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(Ultra-)long-acting insulin analogues for people with type 1 diabetes mellitus (Review)

Hemmingsen B, Metzendorf MI, Richter B

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TABLE OF CONTENTS

ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
SUMMARY OF FINDINGS 4
BACKGROUND 16
OBJECTIVES 17
METHODS 17
RESULTS 21
Figure 1. 22
Figure 2. 23
Figure 3. 27
Figure 4. 33
Figure 5. 38
Figure 6. 40
Figure 7. 43
DISCUSSION 46
AUTHORS' CONCLUSIONS 48
ACKNOWLEDGEMENTS 49
REFERENCES 50
CHARACTERISTICS OF STUDIES 62
RISK OF BIAS 102
DATA AND ANALYSES 129
Analysis 1.1. Comparison 1: Insulin detemir versus NPH insulin, Outcome 1: All-cause mortality 133
Analysis 1.2. Comparison 1: Insulin detemir versus NPH insulin, Outcome 2: All-cause mortality (published vs. unpublished data) 134
Analysis 1.3. Comparison 1: Insulin detemir versus NPH insulin, Outcome 3: Severe hypoglycaemia 135
Analysis 1.4. Comparison 1: Insulin detemir versus NPH insulin, Outcome 4: Severe hypoglycaemia (published vs. unpublished data) 136
Analysis 1.5. Comparison 1: Insulin detemir versus NPH insulin, Outcome 5: Hypoglycaemia reported as a serious adverse event 137
Analysis 1.6. Comparison 1: Insulin detemir versus NPH insulin, Outcome 6: Cardiovascular mortality 138
Analysis 1.7. Comparison 1: Insulin detemir versus NPH insulin, Outcome 7: Non-fatal myocardial infarction 138
Analysis 1.8. Comparison 1: Insulin detemir versus NPH insulin, Outcome 8: Serious adverse events 139
Analysis 1.9. Comparison 1: Insulin detemir versus NPH insulin, Outcome 9: Serious adverse events (published vs. unpublished data) 140
Analysis 1.10. Comparison 1: Insulin detemir versus NPH insulin, Outcome 10: Diabetic ketoacidosis 141
Analysis 1.11. Comparison 1: Insulin detemir versus NPH insulin, Outcome 11: Diabetic ketoacidosis (published vs. unpublished data) 142
Analysis 1.12. Comparison 1: Insulin detemir versus NPH insulin, Outcome 12: Non-serious adverse events 143
Analysis 1.13. Comparison 1: Insulin detemir versus NPH insulin, Outcome 13: Non-serious adverse events (published vs unpublished data) 144
Analysis 1.14. Comparison 1: Insulin detemir versus NPH insulin, Outcome 14: Withdrawals due to adverse events 145
Analysis 1.15. Comparison 1: Insulin detemir versus NPH insulin, Outcome 15: Any nocturnal hypoglycaemia 146
Analysis 1.16. Comparison 1: Insulin detemir versus NPH insulin, Outcome 16: Mild nocturnal hypoglycaemia 147
Analysis 1.17. Comparison 1: Insulin detemir versus NPH insulin, Outcome 17: Nocturnal hypoglycaemia (symptoms) 147
Analysis 1.18. Comparison 1: Insulin detemir versus NPH insulin, Outcome 18: Severe nocturnal hypoglycaemia 148
Analysis 1.19. Comparison 1: Insulin detemir versus NPH insulin, Outcome 19: Any nocturnal hypoglycaemia (published vs. unpublished data) 149
Analysis 1.20. Comparison 1: Insulin detemir versus NPH insulin, Outcome 20: Mild nocturnal hypoglycaemia (published vs. unpublished data) 150
Analysis 1.21. Comparison 1: Insulin detemir versus NPH insulin, Outcome 21: Nocturnal hypoglycaemia, symptoms only (published vs. unpublished data) 151
Analysis 1.22. Comparison 1: Insulin detemir versus NPH insulin, Outcome 22: Severe nocturnal hypoglycaemia (published vs. unpublished data) 152

Analysis 1.23. Comparison 1: Insulin detemir versus NPH insulin, Outcome 23: Nocturnal hypoglycaemia, asymptomatic (children vs. adults) 152
Analysis 1.24. Comparison 1: Insulin detemir versus NPH insulin, Outcome 24: Mild/moderate hypoglycaemia 153
Analysis 1.25. Comparison 1: Insulin detemir versus NPH insulin, Outcome 25: Mild/moderate hypoglycaemia (published vs. unpublished data) 154
Analysis 1.26. Comparison 1: Insulin detemir versus NPH insulin, Outcome 26: HbA1c 155
Analysis 1.27. Comparison 1: Insulin detemir versus NPH insulin, Outcome 27: HbA1c (published vs. unpublished data) 156
Analysis 2.1. Comparison 2: Insulin glargine versus NPH insulin, Outcome 1: All-cause mortality 160
Analysis 2.2. Comparison 2: Insulin glargine versus NPH insulin, Outcome 2: Health-realted quality of life 160
Analysis 2.3. Comparison 2: Insulin glargine versus NPH insulin, Outcome 3: Severe hypoglycaemia 161
Analysis 2.4. Comparison 2: Insulin glargine versus NPH insulin, Outcome 4: Severe hypoglycaemia (published vs. unpublished data) 162
Analysis 2.5. Comparison 2: Insulin glargine versus NPH insulin, Outcome 5: Hypoglycaemia reported as a serious adverse event 163
Analysis 2.6. Comparison 2: Insulin glargine versus NPH insulin, Outcome 6: Cardiovascular mortality 163
Analysis 2.7. Comparison 2: Insulin glargine versus NPH insulin, Outcome 7: Non-fatal myocardial infarction 164
Analysis 2.8. Comparison 2: Insulin glargine versus NPH insulin, Outcome 8: Non-fatal stroke 164
Analysis 2.9. Comparison 2: Insulin glargine versus NPH insulin, Outcome 9: Serious adverse events 165
Analysis 2.10. Comparison 2: Insulin glargine versus NPH insulin, Outcome 10: Serious adverse events (published vs. unpublished data) 166
Analysis 2.11. Comparison 2: Insulin glargine versus NPH insulin, Outcome 11: Diabetic ketoacidosis 167
Analysis 2.12. Comparison 2: Insulin glargine versus NPH insulin, Outcome 12: Diabetic ketoacidosis (published vs. unpublished data) 168
Analysis 2.13. Comparison 2: Insulin glargine versus NPH insulin, Outcome 13: Non-serious adverse events 169
Analysis 2.14. Comparison 2: Insulin glargine versus NPH insulin, Outcome 14: Non-serious adverse events (published vs. unpublished data) 170
Analysis 2.15. Comparison 2: Insulin glargine versus NPH insulin, Outcome 15: Withdrawals due to adverse events 171
Analysis 2.16. Comparison 2: Insulin glargine versus NPH insulin, Outcome 16: Nocturnal hypoglycaemia 172
Analysis 2.17. Comparison 2: Insulin glargine versus NPH insulin, Outcome 17: Mild nocturnal hypoglycaemia 172
Analysis 2.18. Comparison 2: Insulin glargine versus NPH insulin, Outcome 18: Nocturnal hypoglycaemia (symptoms) 173
Analysis 2.19. Comparison 2: Insulin glargine versus NPH insulin, Outcome 19: Severe nocturnal hypoglycaemia 174
Analysis 2.20. Comparison 2: Insulin glargine versus NPH insulin, Outcome 20: Nocturnal hypoglycaemia (published vs. unpublished data) 175
Analysis 2.21. Comparison 2: Insulin glargine versus NPH insulin, Outcome 21: Symptomatic nocturnal hypoglycaemia (published vs. unpublished data) 175
Analysis 2.22. Comparison 2: Insulin glargine versus NPH insulin, Outcome 22: Mild/moderate hypoglycaemia 176
Analysis 2.23. Comparison 2: Insulin glargine versus NPH insulin, Outcome 23: Mild/moderate hypoglycaemia (published vs. unpublished data) 177
Analysis 2.24. Comparison 2: Insulin glargine versus NPH insulin, Outcome 24: HbA1c 178
Analysis 2.25. Comparison 2: Insulin glargine versus NPH insulin, Outcome 25: HbA1c (published vs unpublished data) 179
Analysis 2.26. Comparison 2: Insulin glargine versus NPH insulin, Outcome 26: HbA1c (NPH < 2x/day vs ≥ 2x/day) 180
Analysis 3.1. Comparison 3: Insulin detemir versus insulin glargine, Outcome 1: All-cause mortality 182
Analysis 3.2. Comparison 3: Insulin detemir versus insulin glargine, Outcome 2: Severe hypoglycaemia 182
Analysis 3.3. Comparison 3: Insulin detemir versus insulin glargine, Outcome 3: Severe hypoglycaemia (published vs. unpublished data) 183
Analysis 3.4. Comparison 3: Insulin detemir versus insulin glargine, Outcome 4: Hypoglycaemia reported as a serious adverse event 183
Analysis 3.5. Comparison 3: Insulin detemir versus insulin glargine, Outcome 5: Cardiovascular mortality 184
Analysis 3.6. Comparison 3: Insulin detemir versus insulin glargine, Outcome 6: Non-fatal myocardial infarction 184
Analysis 3.7. Comparison 3: Insulin detemir versus insulin glargine, Outcome 7: Non-fatal stroke 184
Analysis 3.8. Comparison 3: Insulin detemir versus insulin glargine, Outcome 8: Serious adverse events 185
Analysis 3.9. Comparison 3: Insulin detemir versus insulin glargine, Outcome 9: Diabetic ketoacidosis 185
Analysis 3.10. Comparison 3: Insulin detemir versus insulin glargine, Outcome 10: Non-serious adverse events 185

Analysis 3.11. Comparison 3: Insulin detemir versus insulin glargine, Outcome 11: Non-serious adverse events (published vs. unpublished data) 186
Analysis 3.12. Comparison 3: Insulin detemir versus insulin glargine, Outcome 12: Withdrawals due to adverse events 186
Analysis 3.13. Comparison 3: Insulin detemir versus insulin glargine, Outcome 13: Any nocturnal hypoglycaemia 187
Analysis 3.14. Comparison 3: Insulin detemir versus insulin glargine, Outcome 14: Confirmed nocturnal hypoglycaemia (PG < 3.1 mmol/L and no assistance) 187
Analysis 3.15. Comparison 3: Insulin detemir versus insulin glargine, Outcome 15: Symptomatic nocturnal hypoglycaemia (PG ≥ 3.1 or no PG and no assistance required) 188
Analysis 3.16. Comparison 3: Insulin detemir versus insulin glargine, Outcome 16: Severe nocturnal hypoglycaemia 188
Analysis 3.17. Comparison 3: Insulin detemir versus insulin glargine, Outcome 17: Mild/moderate hypoglycaemia 189
Analysis 3.18. Comparison 3: Insulin detemir versus insulin glargine, Outcome 18: HbA1c 189
Analysis 3.19. Comparison 3: Insulin detemir versus insulin glargine, Outcome 19: Individuals with HbA1c < 7% without severe hypoglycaemia 190
Analysis 4.1. Comparison 4: Insulin degludec versus insulin detemir, Outcome 1: All-cause mortality 193
Analysis 4.2. Comparison 4: Insulin degludec versus insulin detemir, Outcome 2: Health-related quality of life 193
Analysis 4.3. Comparison 4: Insulin degludec versus insulin detemir, Outcome 3: Severe hypoglycaemia 194
Analysis 4.4. Comparison 4: Insulin degludec versus insulin detemir, Outcome 4: Hypoglycaemia reported as a serious adverse event 194
Analysis 4.5. Comparison 4: Insulin degludec versus insulin detemir, Outcome 5: Cardiovascular mortality 195
Analysis 4.6. Comparison 4: Insulin degludec versus insulin detemir, Outcome 6: Non-fatal myocardial infarction 195
Analysis 4.7. Comparison 4: Insulin degludec versus insulin detemir, Outcome 7: Non-fatal stroke 195
Analysis 4.8. Comparison 4: Insulin degludec versus insulin detemir, Outcome 8: End stage renal disease 196
Analysis 4.9. Comparison 4: Insulin degludec versus insulin detemir, Outcome 9: Blindness 196
Analysis 4.10. Comparison 4: Insulin degludec versus insulin detemir, Outcome 10: Serious adverse events 197
Analysis 4.11. Comparison 4: Insulin degludec versus insulin detemir, Outcome 11: Diabetic ketoacidosis 197
Analysis 4.12. Comparison 4: Insulin degludec versus insulin detemir, Outcome 12: Non-serious adverse events 198
Analysis 4.13. Comparison 4: Insulin degludec versus insulin detemir, Outcome 13: Withdrawals due to adverse events 198
Analysis 4.14. Comparison 4: Insulin degludec versus insulin detemir, Outcome 14: Nocturnal hypoglycaemia 199
Analysis 4.15. Comparison 4: Insulin degludec versus insulin detemir, Outcome 15: Mild nocturnal hypoglycaemia 199
Analysis 4.16. Comparison 4: Insulin degludec versus insulin detemir, Outcome 16: Nocturnal hypoglycaemia (symptomatic) 200
Analysis 4.17. Comparison 4: Insulin degludec versus insulin detemir, Outcome 17: Nocturnal hypoglycaemia (asymptomatic) 200
Analysis 4.18. Comparison 4: Insulin degludec versus insulin detemir, Outcome 18: Severe nocturnal hypoglycaemia 201
Analysis 4.19. Comparison 4: Insulin degludec versus insulin detemir, Outcome 19: Mild/moderate hypoglycaemia 201
Analysis 4.20. Comparison 4: Insulin degludec versus insulin detemir, Outcome 20: HbA1c 202
Analysis 4.21. Comparison 4: Insulin degludec versus insulin detemir, Outcome 21: Individuals with HbA1c < 7% without severe hypoglycaemia 202
Analysis 5.1. Comparison 5: Insulin degludec versus insulin glargine, Outcome 1: All-cause mortality 205
Analysis 5.2. Comparison 5: Insulin degludec versus insulin glargine, Outcome 2: All-cause mortality (published vs. unpublished data) 206
Analysis 5.3. Comparison 5: Insulin degludec versus insulin glargine, Outcome 3: Health-related quality of life (physical health) 206
Analysis 5.4. Comparison 5: Insulin degludec versus insulin glargine, Outcome 4: Health-related quality of life (mental health) 207
Analysis 5.5. Comparison 5: Insulin degludec versus insulin glargine, Outcome 5: Severe hypoglycaemia 207
Analysis 5.6. Comparison 5: Insulin degludec versus insulin glargine, Outcome 6: Hypoglycaemia reported as a serious adverse event 208
Analysis 5.7. Comparison 5: Insulin degludec versus insulin glargine, Outcome 7: Cardiovascular mortality 208
Analysis 5.8. Comparison 5: Insulin degludec versus insulin glargine, Outcome 8: Non-fatal myocardial infarction 209
Analysis 5.9. Comparison 5: Insulin degludec versus insulin glargine, Outcome 9: Non-fatal stroke 209
Analysis 5.10. Comparison 5: Insulin degludec versus insulin glargine, Outcome 10: Serious adverse events 210
Analysis 5.11. Comparison 5: Insulin degludec versus insulin glargine, Outcome 11: Diabetic ketoacidosis 211
Analysis 5.12. Comparison 5: Insulin degludec versus insulin glargine, Outcome 12: Diabetic ketoacidosis (published vs. unpublished data) 212
Analysis 5.13. Comparison 5: Insulin degludec versus insulin glargine, Outcome 13: Non-serious adverse events 213
Analysis 5.14. Comparison 5: Insulin degludec versus insulin glargine, Outcome 14: Withdrawals due to adverse events 213

Analysis 5.15. Comparison 5: Insulin degludec versus insulin glargine, Outcome 15: Nocturnal hypoglycaemia 214
Analysis 5.16. Comparison 5: Insulin degludec versus insulin glargine, Outcome 16: Mild nocturnal hypoglycaemia 214
Analysis 5.17. Comparison 5: Insulin degludec versus insulin glargine, Outcome 17: Nocturnal hypoglycaemia (asymptomatic) 214
Analysis 5.18. Comparison 5: Insulin degludec versus insulin glargine, Outcome 18: Nocturnal hypoglycaemia (symptomatic) . 215
Analysis 5.19. Comparison 5: Insulin degludec versus insulin glargine, Outcome 19: Severe nocturnal hypoglycaemia 215
Analysis 5.20. Comparison 5: Insulin degludec versus insulin glargine, Outcome 20: Mild/moderate hypoglycaemia 216
Analysis 5.21. Comparison 5: Insulin degludec versus insulin glargine, Outcome 21: HbA1c 216
Analysis 5.22. Comparison 5: Insulin degludec versus insulin glargine, Outcome 22: HbA1c (published vs. unpublished data) .. 217
Analysis 5.23. Comparison 5: Insulin degludec versus insulin glargine, Outcome 23: Individuals with HbA1c < 7% without severe hypoglycaemia 217
ADDITIONAL TABLES 218
APPENDICES 227
WHAT'S NEW 414
HISTORY 414
CONTRIBUTIONS OF AUTHORS 415
DECLARATIONS OF INTEREST 415
SOURCES OF SUPPORT 415
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 415
NOTES 415
INDEX TERMS 416

[Intervention Review]

(Ultra-)long-acting insulin analogues for people with type 1 diabetes mellitus

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ABSTRACT

Background

People with type 1 diabetes mellitus (T1DM) need treatment with insulin for survival. Whether any particular type of (ultra-)long-acting insulin provides benefit especially regarding risk of diabetes complications and hypoglycaemia is unknown.

