or for progression of retinopathy and related events (retinal bleeding).

The proposed aim of the Cochrane review is to review clinical efficacy and safety. In this context, reference to the "increased mitogenic potential" should be discontinued because the scientific evidence has been evaluated by the competent authorities (EMEA and FDA), and periodic safety updates are evaluated which do not provide evidence or support the contentions of "increased mitogenic potential" in the therapeutic dose range used for both type 1 diabetes and type 2 diabetes.

The inclusion criteria for studies with combination therapy should clearly state "long acting analogue combined with other antihyperglycaemic drugs", and should not be limited to combination with one antihyperglycaemic drug, because the clinical study protocols frequently included more than one orally active antihyperglycaemic drug. There are also studies comparing combination treatment (NPH insulin plus OAD vs. long acting insulin analogue alone). Excluding such studies from the evaluation would create unnecessary bias and loss of evidence. The clinical relevance of combination treatment reflects the reality of present-day therapy. Comparing basal insulin therapy alone with combination therapy in RCT-24 studies is important for EBM assessment.
The statement "only studies reporting on insulin regiments (schemata) with subcutaneous application" should be omitted because the two long acting insulin analogues to be reviewed are approved for subcutaneous application only, both are contraindicated and unsuitable for CSII due to their physicochemical properties.

Page 3: In the primary outcome measure, it is surprising to find hypoglycaemia events first followed by glycaemic control. The clinical evidence is clearly that improving and maintaining glycaemic control is the key objective in type 2 diabetes (as well as in type 1 diabetes). Prevention or a delay of progression of microvascular and macrovascular complications follows from treatment to close hypoglycaemic targets, as defined by IDF, ADA and National Diabetes Societies. The key issue is whether glycaemic control can be achieved to the same extent as by conventional NPH insulin, and whether the risk of hypoglycaemic events can be reduced by new treatment regimens, using long acting insulins alone, combination with orally active antidiabetic drugs (OAD), and early insulinisation.

For the secondary outcome measure, it is suggested to evaluate first the evidence for reduced microvascular complications. This may be followed by evaluation of reduction of macrovascular complications, for which supporting evidence from studies of "duration of 24 weeks or longer" (Page 2) cannot be expected at the present time, because longer observation periods are clearly required, as is well-established from similar long term observations in diabetes type 1.

References: Concerning the "additional references" on pages 6 and 7 of the protocol, it is suggested to update this reference list considerably because much of the recent evidence for effective treatment of type 2 diabetes and related studies in type 1 diabetes and the effect on microvascular/macrovascular complications needs to be included.
It is proposed to omit reference to the "increased mitogenicity" arguments, or to include an updated and comprehensive discussion of the topic with relevant contemporary references. [Reference and reprints forwarded by separate mail]

Reply

Many thanks for your comments on this important topic.

Regarding the first comment, we will not make any changes because our interpretation of the statement that the "evidence for the beneficial effects of antihyperglycaemic therapy is conflicting" is based on the currently published results of randomised controlled trials dealing with drugs that lower blood glucose.
According your suggestions, we will extend the definition of insulin analogues and provide a more precise definition of insulin glargine.

Though the content of the paragraph about carcinogenicity and mitogenic potency is correct, we have rephrased it to make it more comprehensive.

Our review will aim to assess advantages or disadvantages of long-acting insulin analogues as compared to NPH insulin. To detect any differences between both treatment arms any additional anti hyperglycaemic agents have to be part of each treatment group.

We do not understand the comment that our statement "only studies reporting on insulin regimens with subcutaneous application" should be omitted because e.g. studies using inhalative insulin as additional treatment in both groups will be excluded as well.

Concerning the criticism of the ranking of our outcome measures, it was the decision reached by consensus of all protocol authors in terms of patient-relevant endpoints.

Contributors

Prof Dr Juergen Sandow. Submitter has modified conflict of interest statement: I am a member of the diabetes research group at Sanofi Aventis.