Objectives

To compare the effects of long-term treatment with (ultra-)long-acting insulin analogues to NPH insulin (neutral protamine Hagedorn) or another (ultra-)long-acting insulin analogue in people with type 1 diabetes mellitus.

Search methods

We searched the Cochrane Central Register of Controlled Trials, MEDLINE, Scopus, ClinicalTrials.gov, the World Health Organization (WHO) International Clinical Trials Registry Platform and the reference lists of systematic reviews, articles and health technology assessment reports. We explored the US Food and Drug Administration (FDA) and European Medical Agency (EMA) web pages. We asked pharmaceutical companies, EMA and investigators for additional data and clinical study reports (CSRs). The date of the last search of all databases was 24 August 2020.

Selection criteria

We included randomised controlled trials (RCTs) with a duration of 24 weeks or more comparing one (ultra-)long-acting insulin to NPH insulin or another (ultra-)long-acting insulin in people with T1DM.

Data collection and analysis

Two review authors assessed risk of bias using the new Cochrane 'Risk of bias' 2 (RoB 2) tool and extracted data. Our main outcomes were all-cause mortality, health-related quality of life (QoL), severe hypoglycaemia, non-fatal myocardial infarction/stroke (NFMI/NFS), severe nocturnal hypoglycaemia, serious adverse events (SAEs) and glycosylated haemoglobin A1c (HbA1c). We used a random-effects model to perform meta-analyses and calculated risk ratios (RRs) and odds ratios (ORs) for dichotomous outcomes and mean differences (MDs) for continuous outcomes, using 95% confidence intervals (CIs) and 95% prediction intervals for effect estimates. We evaluated the certainty of the evidence applying the GRADE instrument.

Main results

We included 26 RCTs. Two studies were unpublished. We obtained CSRs, clinical study synopses or both as well as medical reviews from regulatory agencies on 23 studies which contributed to better analysis of risk of bias and improved data extraction. A total of 8784 participants were randomised: 2428 participants were allocated to NPH insulin, 2889 participants to insulin detemir, 2095 participants

to insulin glargine and 1372 participants to insulin degludec. Eight studies contributing 21% of all participants comprised children. The duration of the intervention varied from 24 weeks to 104 weeks.

Insulin degludec versus NPH insulin: we identified no studies comparing insulin degludec with NPH insulin.

Insulin detemir versus NPH insulin (9 RCTs): five deaths reported in two studies including adults occurred in the insulin detemir group (Peto OR 4.97, 95% CI 0.79 to 31.38; 9 studies, 3334 participants; moderate-certainty evidence). Three studies with 870 participants reported QoL showing no true beneficial or harmful effect for either intervention (low-certainty evidence). There was a reduction in severe hypoglycaemia in favour of insulin detemir: 171/2019 participants (8.5%) in the insulin detemir group compared with 138/1200 participants (11.5%) in the NPH insulin group experienced severe hypoglycaemia (RR 0.69, 95% CI 0.52 to 0.92; 8 studies, 3219 participants; moderate-certainty evidence). The 95% prediction interval ranged between 0.34 and 1.39. Only 1/331 participants in the insulin detemir group compared with 0/164 participants in the NPH insulin group experienced a NFMI (1 study, 495 participants; low-certainty evidence). No study reported NFS. A total of 165/2094 participants (7.9%) in the insulin detemir group compared with 102/1238 participants (8.2%) in the NPH insulin group experienced SAEs (RR 0.95, 95% CI 0.75 to 1.21; 9 studies, 3332 participants; moderate-certainty evidence). Severe nocturnal hypoglycaemia was observed in 70/1823 participants (3.8%) in the insulin detemir group compared with 60/1102 participants (5.4%) in the NPH insulin group (RR 0.67, 95% CI 0.39 to 1.17; 7 studies, 2925 participants; moderate-certainty evidence). The MD in HbA1c comparing insulin detemir with NPH insulin was 0.01%, 95% CI -0.1 to 0.1; 8 studies, 3122 participants; moderate-certainty evidence.

Insulin glargine versus NPH insulin (9 RCTs): one adult died in the NPH insulin group (Peto OR 0.14, 95% CI 0.00 to 6.98; 8 studies, 2175 participants; moderate-certainty evidence). Four studies with 1013 participants reported QoL showing no true beneficial effect or harmful effect for either intervention (low-certainty evidence). Severe hypoglycaemia was observed in 122/1191 participants (10.2%) in the insulin glargine group compared with 145/1159 participants (12.5%) in the NPH insulin group (RR 0.84, 95% CI 0.67 to 1.04; 9 studies, 2350 participants; moderate-certainty evidence). No participant experienced a NFMI and one participant in the NPH insulin group experienced a NFS in the single study reporting this outcome (585 participants; low-certainty evidence). A total of 109/1131 participants (9.6%) in the insulin glargine group compared with 110/1098 participants (10.0%) in the NPH insulin group experienced SAEs (RR 1.08, 95% CI 0.63 to 1.84; 8 studies, 2229 participants; moderate-certainty evidence). Severe nocturnal hypoglycaemia was observed in 69/938 participants (7.4%) in the insulin glargine group compared with 83/955 participants (8.7%) in the NPH insulin group (RR 0.83, 95% CI 0.62 to 1.12; 6 studies, 1893 participants; moderate-certainty evidence). The MD in HbA1c comparing insulin glargine with NPH insulin was 0.02%, 95% CI -0.1 to 0.1; 9 studies, 2285 participants; moderate-certainty evidence.

Insulin detemir versus insulin glargine (2 RCTs),**insulin degludec versus insulin detemir** (2 RCTs), **insulin degludec versus insulin glargine** (4 RCTs): there was no evidence of a clinically relevant difference for all main outcomes comparing (ultra-)long-acting insulin analogues with each other.

For all outcomes none of the comparisons indicated differences in tests of interaction for children versus adults.

Authors' conclusions

Comparing insulin detemir with NPH insulin for T1DM showed lower risk of severe hypoglycaemia in favour of insulin detemir (moderate-certainty evidence). However, the 95% prediction interval indicated inconsistency in this finding. Both insulin detemir and insulin glargine compared with NPH insulin did not show benefits or harms for severe nocturnal hypoglycaemia. For all other main outcomes with overall low risk of bias and comparing insulin analogues with each other, there was no true beneficial or harmful effect for any intervention. Data on patient-important outcomes such as QoL, macrovascular and microvascular diabetic complications were sparse or missing. No clinically relevant differences were found between children and adults.

PLAIN LANGUAGE SUMMARY

Do people with type 1 diabetes mellitus benefit from using a different type of insulin as their basal insulin?

Background

Diabetes is a condition that causes a person's blood sugar (glucose) level to become too high. Insulin is a hormone that is released by the pancreas (a small organ behind the stomach) which controls the blood levels of glucose. In people with type 1 diabetes mellitus (T1DM) the pancreas does not produce any insulin, so the person has to inject insulin to control the glucose levels and keep well. The goal of insulin therapy is to provide insulin that mimics physiologic insulin secretion. Insulin is given by an injection under the skin (subcutaneous) by means of insulin syringes, insulin pens or insulin pumps. In order to control blood glucose levels in periods of fasting, basal or background insulin is needed. Basal insulin can be given by means of daily or twice-daily injections of an intermediate-acting or (ultra-)long-acting insulin. Basal insulin can be given as intermediate-acting human neutral protamine Hagedorn (NPH) insulin or as (ultra-)long-acting analogue insulin (synthetic insulin). Bolus insulin is taken at mealtime (prandial insulin) to control blood glucose levels following a meal and is given by means of short-acting or rapid-acting insulin. The aim for most people with T1DM is to achieve near-normal blood glucose levels to avoid long-term complications such as kidney and eye disease and to allow flexibility regarding time, type and amount of food intake. The major unwanted effect of insulin therapy is hypoglycaemia (low blood glucose) which can be severe.

We wanted to find out whether one type of (ultra-)long-acting insulin compared with NPH insulin or another type of (ultra-)long-acting insulin is better for people with T1DM. The outcomes we were specifically interested in were death, health-related quality of life, severe (night-time) hypoglycaemia, serious unwanted events, non-fatal complications of diabetes (heart attacks, strokes) and levels of glycosylated haemoglobin A1c (HbA1c) which is an indicator of long-term glucose control.

What did we look for?

We searched medical databases and contacted pharmaceutical manufacturers and drug regulatory agencies for studies that:
— were randomised controlled trials (medical studies where participants are put randomly into one of the treatment groups);
— included people with T1DM;
— compared one (ultra-)long-acting insulin with another (ultra-)long-acting insulin or NPH insulin;
— lasted at least 24 weeks.

What did we find?
We found 26 studies including a total of 8780 participants (21% were children). The studies lasted between 24 weeks and two years. They compared:
— NPH insulin with insulin detemir (nine studies);
— NPH insulin with insulin glargine (nine studies);
— Insulin detemir with insulin glargine (two studies);
— Insulin degludec with insulin detemir (two studies);
— Insulin degludec with insulin glargine (four studies).

No study compared NPH insulin with insulin degludec.

Key results

There were no clear differences for all main outcomes comparing (ultra-)long-acting insulin analogues with each other.

Severe hypoglycaemic episodes were reduced with insulin detemir: among 1000 participants using NPH insulin, 115 would experience severe hypoglycaemia; using insulin detemir there would be 36 participants fewer (9 to 55 participants fewer) experiencing severe hypoglycaemia. However, the results were inconsistent, meaning if another study was performed there may not be a clear difference between insulin detemir and NPH insulin. There was no clear difference regarding the risk of severe night-time hypoglycaemia. There were no clear differences for health-related quality of life, serious unwanted effects or HbA1c levels. Very few people experienced a heart attack or died, and stroke was not reported.

There were no clear differences comparing insulin glargine with NPH insulin for all main outcomes. Very few people experienced a heart attack, stroke or died.

There were also no clear differences for all comparisons between children and adults.

Certainty of the evidence
In the comparison of the insulin analogues detemir and glargine with NPH insulin, we are moderately confident about the results for death, severe (night-time) hypoglycaemia, serious unwanted effects and HbA1c levels. We are uncertain about the effects on heart attacks, stroke and health-related quality of life, mainly because there were only a few studies which did not last long enough to reliably investigate these outcomes.

How up to date is this review?
This evidence is up-to-date as of 24 August 2020.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings: insulin detemir versus NPH insulin

Insulin detemir compared with NPH insulin for T1DM

Patients: people with T1DM

Settings: outpatients

Intervention: insulin detemir

Comparison: NPH insulin

Outcomes	NPH insulin	Insulin detemir	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
All-cause mortality Follow-up: 24-104 weeks	See comment		**Peto OR 4.97** (0.79 to 31.38)	3334 (9)	⊕⊕⊕⊖ **moderate**[a]	All 5 deaths reported in 2 studies including adults occurred in the insulin detemir group
Health-related quality of life Description: diabetes health profile; insulin therapy-related quality of life at night (scale not specified) Follow-up: 26-48 weeks	See comment			870 (3)	⊕⊕⊖⊖ **low**[b]	No study reported health-related quality of life in a format making it suitable for meta-analysis 1 study including adults reported higher scores in the insulin detemir group vs the NPH insulin group (Kobayashi 2007) 2 studies did not show evidence of a difference between intervention groups (NCT00595374 included children; Standl 2004 included adults)
Severe hypoglycaemia (n/N) Definition: hypoglycaemia requiring third party assistance (Bartley 2008; Kobayashi 2007; NCT00605137; Robertson 2007; Russell-Jones 2004; Standl 2004; Thalange 2013; Vague 2003); episodes where the children were semi-conscious, unconscious or in a	**115 per 1000**	**79 per 1000** (60 to 106)	**RR 0.69** (0.52 to 0.92)	3219 (8)	⊕⊕⊕⊖ **moderate**[c]	The 95% prediction interval ranged between 0.34 and 1.39 5 studies included adults, 3 studies included children (the test for subgroup differences did not indicate interaction)

coma, with or without convulsions (Thalange 2013) Follow-up: 24-104 weeks						
Non-fatal myocardial infarction/stroke Definition: myocardial infarction Follow-up: 24 months	See comment			495 (1)	⊕⊕⊖⊖ **low**[d]	1/331 participants in the insulin detemir group vs 0/164 participants in the NPH insulin group experienced a non-fatal myocardial infarction (Bartley 2008) Stroke was not reported Study included adults
Severe nocturnal hypoglycaemia (n/N) Definition: severe hypoglycaemia occurring 23:00-06:00 (Bartley 2008; NCT00605137; Russell-Jones 2004; Standl 2004; Vague 2003); occurring 22:00-07:00 (Robertson 2007; Thalange 2013) Follow-up: 24 weeks - 24 months	**54 per 1000**	**36 per 1000** (21 to 64)	**RR 0.67** (0.39 to 1.17)	2925 (7)	⊕⊕⊕⊖ **moderate**[e]	The 95% prediction interval ranged between 0.16 and 2.87 4 studies included adults, 3 studies included children (the test for subgroup differences did not indicate interaction)
Serious adverse events (n/N) Follow-up: 24-104 weeks	**82 per 1000**	**78 per 1000** (62 to 100)	**RR 0.95** (0.75 to 1.21)	3332 (9)	⊕⊕⊕⊖ **moderate**[e]	The 95% prediction interval ranged between 0.71 and 1.27 6 studies included adults, 3 studies included children (the test for subgroup differences did not indicate interaction)
HbA1c (%) Follow-up: 24 weeks - 24 months	The mean HbA1c ranged across the NPH insulin groups from 7.3% to 8.6%	The mean HbA1c in the insulin detemir groups was **0.01% higher** (0.1% lower to 0.1% higher)	—	3122 (8)	⊕⊕⊕⊖ **moderate**[e]	The 95% prediction interval ranged between -0.1% and 0.1% 5 studies included adults, 3 studies included children (the test for subgroup differences did not indicate interaction)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **CSR**: clinical study report; **HbA1c**: glycosylated haemoglobin A1c; **n/N**: number of people experiencing an event; **NPH**: neutral protamine Hagedorn; **OR**: odds ratio **RR:** risk ratio; **T1DM**: type 1 diabetes mellitus.

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.

*Assumed risk was derived from the event rates in the comparator groups.
[a]Downgraded by one level because of indirectness (insufficient time frame) - see Appendix 1.
[b]Downgraded by two levels because of overall risk of bias ('some concerns') and imprecision (few studies) - see Appendix 1.
[c]Downgraded by one level because of inconsistency (95% prediction interval consistent with benefit and harm) - see Appendix 1.
[d]Downgraded by two levels because of indirectness (insufficient time frame) and imprecision (few studies) - see Appendix 1.
[e]Downgraded by one level because of imprecision (CI consistent with benefit and harm) - see Appendix 1.

Summary of findings 2. Summary of findings: insulin glargine versus NPH insulin

Insulin glargine compared with NPH insulin for T1DM

Patients: people with T1DM

Settings: outpatients

Intervention: insulin glargine

Comparison: NPH insulin

Outcomes	NPH insulin	Insulin glargine	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
All-cause mortality Follow-up: 24-52 weeks	See comment		**Peto OR 0.14** (0.00 to 6.98)	2175 (8)	⊕⊕⊕⊖ **moderate**[a]	1 study including adults reported 0/1207 participants died in the insulin glargine group vs 1/1068 participants in the NPH insulin group 4 studies included adults, 4 studies included children (the test for subgroup differences could not be performed)
Health-related quality of life	See comment			1013 (4)	⊕⊕⊖⊖ **low**[b]	1 study including adults (Bolli 2009) reported greater im-

Scales: Well-Being Enquiry for Diabetics; General Well-being; Diabetes Quality of Life for Youth and Parents' Diabetes Quality of Life Follow-up: 24-28 weeks						provements in the insulin glargine group compared with NPH insulin in one domain (diabetes-related worries) There was no evidence of a difference in 3 studies (Chase 2008 included children; Home 2005 and Ratner 2000 included adults)
Severe hypoglycaemia (n/N) Definition: symptomatic hypoglycaemia requiring third party assistance, with either a blood glucose level < 2.8 mmol/L or prompt recovery after administration of oral carbohydrate, iv glucose or glucagon (Fulcher 2005; Home 2005; Schober 2002); requiring third party assistance and associated with either blood glucose < 2.0 mmol/L or prompt recovery after oral carbohydrate, iv glucose, or intramuscular or subcutaneous glucagon administration (Chase 2008); hypoglycaemia requiring third party assistance or involving a seizure, coma, unconsciousness or the use of glucagon (Liu 2016); hypoglycaemia requiring third party assistance (Porcellati 2004; PRESCHOOL; Ratner 2000) Follow-up: 24-52 weeks	**125 per 1000**	**105 per 1000** (84 to 130)	**RR 0.84** (0.67 to 1.04)	2350 (9)	⊕⊕⊕⊖ **moderate**[c]	The 95% prediction interval ranged between 0.65 and 1.09 5 studies included adults, 4 studies included children (the test for subgroup differences did not indicate interaction)
Non-fatal myocardial infarction/stroke Definition: myocardial infarction/cerebral ischaemia Follow-up: 28 weeks	See comment			585 (1)	⊕⊕⊖⊖ **low**[d]	No participant experienced a non-fatal myocardial infarction 1 study including adults reported 0/292 participants in the insulin glargine group vs 1/293 participants in the NPH insulin group experienced cerebral ischaemia (Home 2005)
Severe nocturnal hypoglycaemia (n/N)	**87 per 1000**	**72 per 1000** (54 to 97)	**RR 0.83** (0.62 to 1.12)	1893 (6)	⊕⊕⊕⊖ **moderate**[c]	The 95% prediction interval ranged between 0.54 and 1.27

Definition: severe hypoglycaemia occurring 23:00-07:00 (PRESCHOOL); severe hypoglycaemia occurring after the evening insulin injection and before the morning insulin dose (Fulcher 2005); severe hypoglycaemia occurring during sleep between bedtime and rising in the morning, or before the morning pre-breakfast self-blood glucose measurement and the morning insulin injection (Home 2005); severe hypoglycaemia occurring while asleep after the bedtime insulin dose and before the morning insulin dose and before the morning blood glucose measurement (Ratner 2000); severe hypoglycaemia while the participant was sleeping between bedtime and after the evening injection and before getting up in the morning (Schober 2002); severe hypoglycaemia occurring 00:00-06:00 (Chase 2008) Follow-up: 24-28 weeks						3 studies included adults, 3 studies included children (the test for subgroup differences did not indicate interaction)
Serious adverse events (n/N) Follow-up: 24-30 weeks	**100 per 1000**	**108 per 1000** (63 to 184)	**RR 1.08** (0.63 to 1.84)	2229 (8)	⊕⊕⊕⊖ **moderate**[c]	The 95% prediction interval ranged between 0.22 and 5.21 4 studies included adults, 4 studies included children (the test for subgroup differences did not indicate interaction)
HbA1c (%) Follow-up: 24 weeks - 1 year	The mean HbA1c ranged across the NPH insulin groups from 7.1% to 7.3%	The mean HbA1c in the insulin glargine groups was **0.02% higher** (0.1% lower to 0.1% higher)	—	2285 (9)	⊕⊕⊕⊖ **moderate**[c]	The 95% prediction interval ranged between -0.5% and 0.5% 5 studies included adults, 4 studies included children (the test for subgroup differences did not indicate interaction)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
a.m.: ante meridiem; **CI**: confidence interval; **HbA1c**: glycosylated haemoglobin A1c; **iv**: intravenous; **n/N**: number of people experiencing an event; **NPH**: neutral protamine Hagedorn; **RR:** risk ratio; **T1DM**: type 1 diabetes mellitus.

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.
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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.

*Assumed risk was derived from the event rates in the comparator groups.
[a]Downgraded by one level because of indirectness (insufficient time frame) - see Appendix 2.
[b]Downgraded by two levels because of overall risk of bias ('some concerns') and imprecision (few studies) - see Appendix 2.
[c]Downgraded by one level because of imprecision (CI consistent with benefit and harm) - see Appendix 2.
[d]Downgraded by two levels because of indirectness (insufficient time frame) and imprecision (few studies) - see Appendix 2.

Summary of findings 3. Summary of findings: insulin detemir versus insulin glargine

Insulin detemir compared with insulin glargine for T1DM

Patients: people with T1DM

Settings: outpatients

Intervention: insulin detemir

Comparison: insulin glargine

Outcomes	Insulin glargine	Insulin detemir	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
All-cause mortality Follow-up: 26 and 52 weeks	See comment			763 (2)	⊕⊕⊖⊖ **low[a]**	No participant died 2 studies included adults
Health-related quality of life	**Not reported**					
Severe hypoglycaemia (n/N) Definition: hypoglycaemia requiring third party assistance Follow-up: 26 and 52 weeks	**116 per 1000**	**68 per 1000** (15 to 304)	**RR 0.59** (0.13 to 2.63)	763 (2)	⊕⊖⊖⊖ **very low[b]**	2 studies included adults
Non-fatal myocardial infarction/stroke	See comment			443 (1)	⊕⊕⊖⊖ **low[a]**	1 study including adults reported 1/299 participants in the insulin detemir group vs 1/144 participants in

Definition: non-fatal myocardial infarction/stroke Follow-up: 52 weeks						the insulin glargine group experienced a non-fatal myocardial infarction One study including adults reported 2/299 participants in the insulin detemir group vs 0/144 participants in the insulin glargine group experienced a non-fatal stroke
Severe nocturnal hypoglycaemia (n/N) Definition: severe hypoglycaemia occurring from 11 p.m. to 6 a.m. Follow-up: 26 and 52 weeks	**50 per 1000**	**27 per 1000** (3 to 253)	**RR 0.55** (0.06 to 5.12)	763 (2)	⊕⊖⊖⊖ **very low**[b]	2 studies included adults
Serious adverse events (n/N) Follow-up: 26 and 52 weeks	**59 per 1000**	**102 per 1000** (54 to 195)	**RR 1.72** (0.91 to 3.28)	763 (2)	⊕⊕⊖⊖ **low**[c]	The fixed-effect statistical model showed an RR of 1.79 (1.04 to 3.08) in favour of insulin glargine 2 studies included adults
HbA1c (%) Follow-up: 26 and 52 weeks	The mean HbA1c ranged across the insulin glargine groups from 7.6% to 8.2%	The mean HbA1c in the insulin detemir groups was **0.01% lower** (0.1% lower to 0.1% higher)	—	763 (2)	⊕⊕⊖⊖ **low**[c]	2 studies included adults

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
a.m.: ante meridiem; **CI:** confidence interval; **HbA1c**: glycosylated haemoglobin A1c; **n/N**: number of people experiencing an event; **p.m.**: post meridiem; **RR:** risk ratio; **T1DM**: type 1 diabetes mellitus.

GRADE Working Group grades of evidence

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[*]Assumed risk was derived from the event rates in the comparator groups.
[a]Downgraded by two levels because of indirectness (insufficient time frame) and imprecision (few studies) - see Appendix 3.

[b]Downgraded by three levels because of inconsistency (point estimates varied widely, non-consistent direction of effect) and serious imprecision (CI consistent with benefit and harm, few studies) - see Appendix 3.
[c]Downgraded by two levels because of serious imprecision (CI consistent with benefit and harm, few studies) - see Appendix 3.

Summary of findings 4. Summary of findings: insulin degludec versus insulin detemir

Insulin degludec compared with insulin detemir for T1DM

Patients people with T1DM

Settings: outpatients

Intervention: insulin degludec

Comparison: insulin detemir

Outcomes	Insulin detemir	Insulin degludec	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
All-cause mortality Follow-up: 26 weeks	See comment			802 (2)	⊕⊕⊖⊖ **low**[a]	No participant died 1 study included adults, 1 study included children
Health-related quality of life Scale: Short-Form 36 version 2 (higher values mean better health-related quality of life) Follow-up: 26 weeks	**Physical health score**: the mean score in the insulin detemir group was 52.5 **Mental health score**: the mean score in the insulin detemir group was 52.5	**Physical health score**: the mean score in the insulin degludec group was **0.60 points lower** (1.83 points lower to 0.63 points higher) **Mental health score**: the mean score in the insulin degludec group was **3.00 points lower** (4.44 points lower to 1.56 points lower)	—	454 (1)	⊕⊕⊖⊖ **low**[b]	Physical health score: MID is 2-3 points Mental health score: MID is 3 points Study included adults
Severe hypoglycaemia (n/N) Definition: hypoglycaemia requiring third party assistance (Davies 2014) or altered mental status and	**122 per 1000**	**143 per 1000** (99 to 207)	**RR 1.17** (0.81 to 1.69)	802 (2)	⊕⊕⊖⊖ **low**[c]	1 study included adults, 1 study included children (the test for subgroup differences did not indicate interaction)

cannot assist in their own care, is semiconscious or unconscious, or in a coma ± convulsions and may require parenteral therapy (glucagon or iv glucose) (BEGIN Young) Follow-up: 26 weeks						
Non-fatal myocardial infarction/stroke Definition: non-fatal myocardial infarction/stroke Follow-up: 26 weeks	See comment			453 (1)	⊕⊕⊖⊖ **low**[a]	No participant experienced a non-fatal myocardial infarction or stroke Study included adults
Severe nocturnal hypoglycaemia (n/N) Definition: severe hypoglycaemia occurring 00:01-05:59 (Davies 2014) or 23:00-07:00 (BEGIN Young) Follow-up: 26 weeks	**31 per 1000**	**34 per 1000** (16 to 75)	**RR 1.12** (0.51 to 2.46)	802 (2)	⊕⊕⊖⊖ **low**[c]	1 study included children, 1 study included adults (the test for subgroup differences did not indicate interaction)
Serious adverse events (n/N) Follow-up: 26 weeks	**73 per 1000**	**92 per 1000** (56 to 150)	**RR 1.25** (0.76 to 2.05)	802 (2)	⊕⊕⊖⊖ **low**[c]	1 study included children, 1 study included adults (the test for subgroup differences did not indicate interaction)
HbA1c (%) Follow-up: 26 weeks	The mean HbA1c in the insulin glargine groups was 7.3%	The mean HbA1c in the insulin detemir groups was **0.05% lower** (0.1% lower to 0.2% higher)	—	802 (2)	⊕⊕⊖⊖ **low**[c]	1 study included children, 1 study included adults (the test for subgroup differences did not indicate interaction)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
a.m.: ante meridiem; **CI:** confidence interval; **HbA1c**: glycosylated haemoglobin A1c; **iv**: intravenous; **MID:** minimal important difference; **n/N**: number of people experiencing an event; **p.m.**: post meridiem; **RR:** risk ratio; **T1DM**: type 1 diabetes mellitus.

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.

*Assumed risk was derived from the event rates in the comparator groups.
[a]Downgraded by two levels because of indirectness (insufficient time frame) and imprecision (few studies) - see Appendix 4.
[b]Downgraded by two levels because of overall risk of bias ('some concerns') and imprecision (few studies) - see Appendix 4.
[c]Downgraded by two levels because of serious imprecision (CI consistent with benefit and harm, few studies) - see Appendix 4.

Summary of findings 5. Summary of findings: insulin degludec versus insulin glargine

Insulin degludec compared with insulin glargine for T1DM

Patients: people with T1DM

Settings: outpatients

Intervention: insulin degludec

Comparison: insulin glargine

Outcomes	Insulin glargine	Insulin degludec	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
All-cause mortality Follow-up: 26 - 52 weeks	**3 per 1000**	**4 per 1000** (0 to 36)	**Peto OR 1.34** (0.15 to 11.93)	973 (3)	⊕⊖⊖⊖ **very low[a]**	A total of 3/646 participants in the insulin degludec group vs 1/327 participants in the insulin glargine group died 2 studies included adults 1 study included children
Health-related quality of life Scale: Short-Form 36 version 2 (higher values mean better health-related quality of life) Follow-up: 32 and 52 weeks	**Physical health score**: the mean score ranged across the insulin glargine groups from 50.6 to 51.8 **Mental health score**: the mean score ranged across the insulin glargine	**Physical health score**: the mean score in the insulin degludec groups was **0.04 points lower** (1.21 points lower to 1.13 points higher) **Mental health score**: the mean score in the insulin degludec groups was **0.09**	—	1042 (2)	⊕⊖⊖⊖ **very low[b]**	Physical health score: MID is 2-3 points Mental health score: MID is 3 points 2 studies included adults

	groups from 49.9 to 50.4	**points lower** (1.03 points lower to 0.85 points higher)				
Severe hypoglycaemia (n/N) Definition: hypoglycaemia requiring third party assistance (BEGIN Flex T1; BEGIN Young) or an event associated with impaired consciousness or seizure (Urakami 2017) Follow-up: 24 and 52 weeks	**102 per 1000**	**124 per 1000** (83 to 185)	**RR 1.22** (0.82 to 1.82)	970 (3)	⊕⊕⊖⊖ **low**[c]	2 studies included adults 1 study including children reported no child experienced severe hypoglycaemia (Urakami 2017)
Non-fatal myocardial infarction/stroke Definition: non-fatal myocardial infarction/cerebral ischaemia Follow-up: 24 and 52 weeks	See comment			970 (3)/970 (3)	⊕⊕⊖⊖ **low**[d]	2 studies including adults reported 1/637 participants in the insulin degludec group vs 0/315 participants in the insulin glargine group experienced a non-fatal myocardial infarction; there were no events in 1 study including children (Urakami 2017) 2 studies including adults reported 1/637 participants in the insulin degludec group vs 0/315 in the insulin glargine group experienced cerebral ischaemia; there were no events in 1 study including children (Urakami 2017)
Severe nocturnal hypoglycaemia (n/N) Definition: severe hypoglycaemia occurring from 22:00 to 06:59 h Follow-up: 24 - 52 weeks	**25 per 1000**	**35 per 1000** (15 to 83)	**RR 1.39** (0.59 to 3.27)	970 (3)	⊕⊕⊖⊖ **low**[c]	2 studies included adults 1 study include children
Serious adverse events (n/N) Follow-up: 24 and 52 weeks	**77 per 1000**	**71 per 1000** (45 to 113)	**RR 0.92** (0.58 to 1.46)	970 (3)	⊕⊕⊖⊖ **low**[c]	2 studies included adults 1 study including children reported no child experienced a serious adverse event (Urakami 2017)

HbA1c (%) Follow-up: 24 and 52 weeks	The mean HbA1c ranged across the insulin glargine groups from 6.9% to 7.8%	The mean HbA1c in the insulin degludec groups was **0.1% higher** (0% lower to 0.2% higher)	—	1388 (4)	⊕⊕⊖⊖ **low**[c]	The 95% prediction interval ranged between -0.1% and 0.3% 3 studies included adults, 1 study included children (the test for subgroup differences did not indicate interaction)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **CSR**: clinical study report; **HbA1c**: glycosylated haemoglobin A1c; **MID:** minimal important difference; **n/N**: number of people experiencing an event; **OR**: odds ratio; **RR:** risk ratio; **T1DM**: type 1 diabetes mellitus:

GRADE Working Group grades of evidence

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Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
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*Assumed risk was derived from the event rates in the comparator groups.
[a]Downgraded by three levels because of indirectness (insufficient time frame) and serious imprecision (CI consistent with benefit and harm, few studies) - see Appendix 5.
[b]Downgraded by three levels because of overall risk of bias ('some concerns') and serious imprecision (CI consistent with benefit and harm, few studies) - see Appendix 5.
[c]Downgraded by two levels because of serious imprecision (CI consistent with benefit and harm, few studies) - see Appendix 5.
[d]Downgraded by two levels because of indirectness (insufficient time frame) and imprecision (few studies) - see Appendix 5.

BACKGROUND

Description of the condition

Onset of type 1 diabetes mellitus (T1DM) can occur at any age and accounts for about 5% to 10% of all diabetes mellitus cases (Daneman 2006). It is a metabolic disease caused by an autoimmune destruction of pancreatic β-cells which results in a deficiency of insulin secretion. What causes the pathological autoimmune response is not yet fully understood but includes genetic susceptibility in combination with an environmental trigger (Field 1997; Maahs 2010; van der Werf 2007). The incidence of T1DM varies geographically, being highest in Northern Europe (Karvonen 1993). Over the years, a worldwide increase in incidence has been observed, the reasons for which are not yet clear (Onkamo 1999; Pitkaniemi 2004).

Description of the intervention

For people with T1DM, the goal of insulin therapy is to provide insulin that mimics physiologic insulin secretion. The most commonly used administration of insulin is by subcutaneous injection (ADA 2019). Insulin is usually applied through insulin syringes, insulin pens or insulin pumps. In order to control blood glucose levels in periods of fasting and to enable cells to incorporate glucose for production of energy, basal or background insulin is needed, which can be given by means of daily or twice-daily injections of an intermediate-acting or (ultra-)long-acting insulin preparation. Bolus insulin is taken at mealtime (prandial insulin) to control blood glucose levels following a meal and is given by means of short-acting or rapid-acting insulin, usually before meals (ADA 2019). With insulin pump-based treatments, a continuous delivery of rapid-acting insulin is administered through the pump, with the addition of mealtime insulin bolus (basal-bolus regimen). The aim for most people with T1DM is to achieve near-normal glycaemic levels (ADA 2019) and to allow flexibility regarding time, type and amount of food intake which can best be mastered through structured patient-education programmes (Pillay 2015).