Response to Horvath and colleagues,

Summary

Horvath et al. concluded their review with the following statement "If at all, only a minor clinical benefit of treatment with long-acting insulin analogues (LAIA) for patients with diabetes mellitus type 2 treated with "basal" insulin regarding symptomatic nocturnal hypoglycaemic events. Until long-term efficacy and safety data are available, we suggest a cautious approach to therapy with insulin glargine or detemir."

We believe this interpretation is overly critical of the long-acting analogues, and fails to take into consideration some important points. Defined as a "minor clinical benefit", the consistent finding of reduced risk of hypoglycaemia with LAIA reflects the authors' preconceived bias that contradicts the very essence of the Cochrane reviews, and it disregards the importance of hypoglycaemia in clinical diabetes. Firstly, hypoglycaemia is not a trivial problem from the point of view of many patients and physicians, and is a leading barrier to effective use of insulin.

The widespread use of both glargine and detemir has occurred in part due to the experience, both in studies and in clinical practice, that hypoglycaemia is reduced when they are used instead of human intermediate insulins. However, the authors counter this beneficial effect of LAIA in their discussion, using the argument that there is a possibility of bias because the studies were not blinded. Although lack of blinding is a conventional objection that might have influenced hypoglycaemia reporting, measurements of glucose confirming hypoglycaemic events are quite objective and less likely to be affected by lack of blinding of treatment. In fact, blinding was not possible owing to the cloudy physical characteristics of NPH and the clear nature of the soluble LAIAs that have consistently shown less frequent hypoglycaemic events.

Secondly, with regards to the methodology of the paper, most of the studies selected were equivalence studies or non-inferiority trials performed as required for regulatory approval. Thus, not surprisingly, if the hypothesis that preceded the meta-analysis was to demonstrate HbA1c superiority of LAIAs over NPH, this was not found because it was not the intent, nor was it in concordance with the objective of the majority of the published study data used for the analysis. Moreover, the differences in hypoglycaemia observed between human insulins and insulin analogues are greater as glycaemic control approaches the usual target levels, HbA1c 7.0 or 6.5%. Non-inferiority studies generally do not aim to optimise control, and therefore may minimise this advantage. A statistical analysis of this problem of interpretation has recently been published (Mullins et al, 2007) and is very relevant to the conclusions of the meta-analysis. A leading point is that when rates of hypoglycaemia are adjusted for baseline or achieved HbA1c levels, differences between human insulin and analogues become more apparent.

Thirdly, the authors stated that "no trial reported data on quality of life". We believe this is misleading and inaccurate, as aspects of quality of life, such as treatment satisfaction, have been reported at various congresses with full reports in progress. Data sets would have been fully available from the sponsors had the authors requested them. Their findings are consistent with the study by Eliaschewitz, which is cited in the review.

Finally, the secondary endpoints of the meta-analysis were mortality/cardiovascular morbidity/diabetic late complications. The studies analysed did not aim to investigate these variables and their duration was not long enough to take these into consideration. Even though the authors acknowledge this in their discussion, they still conclude that no important improvements in the development of microvascular complications would be expected from treatment with LAIAs. This is correct because there is no reason to believe that these new insulins should have any intrinsic or direct effect to benefit complications. What it is incorrect is to advise caution in the conclusion when using LAIA. Caution implies by definition "avoiding danger or harm; close attention or vigilance to minimize risk". We think this advice is premature, and the evidence for potential harm is scanty and should not have been given a place in their conclusion. Any strong remarks or recommendations based on theoretical risks of LAIAs should await completion of ongoing outcome studies on retinopathy and cardiovascular parameters, and results fully analysed and published.

In conclusion, we believe the clinical benefits of LAIA over NPH insulin are more than "minor" in many situations, and that the advice to use LAIAs with "caution" is not warranted and is inappropriate on the basis of existing findings. Long-acting insulin analogues are widely used tools that have facilitated insulin management to achieve glycaemic control more safely and more predictably with significantly less risk of hypoglycaemia, allowing more active self-titration by patients with type 2 diabetes. Ongoing studies will provide more complete answers to the questions about long-term risks and benefits of these agents, and will allow more definitive conclusions.