Since the early 1920s, people with diabetes were treated with insulin, which was purified from bovine or porcine pancreas (animal insulin). Recombinant 'human' insulin was first produced in *Escherichia coli* in 1978 by combining the expressed insulin A- and B-chains (Chance 1993). In 1982, the first insulin utilising recombinant deoxyribonucleic acid (DNA) technology was marketed. At present, insulin is being produced predominantly in *Escherichia coli* and yeasts (Chance 1993).

The choice of basal insulin depends upon patient and prescriber preferences, 'lifestyle' and economic and health system considerations. Historically, intermediate- and long-acting insulin preparations were obtained by crystallising either protamine (Neutral Protamin Hagedorn (NPH) type, also known as isophane insulin) or zinc (Lente type). Most insulins have a concentration of 100 units per mL (U100) but more concentrated insulin formulations (U200, U300, U500) are currently available (Heinemann 2019). Soluble human insulin consists of different oligomers (monomers, dimers and hexamers). When administered subcutaneously, insulin monomers and dimers are readily absorbed by blood capillaries. Before dissociation of hexamers into dimers and monomers, the crystalline structures need to dissolve, and this process prolongs the absorption phase and contributes to pharmacokinetic variability between injections. Hence, the rate of insulin absorption is fastest for monomers followed by dimers and hexamers, respectively (Gradel 2018). Treatment with intermediate-acting human insulins has drawbacks: NPH is associated with a pronounced insulin peak following injection, which seems to be associated with variable absorption (Heinemann 2000; Lepore 2000) and an increased risk of hypoglycaemia (Tricco 2014).

In order to achieve the potential benefits of near-normal glycaemic control with a reduced risk of hypoglycaemia, new insulins have been introduced to the market. In an effort to provide insulin with a more suitable physiological time course to persons with diabetes mellitus, 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 main (ultra-)long-acting insulin analogues are currently available on the market: two long-acting insulin analogues (insulin detemir and insulin glargine U100), and two ultra-long-acting insulin analogues (insulin degludec and insulin glargine U300). The glargine U300 formulation has a more extended time-action profile than glargine U100 and is thought to achieve a more stable glycaemic control (Yale 2018).

Because the patent of insulin glargine has expired, biosimilar insulins have become available on the market. Biosimilar insulin glargine is a biological copy of the original insulin glargine which is believed to have comparable quality, efficacy and safety. Biosimilar insulin glargine is cheaper than the original insulin glargine (Soldatov 2019).

Adverse effects of the intervention

The risk of developing hypoglycaemic episodes varies among studies depending on the definition of hypoglycaemia and the desired glycaemic target (Kahler 2014). Due to a more sustainable molecule structure of insulin analogues, studies have indicated a reduced risk of severe hypoglycaemia compared with NPH insulin (Tricco 2014). However, data are conflicting (Laranjeira 2018). Targeting lower glycosylated haemoglobin A1c (HbA1c) levels is often difficult to achieve and leads to a higher incidence of hypoglycaemic events (Kahler 2014). However, targeting near-normal glucose levels in order to avoid detrimental long-term consequences of hyperglycaemia is currently recommended in most people with type 1 diabetes (ADA 2019).

Compared to human insulin, some insulin analogues have shown higher mitogenic potency and insulin-growth factor binding affinity in 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 agencies, 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). Observational studies have shown conflicting results regarding cancer risk with insulin analogues compared with human insulin (Hemkens 2009; Ruiter 2012).

The insulin analogues are usually more expensive than NPH insulin (Ewen 2019). While price differences may not be a major 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 (ultra-)long-acting insulin analogues, a number of possible advantages in the therapy of people with T1DM have been suggested. For instance, it has been hypothesised that the longer action and the less pronounced insulin peak will enable both improved glycaemic control and reduced risk of hypoglycaemia (Tricco 2014).

Why it is important to do this review

Although their pharmacokinetic profiles appeared to indicate that (ultra-)long-acting insulin analogues improve the insulin therapy of people with diabetes mellitus, their superiority in a clinical setting has still to be demonstrated (Hemmingsen 2019). Systematic reviews comparing the benefits and harms of insulin analogues with NPH insulin exist, but they have methodological deficiencies due to lack of identification of all relevant studies, missing analysis of clinical study reports (CSR) and poor 'Risk of bias' assessment (Laranjeira 2018; Tricco 2014).

OBJECTIVES

To compare the effects of long-term treatment with (ultra-)long-acting insulin analogues to NPH insulin (neutral protamine Hagedorn) or another (ultra-)long-acting insulin analogue in people with type 1 diabetes mellitus.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs).

Types of participants

Non-pregnant people withT1DM.

Types of interventions

We planned to investigate the following comparisons of intervention versus comparator.

Intervention

- Long-acting insulin analogues (insulin glargine U100 or insulin detemir) and their biosimilar insulins.
- Ultra-long-acting insulin analogues (insulin glargine U300 or insulin degludec).

Comparisons

- Long-acting insulin analogue or its biosimilar insulin versus human NPH insulin.
- Ultra-long-acting insulin analogue or its biosimilar insulin versus human NPH insulin.
- (Ultra-)long-acting insulin analogue versus another (ultra-)long-acting insulin analogue.

Concomitant interventions had to be the same in both the intervention and comparator groups to establish fair comparisons.

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

If a study included multiple arms, we included any arm that met our inclusion criteria.

Minimum duration of intervention

We included studies with a minimum duration of 24 weeks. In the case of a cross-over RCT, each intervention period had to be at least 24 weeks.

Minimum duration of follow-up

Minimum duration of follow-up was 24 weeks. In the case of a cross-over RCT, duration of follow-up for each intervention period had to be at least 24 weeks.

We defined any follow-up period going beyond the original time frame for the primary outcome measure as specified in the power calculation of the study's protocol as an extended follow-up period (also called 'open-label extension study') (Buch 2011; Megan 2012).

Types of outcome measures

We did not exclude a study if it failed to report one or several of our primary or secondary outcome measures. If none of our primary or secondary outcomes was reported in the study, we did not include the study but provided some basic information in the 'Characteristics of studies awaiting classification' table.

We investigated the following outcomes using the methods and time points specified below.

Primary outcomes

- All-cause mortality.
- Health-related quality of life.
- Severe hypoglycaemia.

Secondary outcomes

- Cardiovascular mortality.
- Non-fatal myocardial infarction.
- Non-fatal stroke.
- End-stage renal disease.
- Blindness.
- Serious adverse events.
- Diabetic ketoacidosis.
- Non-serious adverse events.
- Nocturnal hypoglycaemia.
- Mild/moderate hypoglycaemia.
- Socioeconomic effects.
- HbA1c levels.
- Combined HbA1c levels and severe hypoglycaemia.

Method of outcome measurement

- All-cause mortality: defined as death from any cause.
- Health-related quality of life: defined as mental and physical health-related quality of life and evaluated by a validated instrument such as Short-Form-36 (SF-36). Scales focusing on treatment satisfaction and not health-related quality of life as main outcome were not included.

- Severe hypoglycaemia: requiring assistance from another person (was planned to be further categorised into 'assistance from other persons', assistance from medical staff, intravenous glucose administration, subcutaneous glucagon administration, hospitalisation, intensive-care unit stay, coma).
- Cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, blindness: defined as reported in studies.
- End-stage renal disease: defined as need for dialysis and renal transplantation.
- Serious adverse events (SAE): defined according to the International Conference on Harmonization (ICH) guidelines as, "any event that leads to death, that is life-threatening, required in-patient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability, and any important medical event which may have had jeopardised the patient or required intervention to prevent it" (ICH 1997) or as reported in studies.
- Diabetic ketoacidosis: potentially life-threatening condition with high levels of ketones in the body which when building up in the blood make the blood more acidic.
- Non-serious adverse events: all adverse events, not classified as SAEs.
- Nocturnal hypoglycaemia: hypoglycaemia during night-time and defined as reported in studies.
- Mild/moderate hypoglycaemia: hypoglycaemic episodes not requiring assistance from another person.
- Socioeconomic effects: such as direct costs defined as admission or readmission rates; average length of stay; visits to general practitioner; accident or emergency visits; medication consumption; indirect costs defined as resources lost due to illness by the participant or their family member.
- HbA1c levels: expressed as percentage or mmol/mol.
- Combined HbA1c levels and severe hypoglycaemia: joint examination of the effects of HbA1c reduction and hypoglycaemia risk.

Timing of outcome measurement

For all outcome measures, we defined short-term follow-up as 24 weeks to ≤ 52 weeks, medium-term follow-up as > 1 year to ≤ 2 years and long-term follow-up as > 2 years.

Search methods for identification of studies

Electronic searches

We searched the following sources from the inception of each database to the date of search and did not place restrictions on the language of publication:

- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO) (searched 24 August 2020);
- MEDLINE (Ovid MEDLINE ALL 1946 to Daily Update) (searched 24 August 2020);
- ClinicalTrials.gov (www.clinicaltrials.gov) (searched 24 August 2020);
- World Health Organization International Clinical Trials Registry Platform (ICTRP) (www.who.int/trialsearch) (searched 24 August 2020);
- HTA database (https://database.inahta.org/) (searched 24 August 2020).

We did not include Embase in our search, as RCTs indexed in Embase are now prospectively added to CENTRAL via a highly sensitive screening process (Cochrane 2020).

For detailed search strategies, see Appendix 6.

Searching other resources

We identified other potentially eligible studies or ancillary publications by searching the reference lists of included studies, systematic reviews, meta-analyses, and health technology assessment reports. In addition, we contacted the investigators of included studies to obtain additional information on the retrieved studies and establish whether we may have missed further studies.

We searched the grey literature, which we defined as searching the HTA database, as well as databases from regulatory agencies (European Medicines Agency (EMA) and Food and Drug Administration (FDA) - Hart 2012;Schroll 2015). We searched for CSRs and clinical study synopses as provided on manufacturers' web sites (e.g. Novo Nordisk Trials) and via contact with manufacturers (Appendix 7).

We did not use abstracts or conference proceedings for data extraction unless full data were available from study authors because this information source does not fulfil the CONSORT requirements which consist of "an evidence-based, minimum set of recommendations for reporting randomized trials" (CONSORT 2018; Scherer 2018). We presented information on abstracts or conference proceedings in the 'Characteristics of studies awaiting classification' table (Characteristics of studies awaiting classification).

Data collection and analysis

Selection of studies

We used Cochrane's Screen4Me workflow to help assess the search results. Screen4Me comprises three components: known assessments – a service that matches records in the search results to records that have already been screened in Cochrane Crowd and been labelled as an 'RCT' or as 'Not an RCT'; the RCT classifier – a machine learning model that distinguishes RCTs from non-RCTs, and, if appropriate, Cochrane Crowd – Cochrane's citizen science platform where the Crowd helped to identify and describe health evidence. Detailed information regarding evaluations of the Screen4Me components can be found in the following publications: Marshall 2018; McDonald 2017; Noel-Storr 2018; Thomas 2017.

Two review authors (BH, BR) independently screened the abstract, title, or both, of all records remaining after the Screen4Me workflow, to determine which studies we should assess further. We obtained the full text of all potentially relevant records. We would have resolved disagreements through consensus or by recourse to a third review author (MIM), if these had occurred. In case we were unable to resolve a disagreement, we planned to categorise the study as a 'Study awaiting classification' and would have contacted the study authors for clarification. We presented an adapted PRISMA flow diagram to show the process of study selection (Liberati 2009). We listed all articles excluded after full-text assessment in a 'Characteristics of excluded studies' table

and provided the reasons for exclusion (Characteristics of excluded studies).

Data extraction and management

For studies that fulfilled our inclusion criteria, two review authors (BH, BR) independently extracted key participant and intervention characteristics. We described interventions according to an adapted version of the 'template for intervention description and replication' (TIDieR) checklist (Hoffmann 2014; Hoffmann 2017).

We reported data on efficacy outcomes and adverse events using standardised data extraction sheets from the CMED Group. We resolved disagreements by discussion or, if required, by consultation with a third review author (MIM).

We provided information including trial identifier for potentially relevant ongoing trials in the 'Characteristics of ongoing studies' table and in a joint appendix 'Matrix of study endpoints (publications and trial documents)'. We tried to find the protocol and CSR for each included study.

We planned to email all authors of included studies, ongoing trials and studies awaiting classification to enquire whether they would be willing to answer questions regarding their studies. We presented the results of this survey in an appendix. We thereafter sought relevant missing information on the study from the primary study author(s), if required.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents, or multiple reports of a primary study, we maximised the information yielded by collating all available data, and we used the most complete data set aggregated across all known publications and records. We listed duplicate publications, companion documents, multiple reports of a primary study, and trial documents of included studies (such as trial registry information and CSRs) as secondary references under the study ID of the included study. Furthermore, we listed duplicate publications, companion documents, multiple reports of a study, and trial documents of excluded studies (such as trial registry information) as secondary references under the study ID of the excluded study.

Data from clinical trials registers and CSR

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

Assessment of risk of bias in included studies

Two review authors (BH, BR) independently assessed the risk of bias for each included study. We would have resolved disagreements by consensus or by consulting a third review author (MIM), if such occurred. If adequate information was unavailable from the publications, trial protocols, CSRs or other sources, we contacted the study authors for more details to request missing data on 'Risk of bias' items.

We undertook 'Risk of bias' assessment according to Chapter 7 and Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Boutron 2020; Higgins 2020). We used the Cochrane 'Risk of bias 2' (RoB 2) tool (version 22, August 2019) - (Higgins 2017; Sterne 2019).

We focused on the assessment of the effect of assignment to the interventions at baseline. The effect was analysed as the result of a comparison between interventions on a certain outcome at a specific time point. The RoB 2 tool evaluates the following domains.

- Bias arising from the randomisation process.
- Bias due to deviations from the intended interventions.
- Bias due to missing outcome data.
- Bias in measurement of the outcome.
- Bias in selection of the reported results.

Within each domain, signalling questions provided information about features of the study that were relevant to risk of bias. Possible answers to the signalling questions were 'Yes', 'Probably yes', 'Probably no', 'No' and 'No information'. After answering the signalling questions, we made a 'Risk of bias' judgement, assigning one of three levels ('low risk of bias', 'some concerns', 'high risk of bias') to each domain.
For each specific outcome, we established an overall 'Risk of bias' judgement using the following criteria.

- Low risk of bias: the study was judged to be at low risk of bias for all domains for this result.
- Some concerns: the study was judged to raise some concern in at least one domain for this result, but not to be at high risk of bias for any domain.
- High risk of bias: the study was either judged to be at high risk of bias in at least one domain for this result, or the study was judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.

We distinguished between participant-reported outcomes, observer-reported outcomes not involving judgement, observer-reported outcomes involving some judgement, outcomes reflecting decisions made by interventions providers and composite outcomes.

- Participant-reported outcomes: health-related quality of life; mild/moderate and non-severe nocturnal hypoglycaemia; non-serious adverse events; socioeconomic effects.
- Observer-reported outcomes not involving judgement: all-cause mortality, end-stage renal disease, blindness, HbA1c levels.
- Observer-reported outcomes involving some judgement: cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, socioeconomic effects.
- Outcomes reflecting decisions made by interventions providers: SAEs, severe hypoglycaemia, severe nocturnal hypoglycaemia.
- Composite outcomes: combined HbA1c levels and severe hypoglycaemia.

Measures of treatment effect

When at least two included studies were available for a comparison of a given outcome, we expressed dichotomous data as a risk ratio (RR) or an odds ratio (OR) with 95% confidence intervals (CI). For

continuous outcomes measured on the same scale (e.g. HbA1c in %), we estimated the intervention effect using the mean difference (MD) with 95% CIs. For continuous outcomes that measured the same underlying concept (e.g. health-related quality of life) but used different measurement scales, we would have calculated the standardised mean difference (SMD). We would have expressed time-to-event data as a hazard ratio (HR) with 95% CIs.

Unit of analysis issues

We took into account the level at which randomisation occurred, such as cross-over studies, cluster-randomised studies, and multiple observations for the same outcome. If more than one comparison from the same study had been eligible for inclusion in the same meta-analysis, we would either have combined groups to create a single pair wise comparison, or we would appropriately reduce the sample size so that the same participants had not contributed data to the meta-analysis more than once (splitting the 'shared' group into two or more groups). Although the latter approach offers some solution for adjusting the precision of the comparison, it does not account for correlation arising from inclusion of the same set of participants in multiple comparisons (Higgins 2011).

We would have re-analysed cluster-RCTs that had not appropriately adjusted for potential clustering of participants within clusters in their analyses. Variance of the intervention effects would have been inflated by a design effect. Calculation of a design effect involves estimation of an intracluster correlation coefficient (ICC). We would have obtained estimates of ICCs by contacting study authors, or by imputing ICC values using either estimates from other included studies that reported ICCs or external estimates from empirical research (e.g. Bell 2013). We would have examined the impact of clustering by performing sensitivity analyses.

Dealing with missing data

If possible, we obtained missing data from the authors of included studies. We carefully evaluated important numerical data such as screened, randomly assigned participants, as well as intention-to-treat 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 use of imputation methods (e.g. last-observation-carried-forward).

If studies were identified in which the standard deviation (SD) of the outcome was not available at follow-up or we could not recreate it, we would have standardised by the mean of the pooled baseline SD from studies that reported this information.