References

Mullins P, Sharplin P, Yki-Jarvinen H, Riddle MC, Haring HU. Negative binomial meta-regression analysis of combined glycosylated haemoglobin and hypoglycaemia outcomes across eleven Phase III and IV studies of insulin glargine compared with neutral protamine Hagedorn insulin in type 1 and type 2 diabetes mellitus. Clin Ther 2007; 29: 1607-1619.

Reply

We thank Drs Rosenstock, Fritsche and Riddle for their interest in our review and their comments.

We agree that hypoglycaemia is indeed an important clinical problem affecting the well being and treatment satisfaction of patients, and the extent to which blood glucose concentration can be lowered. Indeed, the effectiveness of insulin therapy can only be evaluated by considering HbA1c change and the corresponding number of hypoglycaemic events together. The fact that we considered hypoglycaemia as being of high importance is also reflected by the fact that we chose the "number of overall, severe and nocturnal hypoglycaemia" (along with HbA1c) as our primary endpoint.

Also it seems that those same considerations were the basis for conducting the non-inferiority trials at hand: with the same efficacy in reducing HbA1c (non-inferiority) an additional benefit of reduced hypoglycaemic events was expected. Since for our review lowering HbA1c was not the sole crucial endpoint, but corresponding hypoglycaemia rates were considered as important, the inclusion of non-inferiority trials does not undermine the conclusions that can be drawn from our results.

At any rate, it is essential that the studies were conducted in such a way, that results could be considered largely as unbiased. Among those items that determine the methodological quality of trials is blinding of patients and caregivers for treatment.
It is true that blinding was not feasible in the studies comparing insulin glargine or detemir with NPH insulin. However, the simple fact that patients and caregivers were not blinded, does raise the risk for bias regardless of whether blinding would have been possible or not. Also in a situation where blinding is not possible or feasible, other precautionary measures, such as adequate concealment of allocation, blinding of endpoint assessment or unequivocal definitions of endpoints have to be taken to minimise the chance for bias. In most of the included studies either this was not done or not reported (see also Table 03 "Study quality" and Table 07 "definition of hypoglycaemia in study as reported"). Also, the lack of blinding was not the only item leading us to conclude that methodological quality was insufficient to rule out bias. Thus, from the information which is available to us, we have to conclude that the results are open for bias.

"Quality of life" is a multidimensional construct. While quality of life and health status instruments are measuring the outcomes of treatment, treatment satisfaction instruments assess the level of satisfaction with health status outcomes (Revicki 2008). Differentiating

between these two concepts, the published trials did not provide any information on aspects of quality of life. However, we still reported the results on treatment satisfaction.

We also contacted all authors of the included studies, among them Drs. Rosenstock, Riddle and Fritsche, asking for additional information. Not all responded. Among those who did was Dr. Riddle. In his letter he told us, that although he had the information we were asking for, he was not able to disclose them to us, because it was the property of Sanofi-Aventis. We also contacted the producers of long-acting insulin analogues "Sanofi-Aventis" and "Novo Nordisk". In the answering letter from Sanofi Aventis (Dr. Vaur) we were told: "With respect to this request I must unfortunately inform you that our company policy is to not provide any third parties with our confidential information such as, e.g. unpublished information contained in study reports or study databases." We did not receive an answer from Novo Nordisk. In contrast, some authors did provide us with additional data which we incorporated in the review – we also acknowledged this wherever applicable.

For insulin therapy in diabetes mellitus, NPH is an effective, safe substance which has been tested over decades. In such cases where a proven effective therapy is available, the introduction of new substances should only be advised if there is a major improvement in efficacy, or if the new substance is proven both effective and safe. Introducing new substances while safety issues are still unanswered could result in harm to patients, as the examples of rosiglitazone, vioxx and others show. So, our advocacy of a cautious approach to therapy with long-acting insulin analogues at this time is justified.

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(Revicki DA. Patient assessment of treatment satisfaction: methods and practical issues. GUT online 2008.)