If we had identified included studies not reporting means and SDs for outcomes, and we could not receive the requested information from study authors, we would have imputed these values by estimating the mean and the variance from the median, the range and the size of the sample (Hozo 2005).

We would have investigated the impact of imputation on meta-analyses by performing sensitivity analyses, and we would have reported for every outcome which studies had imputed SDs.

Assessment of heterogeneity

In the event of clinical or methodological heterogeneity, we planned not to 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 2017). 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 found heterogeneity, we planned to determine possible reasons for this by examining individual study and subgroup characteristics. If possible, we calculated prediction intervals to elucidate the clinical implication of the observed heterogeneity (for details see Data synthesis).

Assessment of reporting biases

If we had included 10 or more studies that investigated a particular outcome, we would have used 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 publication bias (Sterne 2017). Therefore, we would have interpreted the results carefully (Sterne 2011).

Data synthesis

We undertook (or displayed) a meta-analysis only if we judged participants, interventions, comparisons, and outcomes to be sufficiently similar to ensure an answer that was clinically meaningful. Unless good evidence showed homogeneous effects across studies of different methodological quality, we would have primarily summarised low risk of bias data using a random-effects model (Wood 2008). We interpreted random-effects meta-analyses with due consideration for the whole distribution of effects and presented 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). For rare events such as event rates below 1%, we used the Peto odds ratio method, provided there was no substantial imbalance between intervention and comparator group sizes, and intervention effects were not exceptionally large. In addition, we performed statistical analyses according to the statistical guidelines presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2017).

Subgroup analysis and investigation of heterogeneity

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

- Head-to-head comparisons of insulin analogues.
- Studies designed to blind participants and investigators versus open-label studies.
- NPH once daily versus NPH two- or three-times daily.
- Studies of long duration (more than two years) versus studies of short to medium duration (two years or less).
- Studies performed in high-income countries versus middle-income countries versus low-income countries.
- According to healthcare setting.

Sensitivity analysis

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

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

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

Summary of findings and assessment of the certainty of the evidence

Certainty of the evidence

We presented the overall certainty of the evidence for each outcome specified below, according to the GRADE approach, which takes into account issues related not only to internal validity (risk of bias, inconsistency, imprecision, publication bias), but also to external validity, such as directness of results. Two review authors (BH, BR) independently rated the certainty of the evidence for each outcome. If differences in assessment had occurred, they would have been solved by discussion or by consultation with a third review author (MIM).

We included an appendix entitled 'Checklist to aid consistency and reproducibility of GRADE assessments', to help with standardisation of the 'Summary of findings' tables (Meader 2014). Alternatively, we would have used the GRADEpro Guideline Development Tool (GDT) software and presented evidence profile tables as an appendix (GRADEproGDT 2015). We presented results for outcomes as described in the Types of outcome measures section. 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 by using footnotes, and we made comments to aid the reader's understanding of the Cochrane Review when necessary.

'Summary of findings' table

We presented a summary of the evidence in a 'Summary of findings' table. This provided 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, numbers of participants and studies addressing each important outcome, and a rating of overall confidence in effect estimates for each outcome.

In the 'Summary of findings' table, we reported on the 'intervention' (ultra-)long-acting insulin analogue or its biosimilar insulin versus the 'comparator' human NPH insulin or another (ultra-)long-acting insulin analogue.

We created the 'Summary of findings' table using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2017), along with Review Manager (RevMan 5.3) table editor (RevMan 2014). We reported the following outcomes, listed according to priority.

1. All-cause mortality.
2. Health-related quality of life.
3. Severe hypoglycaemia.
4. Non-fatal myocardial infarction/stroke.
5. Severe nocturnal hypoglycaemia.
6. SAEs.
7. HbA1c levels.

RESULTS

Description of studies

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

Results of the search

The initial search identified a total of 7747 records. In assessing the studies, we used Cochrane's Screen4Me workflow to help identify potential reports of randomised studies. The results of the Screen4Me assessment process can be seen in Figure 1. Subsequently, we assessed the remaining 3265 records, as well as the 570 records retrieved by the update search prior to publication. We excluded most of the references on the basis of their titles and abstracts because they clearly did not meet the inclusion criteria. We evaluated a further 47 records identified as CSRs, clinical study synopses, a study protocol and one additional record identified through handsearching of reference lists of included studies (Figure 2).

Figure 1. Screen4Me: Cochrane´s screening service.

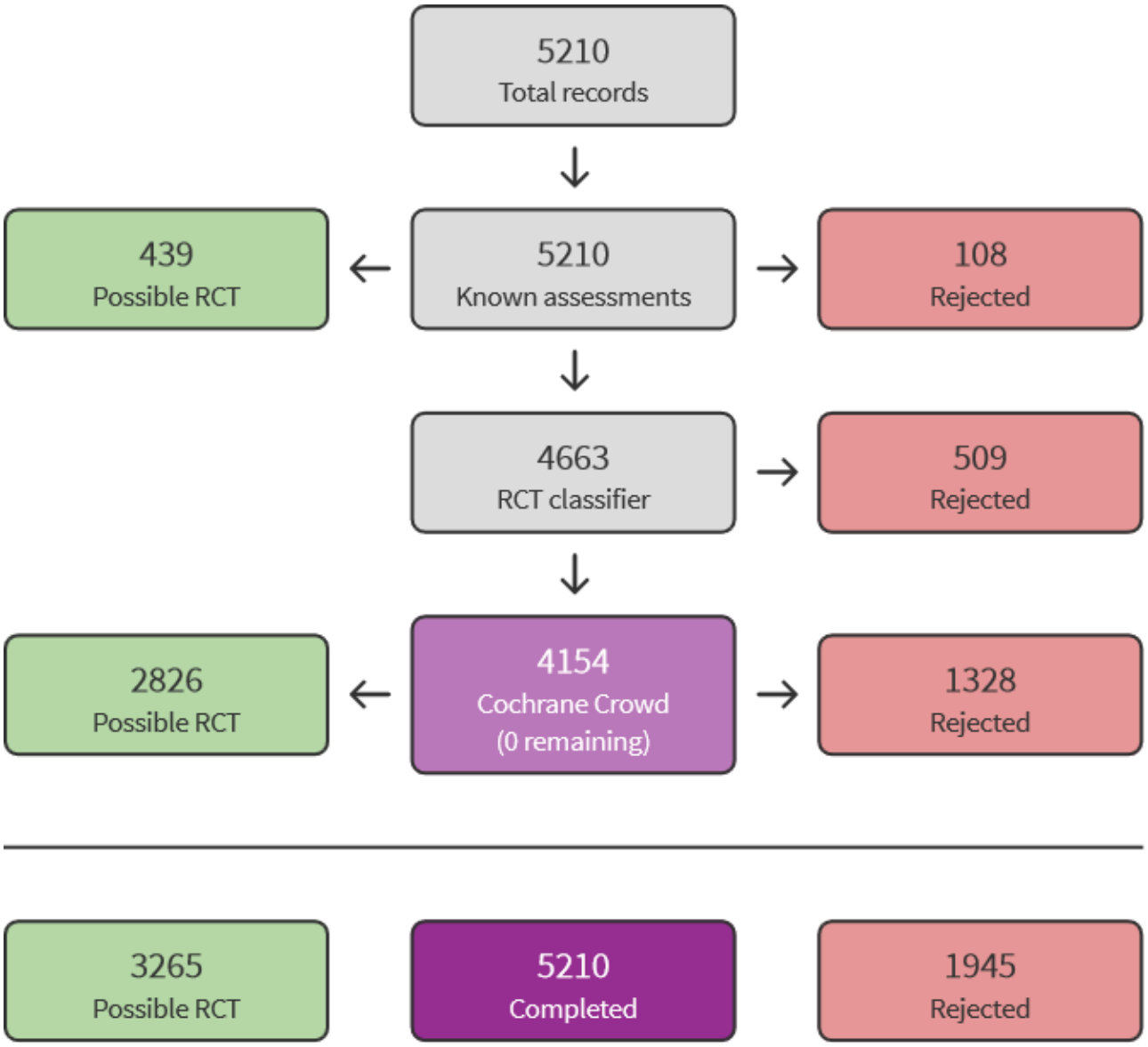
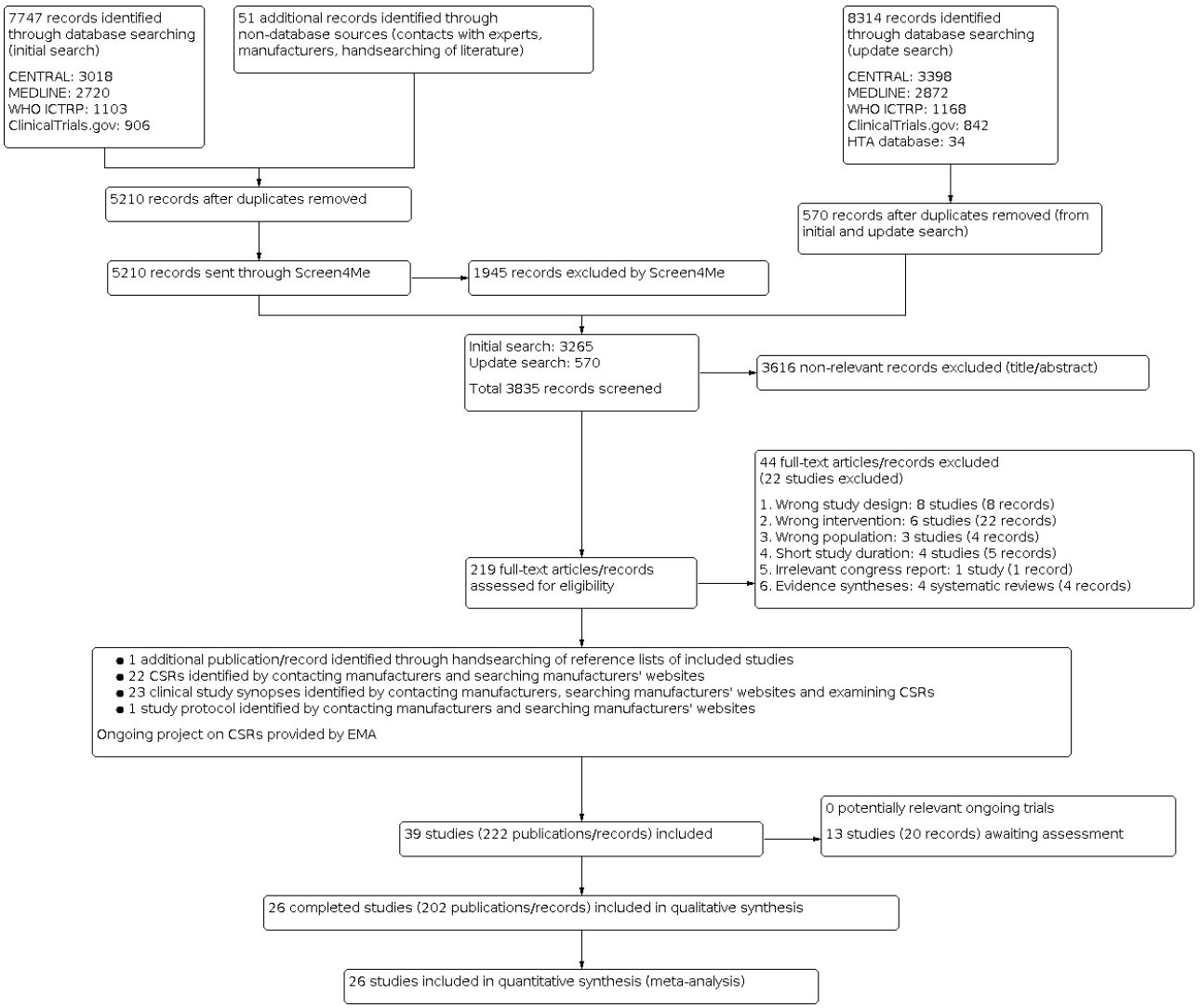


Figure 2. Study flow diagram CSR: clinical study report; EMA: European Medicines Agency; HTA: health technology assessment; Screen4Me: Cochrane's screening service.



Searching the web pages of Novo Nordisk and Sanofi, we identified 23 CSRs, clinical study synopses or both. On request, we received 10 CSRs from Sanofi and six CSRs, sections of two CSRs and one study protocol from Novo Nordisk, respectively. The two studies with sections of CSRs only were Japanese studies (Kobayashi 2007; NCT00605137). For both studies, clinical study synopses were available and we could not get full access to the Japanese versions of the CSRs. For one study, a trial protocol was provided by Novo Nordisk (NCT00605137). One study had a clinical study synopsis only (NCT00595374). The total number of additional references from web pages and contact with manufacturers was 22 CSRs, 23 clinical study synopses and one study protocol.

We identified applications/documents through searching FDA and EMA web sites (EMA 2014; EMA 2015; EMA 2015a; EMA 2015b; FDA 2000; FDA 2002; FDA 2005; FDA 2015). These references did not provide information about additional studies.

In summary, after screening the full texts from the electronic search and additional sources, we identified 26 RCTs published in 202 records that met our inclusion criteria. Two studies were unpublished, but clinical study synopses and parts of the CSRs were obtained and provided data for inclusion (NCT00595374; NCT00605137). The remaining included studies were published. For all studies, except two, it was possible to retrieve additional information from clinical trials registers, documents from regulatory agencies, CSRs, clinical study synopses and investigators (Bolli 2009; Porcellati 2004). The number of records per included studies varied from 1 to 21. Thirteen studies are awaiting assessment.

Included studies

A detailed description of the characteristics of included studies is presented elsewhere (see Characteristics of included studies and 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 20; Appendix 21; Appendix 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5. The following is a succinct overview.

Overview of study populations

Twenty-five studies reported the total number of participants screened (Bartley 2008; BEGIN Basal-Bolus Type 1; BEGIN Flex T1; BEGIN Young; Bolli 2009; Chase 2008; Davies 2014; Fulcher 2005; Heller 2009; Home 2005; Kobayashi 2007; Liu 2016; NCT00595374; NCT00605137; Pieber 2007; Porcellati 2004; PRESCHOOL; Ratner 2000; Robertson 2007; Russell-Jones 2004; Schober 2002; Standl 2004; SWITCH 1; Thalange 2013; Vague 2003).

A total of 8784 participants were randomised: 2428 participants were randomised to NPH insulin, 2889 participants to insulin detemir, 2095 participants to insulin glargine and 1372 participants to insulin degludec (see Table 1). Eight of the studies included children and randomised 1835 participants, i.e. 21% of all participants (BEGIN Young; Chase 2008; Liu 2016; NCT00605137; Robertson 2007; Schober 2002; Thalange 2013; Urakami 2017). The remaining studies included adults.

The proportion of participants finishing the studies varied from 78% to 100% (Fulcher 2005; Porcellati 2004).

Study design

Two studies had a cross-over design (SWITCH 1; Urakami 2017). The remaining studies were parallel-group RCTs. All studies had an open-label design, except for one which was double-blinded (SWITCH 1). The duration of the intervention ranged from 24 weeks to 24 months. Seven studies had an additional extension period (BEGIN Basal-Bolus Type 1; BEGIN Flex T1; BEGIN Young; Davies 2014; Standl 2004; Thalange 2013; Vague 2003).

All studies except two were multicentre studies (Porcellati 2004; Urakami 2017). The number of study centres ranged from 1 to 90. Sixteen studies were multinational (Bartley 2008; BEGIN Basal-Bolus Type 1; BEGIN Flex T1; BEGIN Young; Davies 2014; Heller 2009; Home 2005; Pieber 2007; PRESCHOOL; Robertson 2007; Russell-Jones 2004; Schober 2002; Standl 2004; SWITCH 1; Thalange 2013; Vague 2003). None of the studies was performed in low- or middle-income countries. None of the studies was terminated early.

Participants

Twenty-three studies reported the ethnicity of the participants: 19 studies included mainly white people (Bartley 2008; BEGIN Basal-Bolus Type 1; BEGIN Flex T1; BEGIN Young; Chase 2008; Fulcher 2005; Heller 2009; Home 2005 ¸ NCT00595374; Pieber 2007; PRESCHOOL; Ratner 2000; Robertson 2007; Russell-Jones 2004; Schober 2002; Standl 2004; SWITCH 1; Thalange 2013; Vague 2003), one study mainly Asian people (Davies 2014) and three studies included Asian people only (Kobayashi 2007; Liu 2016; NCT00605137) (Appendix 9).

All studies included both genders. The age of the participants varied from 4.2 to 44 years. The duration of T1DM varied from 2.1 to 23.2 years (Appendix 10).

Interventions

Nine studies compared insulin detemir with NPH insulin (Bartley 2008; Kobayashi 2007; NCT00595374; NCT00605137; Robertson 2007; Russell-Jones 2004; Standl 2004; Thalange 2013; Vague 2003). Nine studies compared insulin glargine with NPH insulin (Bolli 2009; Chase 2008; Fulcher 2005; Home 2005; Liu 2016; Porcellati 2004; PRESCHOOL; Ratner 2000; Schober 2002). Two studies compared insulin detemir with insulin glargine (Heller 2009; Pieber 2007) and two studies compared insulin degludec with insulin detemir (BEGIN Young; Davies 2014). Finally, four studies compared insulin degludec with insulin glargine (BEGIN Basal-Bolus Type 1; BEGIN Flex T1; SWITCH 1; Urakami 2017).

All studies except one applied NPH insulin once or two times daily. Porcellati 2004 applied NPH insulin four times a day.

Studies started insulin administration in different ways: four studies comparing insulin detemir with NPH insulin started with lower doses of insulin detemir compared with NPH insulin (Kobayashi 2007; NCT00605137; Russell-Jones 2004; Standl 2004). One study comparing insulin degludec with insulin glargine stated that if prior basal insulin was taken more than once daily, then the dose of glargine had to be reduced by 20% to 30% and insulin degludec dose was reduced based on the investigators' decision (BEGIN Flex T1). Another study comparing insulin degludec with insulin glargine stated that if more than one daily dose had been taken prior to the study, then the total daily basal dose was calculated and replaced with insulin degludec in a 1:1 ratio and the insulin glargine dose was recommended to be reduced by 20% to 30% (BEGIN Basal-Bolus Type 1). One study comparing insulin detemir with insulin glargine stated that the insulin detemir dose was reduced by 30% in both the morning and evening doses from the previous regimen and insulin glargine was started with a dose of 20% to 30% less than the previous regimen (Pieber 2007).

Eleven studies applied insulin aspart as fast-acting insulin (Bartley 2008; BEGIN Young; Davies 2014; Heller 2009; Kobayashi 2007; Liu 2016; NCT00595374; Pieber 2007; Robertson 2007; Thalange 2013; Vague 2003); five studies applied insulin lispro (Bolli 2009; Chase 2008; Fulcher 2005; Porcellati 2004; PRESCHOOL); five studies applied human insulin (Home 2005; Ratner 2000; Schober 2002; Russell-Jones 2004; Standl 2004) and one study did not specify the type of fast-acting insulin applied (NCT00605137).

Outcomes

We could retrieve detailed study information for 23 studies (Bartley 2008; BEGIN Basal-Bolus Type 1; BEGIN Flex T1; BEGIN Young; Chase 2008; Davies 2014; Fulcher 2005; Heller 2009; Home 2005; Kobayashi 2007; Liu 2016; NCT00595374; NCT00605137; Pieber 2007; PRESCHOOL; Ratner 2000; Robertson 2007; Russell-Jones 2004; Schober 2002; Standl 2004; SWITCH 1; Thalange 2013; Vague 2003). For six of the studies, trial protocols were available through the CSRs (Fulcher 2005; Home 2005; Ratner 2000; Schober 2002; Standl 2004; Vague 2003). For the remaining studies with a trial registration, information could be retrieved from the clinical trials register (see Appendix 12). Three studies provided data through publications only (Bolli 2009; Porcellati 2004; Urakami 2017) and one study author sent additional data (Urakami 2017).

All studies except three had predefined HbA1c as the primary outcome (NCT00605137; PRESCHOOL; SWITCH 1). All studies reported one or more outcome measures of relevance for this review.

Source of data

We contacted all study authors or investigators through email (see Appendix 14). When important information was lacking on ongoing trials and excluded studies, we contacted investigators for clarification (see Appendix 14).

Excluded studies

We excluded 22 studies after full-text evaluation: eight studies had a wrong study design (not an RCT), six studies applied the wrong intervention, three studies included the wrong population, four studies had a short study duration and one reference was an irrelevant congress report. We evaluated four systematic reviews for identification of studies (Laranjeira 2018; Monami 2009; Tricco 2014; Tricco 2018). For further details see Characteristics of excluded studies.

Risk of bias in included studies

For the Cochrane RoB 2 assessment, we obtained CSRs, clinical study reports or both for 23 studies (Bartley 2008; BEGIN Basal-Bolus Type 1; BEGIN Flex T1; BEGIN Young; Chase 2008; Davies 2014; Fulcher 2005; Heller 2009; Home 2005; Kobayashi 2007; Liu 2016; NCT00595374; NCT00605137; Pieber 2007; PRESCHOOL; Ratner 2000; Robertson 2007; Russell-Jones 2004; Schober 2002; Standl 2004; SWITCH 1; Thalange 2013; Vague 2003). We primarily used data from CSRs to evaluate risk of bias because the CSRs provided detailed information on all risk of bias domains for the RoB 2 tool. For two studies, we could obtain only parts of the original CSRs because the original documentation was written in Japanese and we did not get access to the full CSR (Kobayashi 2007; NCT00605137). For two studies, the clinical study synopses and a study protocol were the only source for data extraction (NCT00595374; NCT00605137).

For each specific outcome, we established an overall 'Risk of bias' judgement, as well as judgements per 'Risk of bias' domain (bias arising from the randomisation process, bias due to deviations from the intended interventions, bias due to missing outcome data, bias in measurement of the outcome, bias in selection of the reported results).

All-cause mortality

All studies reporting deaths except two had a low overall risk of bias. Porcellati 2004 and Urakami 2017 had 'some concerns' because in these open-label studies there was scarce information on methodological aspects of the studies.

Health-related quality of life

All studies reporting health-related quality of life except one had 'some concerns' for overall risk of bias because in these open-label studies this outcome measure was primarily participant-reported. SWITCH 1 had a low overall risk of bias for this outcome measure.

Severe hypoglycaemia

All studies reporting severe hypoglycaemia except three had a low overall risk of bias. Bolli 2009, Porcellati 2004 and Urakami 2017 had 'some concerns' because in these open-label studies there was scarce information on methodological aspects of the studies.

Cardiovascular mortality

All studies reporting deaths except two had a low overall risk of bias. Porcellati 2004 and Urakami 2017 had 'some concerns' because in these open-label studies there was scarce information on methodological aspects of the studies.

Non-fatal myocardial infarction/stroke

All studies reporting non-fatal myocardial infarction, non-fatal stroke or both except one had a low overall risk of bias. Urakami 2017 had 'some concerns' because in this open-label study there was scarce information on methodological aspects of the study.

End-stage renal disease/blindness

The single study reporting end-stage renal disease and blindness had a low overall risk of bias.

Serious adverse events

All studies reporting SAEs except two had a low overall risk of bias. Bolli 2009 and Urakami 2017 had 'some concerns' because in these open-label studies there was scarce information on methodological aspects of the studies.

Diabetic ketoacidosis

All studies reporting diabetic ketoacidosis except one had a low overall risk of bias. Urakami 2017 had 'some concerns' because in this open-label study there was scarce information on methodological aspects of the study.

Non-serious adverse events

All studies reporting non-serious adverse events had 'some concerns' for overall risk of bias because in these open-label studies this outcome measurement was primarily participant-reported.

Severe nocturnal hypoglycaemia

All studies reporting severe nocturnal hypoglycaemia except one had a low overall risk of bias. Urakami 2017 had 'some concerns' because in this open-label study there was scarce information on methodological aspects of the study.

Mild/moderate hypoglycaemia

All studies reporting mild/moderate hypoglycaemia had some concerns for overall risk of bias because in these open-label studies this outcome measurement was primarily participant-reported.

Socioeconomic effects

No studies reported the costs of the intervention during the study period.

HbA1c levels

All studies reporting HbA1c except three had a low overall risk of bias. Bolli 2009, Porcellati 2004 and Urakami 2017 had 'some concerns' because in these open-label studies there was scarce information on methodological aspects of the studies.

Combined HbA1c and severe hypoglycaemia

The studies providing some data on combined HbA1c and severe hypoglycaemia had a low overall risk of bias.

In general, referring to detailed information from the CSRs, the risk of bias evaluation was much more exhaustive compared to details reported in the publications. Most of our outcomes represented hard clinical (semi)objective outcomes with overall low risk of bias. However, for some outcomes, due to their subjective, participant-reported nature, we attributed 'some concerns' to overall risk of bias for the outcomes health-related quality of life, non-serious

adverse events, most measures of nocturnal hypoglycaemia and mild/moderate hypoglycaemia.

Risk of bias assessments for each outcome are located in the risk of bias table section after the characteristics of studies awaiting assessment and at the side of forest plots. For further details on the Excel file of risk of bias evaluation stored online in an open repository (Zenodo), please use the following link: https://zenodo.org/record/4549440.

Effects of interventions

See: **Summary of findings 1** Summary of findings: insulin detemir versus NPH insulin; **Summary of findings 2** Summary of findings: insulin glargine versus NPH insulin; **Summary of findings 3** Summary of findings: insulin detemir versus insulin glargine; **Summary of findings 4** Summary of findings: insulin degludec versus insulin detemir; **Summary of findings 5** Summary of findings: insulin degludec versus insulin glargine

Baseline characteristics

For details of baseline characteristics, see Appendix 9; Appendix 10.

Insulin degludec compared with NPH insulin

We identified no studies comparing insulin degludec with NPH insulin.

Insulin detemir compared with NPH insulin

For an overview of main results for this comparison see Summary of findings 1.

Nine studies compared insulin detemir with NPH insulin (Bartley 2008; Kobayashi 2007; NCT00595374; NCT00605137; Robertson 2007; Russell-Jones 2004; Standl 2004; Thalange 2013; Vague 2003). A total of 3345 participants were randomised, 2099 participants to insulin detemir and 1246 participants to NPH insulin (see Table 1). Three studies included children and randomised 781 children, 466 children to insulin detemir and 315 children to NPH insulin (NCT00605137; Robertson 2007; Thalange 2013). The mean age of the children varied from 8.4 to 9.9 years. Two of the studies did not have full-text publications (NCT00595374; NCT00605137). We retrieved unpublished information on baseline variables or outcomes for all studies for this comparison.

Two studies randomised the participants to insulin detemir and NPH insulin once daily (Bartley 2008; Russell-Jones 2004). However, a second dose of insulin detemir and NPH insulin could be added if necessary. For one of the studies, it was reported that 37% of the participants in the insulin detemir group and 45% of the participants in the NPH insulin group completed the study on a once-daily regimen (Bartley 2008). Four studies randomised participants to NPH insulin once or twice daily (Kobayashi 2007; NCT00595374; NCT00605137; Robertson 2007). One study applied insulin detemir and NPH insulin once or twice daily according to a pre-study regimen (Thalange 2013). One study randomised participants to insulin detemir and NPH insulin twice daily (Vague 2003). Six studies applied insulin aspart as fast-acting insulin at meals (Bartley 2008; Kobayashi 2007; NCT00595374; Robertson 2007; Thalange 2013; Vague 2003). Two studies applied human insulin as fast-acting insulin (Russell-Jones 2004; Standl 2004). One study did not specify the type of fast-acting insulin applied (NCT00605137).

The duration of the intervention varied from 24 weeks to 104 weeks (see Table 1).

Primary outcomes

All-cause mortality

We could retrieve data on all-cause mortality from all nine studies. However, only two studies reported mortality in their full-text publication (Bartley 2008; Thalange 2013). We retrieved the remaining data from CSRs/clinical study synopses and medical reviews from regulatory agencies (Kobayashi 2007; NCT00595374; NCT00605137; Robertson 2007; Russell-Jones 2004; Standl 2004; Vague 2003).

A total of 5/2095 participants allocated to insulin detemir died compared with 0/1239 participants allocated to NPH insulin (Peto OR 4.97, 95% CI 0.79 to 31.38; P = 0.09; 9 studies, 3334 participants; moderate-certainty evidence; Analysis 1.1). We judged the overall risk of bias for this outcome as 'low'.

Subgroup and sensitivity analyses

Analysing unpublished data only, 1/1587 participants in the insulin detemir group died compared with 0/905 participants in the NPH insulin group (2492 participants; 7 studies; Analysis 1.2). Analysing published data only 4/508 participants in the insulin detemir group compared with 0/334 in the NPH insulin group died (2 studies, 842 participants; Analysis 1.2). All five deaths occurred in studies including adults. The test for subgroup differences did not indicate interaction (P = 0.84). We did not perform the remaining subgroup and sensitivity analyses due to lack of data (Appendix 20).

Health-related quality of life

We rated the certainty of the evidence of the three studies with 870 participants providing information on health-related quality of life as low. We judged the overall risk of bias for this outcome as 'some concerns'.

No study reported health-related quality of life in a format making the data suitable for meta-analysis. Kobayashi 2007 applied the Insulin Therapy Related Quality of Life at Night questionnaire (ITR-QOLN); data were reported in the clinical study synopsis. The evaluation of ITR-QOLN after 48 weeks showed higher scores in the insulin detemir group compared with the NPH insulin group (Kobayashi 2007). Standl 2004 applied the Diabetes Health Profile scale (only one of the three dimensions of the scale 'Barriers to activity'); data were reported in the CSR. After 26 weeks, the 'Barriers to activity' in the Diabetes Health profile was 0.71 (SD 0.75) in 210 participants in the insulin detemir group compared with 0.20 (SD 0.78) in 208 participants in the NPH insulin group. The P value was 0.52 (Standl 2004). Diabetes treatment satisfaction was also reported in the CSR (Standl 2004). Another unpublished trial reported in the clinical study synopsis that health-related quality of life did not show any statistically significant differences between the interventions after 26 weeks but did not provide numerical data (NCT00595374).

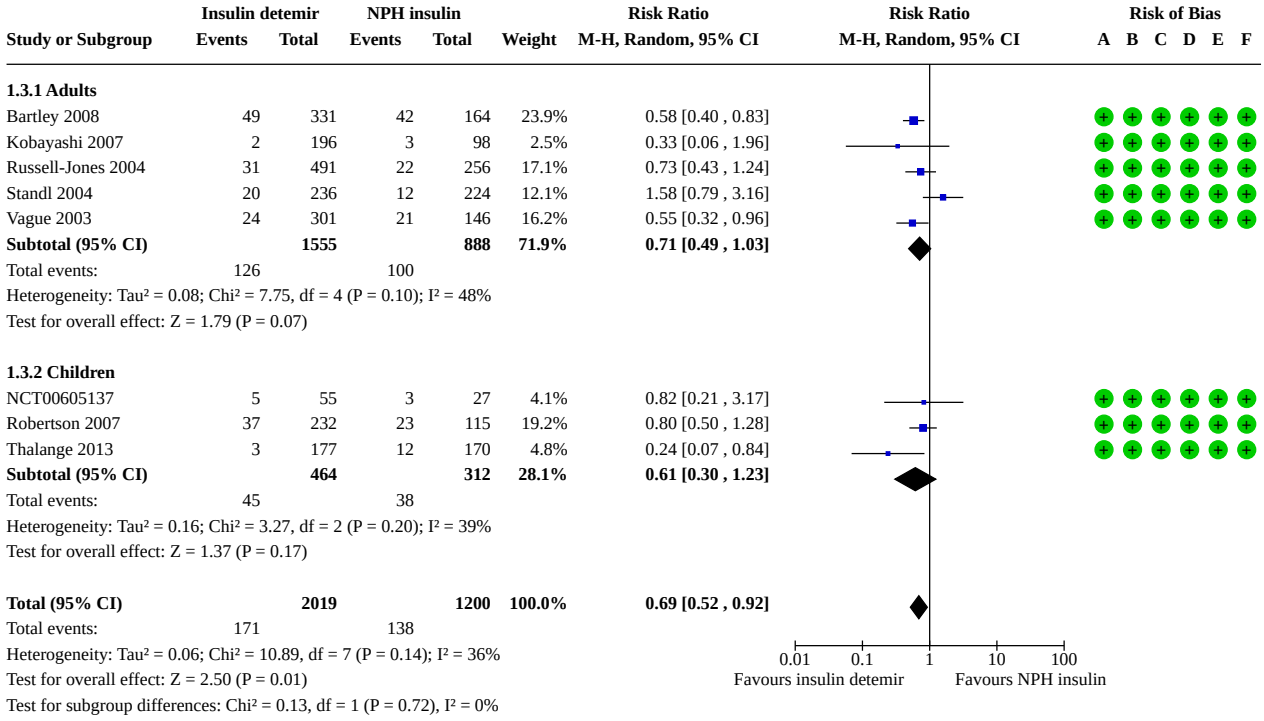
We did not perform subgroup and sensitivity analyses due to lack of data (Appendix 20).

Severe hypoglycaemia

Eight studies reported data on severe hypoglycaemia (Bartley 2008; Kobayashi 2007; NCT00605137; Robertson 2007; Russell-Jones 2004; Standl 2004; Thalange 2013; Vague 2003).

Analysing all available data showed that 171/2019 participants (8.5%) in the insulin detemir group compared with 138/1200 participants (11.5%) in the NPH insulin group experienced severe hypoglycaemia. There was a reduction in severe hypoglycaemia in favour of insulin detemir (RR 0.69, 95% CI 0.52 to 0.92; P = 0.01; 8 studies, 3219 participants; moderate-certainty evidence; Analysis 1.3; Figure 3). The 95% prediction interval ranged between 0.34 and 1.39. We judged the overall risk of bias for this outcome as 'low'.

Figure 3. Severe hypoglycaemia



Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Severe hypoglycaemia
(C) Bias due to missing outcome data: Severe hypoglycaemia
(D) Bias in measurement of the outcome: Severe hypoglycaemia
(E) Bias in selection of the reported result: Severe hypoglycaemia
(F) Overall bias: Severe hypoglycaemia

One study had an extension period (Standl 2004). We used data from the core period (six months) in the meta-analysis. From the publication, only data after the end of the extension period (12 months) were available. However, we could retrieve additional data from the FDA medical review and the CSR (FDA 2002; Standl 2004). One study was unpublished, but data were available from a clinical study synopsis (NCT00605137). Another unpublished study reported no statistically significant differences for severe hypoglycaemia between the intervention groups but did not provide numerical data (NCT00595374). Five studies reported severe hypoglycaemia as requiring third party assistance (Bartley 2008; Kobayashi 2007; NCT00605137; Robertson 2007; Russell-Jones 2004; Standl 2004). One study added to this definition that blood glucose < 2.8 mmol/L should be recorded or symptom reversal with food, glucose or glucagon (Vague 2003). One study defined severe hypoglycaemia as episodes where the children were semi-conscious, unconscious or in a coma, with or without convulsions (Thalange 2013). Bartley 2008 reported most events: data from the CSR of this study showed that 5/331 participants (1.5%) in the insulin detemir group compared with 6/164 participants (3.7%) in the NPH insulin group experienced a hypoglycaemic coma; 2/331 participants (0.6%) in the insulin detemir group compared with 0/164 participants (0%) in the NPH insulin group experienced hypoglycaemic convulsions; 0/331 participants (0%) in the insulin detemir group compared with 1/164 participants (0.6%) in the NPH insulin group experienced loss of consciousness due to hypoglycaemia. Robertson 2007 reported most events in children: 3/232 children (1.3%) in the insulin detemir group compared with 3/115 children (2.6%) in the NPH insulin group were admitted to hospital due to hypoglycaemia; 4/232 children (1.7%) in the insulin detemir group compared with 4/115 children (3.4%) in the NPH insulin group were unconscious due to hypoglycaemia; 2/332 children (0.6%) in the insulin detemir group compared with 4/115 children (3.4%) in the NPH insulin group experienced hypoglycaemia with convulsions; 4/332 children (1.2%) in the insulin detemir group compared with 2/115 children

(1.7%) in the NPH insulin group received glucagon treatment. One study stipulated, that the risk of experiencing hypoglycaemia could have been influenced by lack of blinding: "Investigators and patients in this trial may have been reluctant to aggressively increase the dose of a new basal insulin preparation such as insulin detemir because of the fear of hypoglycemia, especially during the night" (Vague 2003).

Subgroup and sensitivity analyses

Analysing studies including adults only indicated an RR of 0.71, 95% CI 0.49 to 1.03; 5 studies, 2443 participants; Analysis 1.3. Analysing studies including children only indicated an RR of 0.61, 95% CI 0.30 to 1.23; 3 studies, 776 children; Analysis 1.3. The test for subgroup differences did not indicate interaction (P = 0.72).

Restricting the analysis to published data only indicated an RR of 0.62, 95% CI 0.50 to 0.78; 6 studies, 2677 participants; Analysis 1.4; favouring insulin detemir. Restricting the analyses to unpublished data only indicated an RR of 1.42, 95% CI 0.77 to 2.62; 2 studies, 498 participants; Analysis 1.4 . The test for subgroup differences indicated interaction (P = 0.01). This has to be interpreted with caution because the subgroup of studies with unpublished data consisted of two studies only and the CIs slightly overlapped.

A sensitivity analysis excluding the largest study (Russell-Jones 2004) indicated an RR of 0.68, 95% CI 0.48 to 0.97. A sensitivity analysis excluding the longest study (Bartley 2008) indicated an RR of 0.72, 95% CI 0.51 to 1.04.

A sensitivity analysis with data from studies published in English only (Bartley 2008; NCT00605137; Robertson 2007; Russell-Jones 2004; Standl 2004; Thalange 2013; Vague 2003) indicated an RR of 0.70, 95% CI 0.52 to 0.95.

We did not perform the remaining subgroup and sensitivity analyses due to lack of data (Appendix 20).

Hypoglycaemia reported as a serious adverse event

A total of 30/2019 participants (1.5%) in the insulin detemir group compared with 19/1200 participants (1.6%) in the NPH insulin group had a SAE due to hypoglycaemia. There was no evidence of a difference in hypoglycaemia reported as a SAE (RR 0.93, 95% CI 0.51 to 1.71; P = 0.82; 8 studies, 3219 participants; Analysis 1.5). The 95% prediction interval ranged between 0.44 and 1.99. We judged the overall risk of bias for this outcome as 'low' (data not shown).

The test for subgroup differences comparing adults with children did not indicate interaction (P = 1.00). We judged the overall risk of bias for this outcome as 'low' (data not shown).

Secondary outcomes

Cardiovascular mortality

We could retrieve data on cardiovascular mortality from all studies. Only two studies reported cardiovascular mortality in their full-text publication (Bartley 2008; Thalange 2013). We retrieved the remaining data from CSRs/clinical study synopses/medical reviews from regulatory agencies (Kobayashi 2007; NCT00595374; NCT00605137; Robertson 2007; Russell-Jones 2004; Standl 2004; Vague 2003).

Only one adult participant died due to cardiovascular disease (Analysis 1.6). This participant belonged to the insulin detemir group (1/2069 participants). No participant died in the NPH insulin group (0/1221 participants). We judged the overall risk of bias for this outcome as 'low'.

Subgroup analysis and sensitivity analysis

We did not perform subgroup and sensitivity analyses due to lack of data (Appendix 20).

Non-fatal myocardial infarction

None of the included studies reported non-fatal myocardial infarction in the publications. One study had data on non-fatal myocardial infarction from the CSR (Bartley 2008). In this study, 1/331 participants in the insulin detemir group compared with 0/164 participants in the NPH insulin group experienced a non-fatal myocardial infarction (low-certainty evidence; Analysis 1.7). One study reported data at the end of the extension period (duration of intervention was six months with an additional six months extension period) with 1/154 participants in the insulin detemir group and 0/135 participants in the NPH insulin group experiencing a myocardial infarction (Standl 2004). We judged the overall risk of bias for this outcome as 'low'.

We did not perform subgroup and sensitivity analyses due to lack of data (Appendix 20).

Non-fatal stroke

No study reported on non-fatal stroke.

End-stage renal disease

No study reported on end-stage renal disease.

Blindness

No study reported on blindness.

Serious adverse events

We could retrieve data on SAEs from all studies.

In the insulin detemir group, 165/2094 participants (7.9%) reported a SAE compared with 102/1238 participants (8.2%) in the NPH insulin group. There was no evidence of a difference in SAEs (RR 0.95, 95% CI 0.75 to 1.21; P = 0.67; 9 studies, 3332 participants; moderate-certainty evidence; Analysis 1.8). The 95% prediction interval ranged between 0.71 and 1.27. We judged the overall risk of bias for this outcome as 'low'.

Three studies reported SAEs in the main publications in a format making data unsuitable for meta-analysis: one study reported that the frequency and type of adverse events observed during the study were similar with insulin detemir and NPH insulin (Russell-Jones 2004); one study reported that fewer than 5% in each intervention group reported SAEs (Vague 2003) and one study reported that about 10% of participants in both intervention groups experienced SAEs (Standl 2004). However, in the CSRs of these studies, data were reported in a way making them suitable for meta-analysis.

Subgroup and sensitivity analyses

Six studies had data on SAEs for adults: 124/1630 participants (7.6%) in the insulin detemir group compared with 71/926 participants (7.7%) in the NPH insulin group experienced SAEs. The RR was 0.97, 95% CI 0.73 to 1.28; 6 studies, 2556 participants; Analysis 1.8. Three studies had data on SAEs for children: 41/464

children (8.8%) in the insulin detemir group compared with 31/312 children (9.9%) in the NPH insulin group experienced SAEs. The RR was 0.89, 95% CI 0.69 to 1.27; 3 studies, 776 children; Analysis 1.8. The test for subgroup differences did not indicate interaction (P = 0.77).

Restricting the analyses to published data only for SAEs indicated an RR of 0.66, 95% CI 0.40 to 1.09; 2 studies, 641 participants; Analysis 1.9. Restricting analysis to unpublished data only indicated an RR of 1.06, 95% CI 0.80 to 1.39; 6 studies, 2691 participants; Analysis 1.9. The test for subgroup differences did not indicate interaction (P = 0.11).

Sensitivity analysis excluding the largest study (Vague 2003) indicated an RR of 0.93, 95% CI 0.70 to 1.25. Sensitivity analysis excluding the longest study (Bartley 2008) indicated an RR of 0.96, 95% CI 0.72 to 1.29.

A sensitivity analysis with data from studies published in English only indicated an RR of 0.89, 95% CI 0.56 to 1.43 (Bartley 2008; NCT00595374; NCT00605137; Robertson 2007; Russell-Jones 2004; Standl 2004; Thalange 2013; Vague 2003).

We did not perform the remaining subgroup and sensitivity analyses due to lack of data (Appendix 20).

Diabetic ketoacidosis

We could retrieve data on diabetic ketoacidosis from six studies (Bartley 2008; Kobayashi 2007; NCT00605137; Robertson 2007; Thalange 2013; Vague 2003). Two studies reported ketoacidosis in their full-text publications (Robertson 2007; Thalange 2013). One study was unpublished, but we retrieved data from the clinical study synopsis (NCT00605137). Three studies reported diabetic ketoacidosis in CSRs (Bartley 2008; Kobayashi 2007; Vague 2003). It appeared likely that all studies had evaluated this outcome but some did not report this outcome measure (NCT00595374; Russell-Jones 2004; Standl 2004).

A total of 14/1292 participants (1.1%) experienced diabetic ketoacidosis in the insulin detemir group compared with 10/720 participants (1.4%) in the NPH insulin group. There was no evidence of a difference in diabetic ketoacidosis (RR 0.80, 95% CI 0.36 to 1.76; P = 0.58; 6 studies, 2012 participants; Analysis 1.10). We judged the overall risk of bias for this outcome as 'low'.

Subgroup and sensitivity analyses

Three studies reported diabetic ketoacidosis in adults; the RR was 0.84, 95% CI 0.24 to 2.92; 3 studies, 1236 participants; Analysis 1.10. Three studies reported diabetic ketoacidosis in children; the RR was 0.77, 95% CI 0.27 to 2.15; 3 studies, 776 children; Analysis 1.10. The test for subgroup differences did not indicate interaction (P = 0.91).

Restricting the analyses to only published data for diabetic ketoacidosis indicated an RR of 0.83, 95% CI 0.27 to 2.52; 2 studies, 694 participants; Analysis 1.11. Restricting the analyses to only unpublished data for diabetic ketoacidosis indicated an RR of 0.77, 95% CI 0.25 to 2.38; 4 studies, 1318 participants; Analysis 1.11.

Sensitivity analysis excluding the largest study and the longest study indicated an RR of 0.86, 95% CI 0.34 to 2.20 (Bartley 2008).

We did not perform the remaining subgroup and sensitivity analyses due to lack of data (Appendix 20).

Non-serious adverse events

We could retrieve data on non-serious adverse events from all studies. Only four studies reported non-serious adverse events in a format suitable for meta-analysis in their full-text publications (Robertson 2007; Standl 2004; Thalange 2013; Vague 2003). For the remaining studies, we retrieved data from CSRs/clinical study synopses (Bartley 2008; Kobayashi 2007; NCT00595374; NCT00605137; Russell-Jones 2004).

A total of 1622/2094 participants (77.5%) in the insulin detemir group compared with 968/1238 participants (78.2%) in the NPH insulin group experienced a non-serious adverse event. There was no evidence of a difference in non-serious adverse events (RR 0.98, 95% CI 0.94 to 1.01; P = 0.22; 9 studies, 3332 participants; Analysis 1.12). The 95% prediction interval ranged between 0.95 and 1.02. We judged the overall risk of bias for this outcome as 'some concerns'.

Subgroup analysis and sensitivity analysis

Five studies reported non-serious adverse events in adults. A total of 1242/1630 participants (76.2%) in the insulin detemir group compared with 706/926 participants (76.2%) in the NPH insulin group experienced a non-serious adverse event. The RR was 0.99, 95% CI 0.95 to 1.03; Analysis 1.12. Three studies including children reported 380/464 children (81.9%) in the insulin detemir group compared with 262/312 (84.0%) children in the NPH insulin group experienced a non-serious adverse event. The RR was 0.96, 95% CI 0.90 to 1.02; Analysis 1.12. The test for subgroup differences did not indicate interaction (P = 0.40).

Restricting the analyses to only published data indicated 553/710 participants (77.9%) in the insulin detemir group compared with 351/431 participants (81.4%) in the NPH insulin group experienced a non-serious adverse event. The RR was 0.95, 95% CI 0.90 to 1.01; Analysis 1.13. Restricting the analyses to only unpublished data indicated 1069/1384 participants (77.2%) in the insulin detemir group compared with 617/807 participants (76.5%) in the NPH insulin group experienced a non-serious adverse event. The RR was 1.00, 95% CI 0.95 to 1.04; Analysis 1.13. The test for subgroup differences did not indicate interaction (P = 0.25).

Sensitivity analysis excluding the largest study (Russell-Jones 2004) indicated an RR of 0.97, 95% CI 0.93 to 1.01 and excluding the longest study (Bartley 2008) indicated an RR of 0.98, 95% CI 0.94 to 1.02.

A sensitivity analysis with data from studies published in English only indicated an RR of 0.98, 95% CI 0.94 to 1.01 (Bartley 2008; NCT00595374; NCT00605137; Robertson 2007; Russell-Jones 2004; Standl 2004; Thalange 2013; Vague 2003).

We did not perform the remaining subgroup and sensitivity analyses due to lack of data (Appendix 20).

Withdrawals due to adverse events

A total of 30/2020 participants (1.5%) in the insulin detemir group compared with 6/1202 participants (0.5%) in the NPH insulin group withdrew because of adverse events. There was no evidence of a difference in withdrawals due to adverse events (RR 2.23, 95% CI 0.98 to 5.05; P = 0.05; 8 studies, 3222 participants; Analysis 1.14). The 95% prediction interval ranged between 0.80 and 6.19. We judged the overall risk of bias for this outcome as 'low' (data not shown).

Nocturnal hypoglycaemia

We could retrieve data on nocturnal hypoglycaemia from eight studies (Bartley 2008; Kobayashi 2007; NCT00605137; Robertson 2007; Russell-Jones 2004; Standl 2004; Thalange 2013; Vague 2003).

Seven studies reported severe nocturnal hypoglycaemia. A total of 70/1823 participants (3.8%) in the insulin detemir group compared with 60/1102 participants (5.4%) in the NPH insulin group experienced a severe nocturnal hypoglycaemic event. There was no evidence of a difference in severe nocturnal hypoglycaemia (RR 0.67, 95% CI 0.39 to 1.17, P = 0.16; 7 studies, 2925 participants; moderate-certainty evidence; Analysis 1.18). We judged the overall risk of bias for this outcome as 'low'.

The studies applied different ways of reporting nocturnal hypoglycaemia. In the trial synopsis of one study, authors wanted to investigate major nocturnal hypoglycaemia, minor nocturnal hypoglycaemia, nocturnal hypoglycaemia with symptoms only and biochemical nocturnal hypoglycaemia (defined as asymptomatic plasma glucose value). However, only the outcome of any nocturnal hypoglycaemic events was reported (Kobayashi 2007). In the CSR of this study, data for subtypes of hypoglycaemia were provided in a format making them unsuitable for meta-analysis: minor nocturnal hypoglycaemia had an RR of 0.67, 95% CI 0.42 to 1.06; symptoms only nocturnal hypoglycaemia had an RR of 0.58, 95% CI 0.31 to 1.09 and biochemical nocturnal hypoglycaemia had an RR of 0.77, 95% CI 0.45 to 1.33 (Kobayashi 2007). One unpublished study reported nocturnal hypoglycaemia in a format suitable for meta-analysis in the CSR (NCT00605137). Data for another unpublished study (NCT00595374) were reported in a format making them unsuitable for meta-analysis ('no significant differences between the intervention groups').

The data for the analysis of any type of nocturnal hypoglycaemia were available in the full-text articles of six studies (Bartley 2008; Kobayashi 2007; Robertson 2007; Russell-Jones 2004; Thalange 2013; Vague 2003). Two studies provided data in the CSRs (NCT00605137; Standl 2004). Data for mild nocturnal hypoglycaemia and symptomatic nocturnal hypoglycaemia (without confirmed blood glucose values) could be retrieved from seven studies: four studies reported the outcome in the publication (Bartley 2008; Robertson 2007; Russell-Jones 2004; Thalange 2013) and three studies provided the data from unpublished sources (NCT00605137; Standl 2004; Vague 2003). One study reported data on asymptomatic hypoglycaemia (Thalange 2013).

A total of 1041/1555 participants (66.9%) in the insulin detemir group compared with 877/1200 participants (73.1%) in the NPH insulin group experienced any type of nocturnal hypoglycaemic event. There was a reduction in any type of nocturnal hypoglycaemia in favour of insulin detemir (RR 0.91, 95% CI 0.87 to 0.95; P < 0.001; 8 studies, 3219 participants; Analysis 1.15). The 95% prediction interval ranged between 0.86 and 0.96. There was a reduction in mild nocturnal hypoglycaemia in favour of insulin detemir (RR of 0.90, 95% CI 0.85 to 0.96; P = 0.002; 7 studies, 3073 participants; Analysis 1.16). There was a reduction in nocturnal hypoglycaemia with symptoms in favour of insulin detemir (RR 0.88, 95% CI 0.79 to 0.98; P = 0.02; 6 studies, 2578 participants; Analysis 1.17). One study reported asymptomatic nocturnal hypoglycaemia in 83/177 participants (46.9%) in the insulin detemir group compared with 85/170 participants (50%) in the NPH insulin group (Thalange 2013). We judged the overall risk of bias for all these outcomes except for severe nocturnal hypoglycaemia as 'some concerns' (data not shown).

Subgroup and sensitivity analyses

Five studies reported any type of nocturnal hypoglycaemia in adults. A total of 1041/1555 participants (66.9%) in the insulin detemir group compared with 629/888 participants (70.8%) in the NPH insulin group experienced any type of nocturnal hypoglycaemia. The RR was 0.93, 95% CI 0.88 to 0.98; Analysis 1.15; favouring insulin detemir. Three studies including children reported that 337/464 children (72.6%) in the insulin detemir group compared with 258/312 children (82.7%) in the NPH insulin group experienced any type of nocturnal hypoglycaemia. The RR was 0.87, 95% CI 0.81 to 0.94; Analysis 1.15; favouring insulin detemir. The test for subgroup differences did not indicate interaction (P = 0.23).

Four studies reported mild nocturnal hypoglycaemia in adults. The RR was 0.91, 95% CI 0.83 to 1.00; Analysis 1.16; favouring insulin detemir. Three studies reported mild nocturnal hypoglycaemia in children. The RR was 0.88, 95% CI 0.78 to 1.00; Analysis 1.16; favouring insulin detemir. The test for subgroup differences did not indicate interaction (P = 0.66).

Four studies reported nocturnal hypoglycaemia with symptoms in adults. The RR was 0.91, 95% CI 0.82 to 1.01; Analysis 1.17. Two studies reported nocturnal hypoglycaemia with symptoms in children. The RR was 0.55, 95% CI 0.19 to 1.61; Analysis 1.17. The test for subgroup differences did not indicate interaction (P = 0.36).

Four studies reported severe nocturnal hypoglycaemia in adults. The RR was 0.57, 95% CI 0.35 to 0.93; Analysis 1.8; favouring insulin detemir. Three studies including children reported severe nocturnal hypoglycaemia. The RR was 0.64, 95% CI 0.13 to 3.17; Analysis 1.18. The test for subgroup differences did not indicate interaction (P = 0.88).

Six studies had published information on any type of nocturnal hypoglycaemia. The RR was 0.90, 95% CI 0.86 to 0.95; Analysis 1.19; favouring insulin detemir. Two studies had unpublished data on any type of nocturnal hypoglycaemia. The RR was 0.91, 95% CI 0.80 to 1.04; Analysis 1.19. The test for subgroup differences did not indicate interaction (P = 0.90).

Four studies had published information on mild nocturnal hypoglycaemia. The RR was 0.91, 95% CI 0.85 to 0.98; Analysis 1.20; favouring insulin detemir. Three studies had unpublished information on mild nocturnal hypoglycaemia. The RR was 0.89, 95% CI 0.75 to 1.07; Analysis 1.20. The test for subgroup differences did not indicate interaction (P = 0.83).

Three studies had published information on nocturnal hypoglycaemia with symptoms. The RR was 0.90, 95% CI 0.81 to 0.99; Analysis 1.21; favouring insulin detemir. Three studies had unpublished information on nocturnal hypoglycaemia with symptoms. The RR was 0.79, 95% CI 0.57 to 1.08; Analysis 1.21. The test for subgroup differences did not indicate interaction (P = 0.44).

Five studies had published information on severe nocturnal hypoglycaemia. The RR was 0.63, 95% CI 0.32 to 1.25; Analysis 1.22. Two studies had unpublished information on severe nocturnal hypoglycaemia. The RR was 0.90, 95% CI 0.33 to 2.45; Analysis 1.22. The test for subgroup differences did not indicate interaction (P = 0.56).

Sensitivity analysis excluding the longest study (Bartley 2008) for any type of nocturnal hypoglycaemia indicated an RR of 0.90, 95% CI 0.86 to 0.94 favouring insulin detemir.

We did not perform the remaining subgroup and sensitivity analyses due to lack of data (Appendix 20).

Mild/moderate hypoglycaemia

We could retrieve data on mild/moderate hypoglycaemia from eight studies (Bartley 2008; Kobayashi 2007; NCT00605137; Robertson 2007; Russell-Jones 2004; Standl 2004; Thalange 2013; Vague 2003). One unpublished study reported data for mild/moderate hypoglycaemia in a format making the data unsuitable for meta-analysis (NCT00595374). One study did not specify mild hypoglycaemia; for this study we used data for any type of hypoglycaemia (NCT00605137). For the remaining studies, data for mild hypoglycaemia were available (Bartley 2008; Kobayashi 2007; Robertson 2007; Russell-Jones 2004; Standl 2004; Thalange 2013; Vague 2003).

A total of 1726/2019 participants (85.5%) in the insulin detemir compared with 1028/1200 participants (85.7%) in the NPH insulin group experienced mild/moderate hypoglycaemia. There was a reduction in mild/moderate hypoglycaemia in favour of insulin detemir (RR 0.97, 95% CI 0.94 to 0.99; P = 0.01, 8 studies, 3219 participants; Analysis 1.24). The 95% prediction interval ranged between 0.95 and 1.00. We judged the overall risk of bias for this outcome as 'some concerns'.

Subgroup and sensitivity analyses

Five studies reported mild/moderate hypoglycaemia in adults. A total of 1313/1555 participants (84.4%) in the insulin detemir group compared with 742/888 participants (83.4%) in the NPH insulin group experienced mild/moderate hypoglycaemia. The RR was 0.97, 95% CI 0.93 to 1.02; Analysis 1.24. Three studies including children reported 413/464 children (89.0%) in the insulin detemir group compared with 286/312 children (91.7%) in the NPH insulin group experienced mild/moderate hypoglycaemia. The RR was 0.97, 95% CI 0.93 to 1.01; Analysis 1.24. The test for subgroup differences did not indicate interaction (P = 0.82).

Six studies had published information on mild/moderate hypoglycaemia. The RR was 0.97, 95% CI 0.93 to 1.00; Analysis 1.25; favouring insulin detemir. Two studies had unpublished information on mild/moderate hypoglycaemia. The RR was 0.98, 95% CI 0.92 to 1.05; Analysis 1.25. The test for subgroup differences did not indicate interaction (P = 0.69).

Sensitivity analysis excluding the largest study indicated an RR of 0.96, 95% CI 0.93 to 0.98 (Russell-Jones 2004) favouring insulin detemir. Sensitivity analysis excluding the longest study indicated an RR of 0.97, 95% CI 0.94 to 1.00 (Bartley 2008) favouring insulin detemir.

A sensitivity analysis with data from studies published in English only indicated an RR of 0.97, 95% CI 0.94 to 1.00 favouring insulin detemir.

We did not perform the remaining subgroup and sensitivity analyses due to lack of data (Appendix 20).

Socioeconomic effects

No studies reported direct or indirect costs of the intervention during the study period. One study reported economic predictions of the interventions based on simulation cohorts in Belgian, Canadian, French, German, Italian and Spanish, Swedish settings (Bartley 2008).

HbA1c

We could retrieve data on HbA1c levels from eight studies (Bartley 2008; Kobayashi 2007; NCT00605137; Robertson 2007; Russell-Jones 2004; Standl 2004; Thalange 2013; Vague 2003). Six studies reported HbA1c levels in publications (Bartley 2008; Kobayashi 2007; Robertson 2007; Russell-Jones 2004; Thalange 2013; Vague 2003). Standl 2004 only reported HbA1c after the end of the extension period in publications, but through FDA review and CSR, we could retrieve data at the end of the regular intervention period. One unpublished study reported HbA1c in the clinical study synopsis (NCT00605137).

There was no evidence of a difference in HbA1c (MD 0.01%, 95% CI -0.1 to 0.1; P = 0.11; 8 studies, 3122 participants; moderate-certainty evidence; Analysis 1.26). The 95% prediction interval ranged between -0.1% and 0.1%. We judged the overall risk of bias for this outcome as 'low'.

Subgroup and sensitivity analyses

Five studies reported HbA1c levels in adults. The MD of HbA1c was -0.03%, 95% CI -0.1 to 0.1; Analysis 1.26. Three studies including children reported HbA1c levels. The MD of HbA1c was 0.1%, 95% CI -0.04 to 0.3; Analysis 1.26. The test for subgroup differences did not indicate interaction (P = 0.11).

Analysing only published data indicated a MD of HbA1c of -0.02%, 95% -0.1 to 0.1; Analysis 1.27. Analysing only unpublished data indicated a MD of HbA1c of 0.1%, 95% CI -0.1 to 0.3; Analysis 1.27. The test for subgroup differences did not indicate interaction (P = 0.28). One unpublished study reported data for HbA1c in a format making the data unsuitable for meta-analysis (NCT00595374).

Sensitivity analysis excluding the largest study indicated a MD of HbA1c of 0.02%, 95% CI -0.1 to 0.1 (Russell-Jones 2004). Sensitivity analysis excluding the longest study indicated a MD of HbA1c of 0.04%, 95% CI -0.1 to 0.1 (Bartley 2008).

Sensitivity analysis exclusively analysing data from studies published in English indicated a MD of HbA1c of -0.01%, 95% CI -0.1 to 0.1 (Bartley 2008; NCT00605137; Robertson 2007; Russell-Jones 2004; Standl 2004; Thalange 2013; Vague 2003).

We did not perform the remaining subgroup and sensitivity analyses due to lack of data (Appendix 20).

Combined HbA1c and severe hypoglycaemia

No study reported on combined HbA1c and severe hypoglycaemia.

One study provided data on the combined outcome HbA1c and hypoglycaemia (Bartley 2008). We extracted these data from the CSR. This specified the percentage of participants who reached HbA1c ≤ 7.0% at the end of the study without symptomatic hypoglycaemia with a plasma glucose < 4.0 mmol/L or any single plasma glucose value < 3.1 mmol/L during the last month of treatment. This number was 71/321 participants (22.2%) in the

insulin detemir group compared with 21/159 participants (13.2%) in the NPH insulin group.

Two studies stated that similar results were seen for hypoglycaemia when adjusted for HbA1c (Robertson 2007; Vague 2003). One study reported in the CSR that the observed risk of hypoglycaemia was not explained by differences in HbA1c (Russell-Jones 2004).

Insulin glargine compared with NPH insulin

For an overview of main results for this comparison see Summary of findings 2.

Nine studies compared insulin glargine with NPH insulin (Bolli 2009; Chase 2008; Fulcher 2005; Home 2005; Liu 2016; Porcellati 2004; PRESCHOOL; Ratner 2000; Schober 2002). A total of 2387 participants were randomised, 1205 participants to insulin glargine and 1182 participants to NPH insulin (see Table 1). Four studies included children and randomised 823 children, 433 children to insulin glargine and 390 children to NPH insulin (Chase 2008; Liu 2016; PRESCHOOL; Schober 2002). The mean age of the children varied from 4.2 to 13.2 years.

All studies were published as full-text articles in English. However, we retrieved unpublished information from most studies for this comparison (Chase 2008; Fulcher 2005; Home 2005; Liu 2016; PRESCHOOL; Ratner 2000; Schober 2002). Two studies had information solely based on full-text publications (Bolli 2009; Porcellati 2004). We contacted investigators in order to achieve additional information, but did not receive a reply (see Appendix 19).

One study randomised participants to insulin glargine once daily and NPH insulin once daily (Fulcher 2005). One study randomised participants to insulin glargine once daily and NPH insulin or Lente insulin twice daily according to a pre-study regimen. However, only three participants received Lente insulin (Chase 2008). Six studies randomised participants to insulin glargine once daily and NPH insulin (Bolli 2009; Home 2005; PRESCHOOL; Liu 2016; Ratner 2000; Schober 2002). One study randomised participants to insulin glargine once daily and NPH insulin four times a day (Porcellati 2004).

Five studies applied insulin lispro as fast-acting insulin at meals (Bolli 2009; Chase 2008; Fulcher 2005; Porcellati 2004; PRESCHOOL). One study applied insulin aspart as fast-acting insulin (Liu 2016). Three studies applied human insulin as fast-acting insulin (Home 2005; Ratner 2000; Schober 2002).

The duration of the intervention varied from 24 weeks to 30 weeks.

Primary outcomes

All-cause mortality

We could retrieve data on all-cause mortality from eight studies (Chase 2008; Fulcher 2005; Home 2005; Liu 2016; Porcellati 2004; PRESCHOOL; Ratner 2000; Schober 2002). Only one of these studies reported all-cause mortality in the full-text publication (Porcellati 2004). We obtained the remaining data from unpublished sources.

A total of 0/1207 participants allocated to insulin glargine died compared with 1/1068 participants allocated to NPH insulin (Peto OR 0.14, 95% CI 0.00 to 6.98; P = 0.32; 8 studies, 2175 participants; moderate-certainty evidence; Analysis 2.1). We judged the overall risk of bias for this outcome as 'low'.

Subgroup and sensitivity analyses

We did not perform subgroup and sensitivity analyses due to lack of data (Appendix 20).

Health-related quality of life

Four studies reported health-related quality of life (Bolli 2009; Chase 2008; Home 2005; Ratner 2000). We judged the certainty of the evidence for these studies with 1013 participants as low. We judged the overall risk of bias for this outcome as 'some concerns'.

One study applied the Well-Being Enquiry for Diabetics (Bolli 2009), two studies applied the General Well-being scale (Home 2005; Ratner 2000) and one study applied the Diabetes Quality of Life for Youth and Parents' Diabetes Quality of Life (Chase 2008). Bolli 2009 randomised 175 participants. After six months, data from 133 participants were evaluated for impact domain, 114 participants for level of satisfaction, 108 participants for general worries and 111 participants for diabetes-related worries. It was not reported how many participants in each intervention arm were included in the analysis. The only domain showing a statistically significant difference after six months was diabetes-related worries, which showed greater improvements in the insulin glargine group (P = 0.05). At six months, the impact domain score was 77 (quartiles 73 to 82) in the insulin glargine group and 80 (quartiles 73 to 85) in the NPH insulin group. Changes in percentage from baseline were -1.4 (quartiles -10 to 8) in the insulin glargine group and -4.4 (quartiles -14 to 7) in the NPH insulin group. At six months, the level of satisfaction score was 31 (quartiles 27 to 35) in the insulin glargine group and 32 (quartiles 27 to 38) in the NPH insulin group. Changes in percentage from baseline were 0.0 (quartiles -10 to 8) in the insulin glargine group and -3.0 (quartiles -7 to 3) in the NPH insulin group. At six months, the general worries score was 32 (quartiles 27 to 34) in the insulin glargine group and 32 (quartiles 26 to 35) in the NPH insulin group. Changes in percentage from baseline were -1.4 (quartiles -7 to 3) in the insulin glargine group and 0.0 (quartiles -11 to 4) in the NPH insulin group. At six months, the diabetes-related worries score was 32 (quartiles 27 to 34) in the insulin glargine group and 31 (quartiles 25 to 34) in the NPH insulin group. Changes in percentage from baseline were -5.7 (quartiles -12 to 4) in the insulin glargine group and 0.0 (quartiles -8 to 8) in the NPH insulin group (P = 0.05) (Bolli 2009). Two studies applied the General Well-being scale (Home 2005; Ratner 2000). One study reported health-related quality of life through a CSR (Ratner 2000). Home 2005 reported in a co-publication that the mean score for the General Well-being scale showed an increase (i.e. better well-being) of 1.44 points at week 28 in the insulin glargine group compared with 1.57 points in the NPH insulin group with all four subscales contributing to these improvements (Home 2005). In the CSR, health-related quality of life with SDs at the end of intervention were reported (Home 2005). Combining data from the two studies applying the General Well-being scale did not show evidence of a difference (MD 0.62 points, 95% CI -0.71 to 1.96; P = 0.36; 2 studies, 880 participants; Analysis 2.2). For both studies, the difference between the treatments was not statistically significant at the end of follow-up for each separate item of the General Well-being scale (depression, anxiety, energy, positive well-being). One study evaluated health-related quality of life in children (Chase 2008). Data were available from the clinical study synopsis. This study applied the Diabetes Quality of Life for

Youth and Parents' Diabetes Quality of Life (Chase 2008). This study did not find evidence of a difference between the interventions. No information about scores or number of participants included in the analysis was reported.