Contributors

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Submitter has modified conflict of interest statement:
Julio Rosenstock has received grants for research from and/or has been a consultant to Amylin, Boheringer-Ingelhein, Bristol-Myers Squibb, Centocor, Eli Lilly, Emisphere, GlaxoSmithKline, Johnson & Johnson, MannKind, Merck, Novartis, Novo Nordisk, Pfizer, Roche, Sankyo, Sanofi-Aventis and Takeda. Andreas Fritsche has received honoraria for lectures from sanofi-aventis, MSD, NovoNordisk and Bayer. Matthew Riddle has received grant/research support from Amylin, Eli Lilly and Sanofi-Aventis, has been a consultant to Amylin, Eli Lilly, NovoNordisk, Sanofi-Aventis and Valeritas, and has received lecture honoraria from Amylin, Eli Lilly and Sanofi-Aventis.

WHAT'S NEW

Date	Event	Description
7 November 2020	New search has been performed	This is an update of the Cochrane Review published in 2009.
7 November 2020	New citation required and conclusions have changed	Different authors, additional background information and additional studies were included; conclusion has been changed.
18 September 2020	New search has been performed	This is an update of the Cochrane Review first published in Issue 2, 2007

HISTORY

Protocol first published: Issue 1, 2006
Review first published: Issue 2, 2007

Date	Event	Description
17 August 2009	Amended	Missing author added (Thomas Kaiser)

CONTRIBUTIONS OF AUTHORS

All review authors read and approved the final review draft.

TS: assessment of the certainty of the evidence, data extraction and future review updates.

JE: assessment of the certainty of the evidence, data extraction and future review updates.

AS: protocol development, trial selection, data extraction, data analysis, data interpretation, review of drafts and future review updates.

KJ: protocol development, trial search, assessment of the certainty of the evidence, data extraction and future review updates.

AB: protocol development, statistical analysis, development of final review and future review updates.

KH: protocol development, acquisition of trial reports, trial selection, data extraction, data analysis, data interpretation, review of drafts and future review updates.

DECLARATIONS OF INTEREST

KH: was involved in the preparation of the report on long-acting insulin analogues for the treatment of type 2 diabetes mellitus for the Institute for Quality and Efficiency in Health Care (www.iqwig.de). KH has received payment for lectures, travel/accommodations/meeting expenses and consultancy from various sources (Novartis Pharma, Medtronic, AstraZeneca, Novo Nordisk, Sanofi Aventis, Merck Sharp & Dohme, Austrian Diabetes Association).

JE: none.

TS: none.

KJ: was involved in the preparation of the report on long-acting insulin analogues for the treatment of type 2 diabetes mellitus for the Institute for Quality and Efficiency in Health Care (www.iqwig.de).

AB: none.

AS: was involved in the preparation of the report on long-acting insulin analogues for the treatment of type 2 diabetes mellitus for the Institute for Quality and Efficiency in Health Care (www.iqwig.de).

SOURCES OF SUPPORT

Internal sources

- Medical University of Graz, Austria
- Institute of General Practice, Goethe University Frankfurt, Germany

External sources

- Institute for Quality and Efficiency in Health Care (IQWiG), Germany
- German Federal Ministry of Education and Research (FKZ: 01KG1707), Germany

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The review was carried out in accordance with the protocol for the review update. Compared to the protocol for the original review, we changed classifications of some outcomes as primary or secondary endpoints.

NOTES

Portions of the background and methods sections, the appendices, additional tables and figures 1 to 3 of this review are based on a standard template established by the Cochrane Metabolic and Endocrine Disorders Group.

INDEX TERMS

Medical Subject Headings (MeSH)

Bias; Diabetes Mellitus, Type 2 [blood] [complications] [*drug therapy]; Hemoglobin A [metabolism]; Hypoglycemia [chemically induced]; Hypoglycemic Agents [adverse effects] [*therapeutic use]; Insulin Detemir [adverse effects] [*therapeutic use]; Insulin Glargine [adverse effects] [*therapeutic use]; Insulin, Isophane [adverse effects] [*therapeutic use]; Insulin, Long-Acting [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans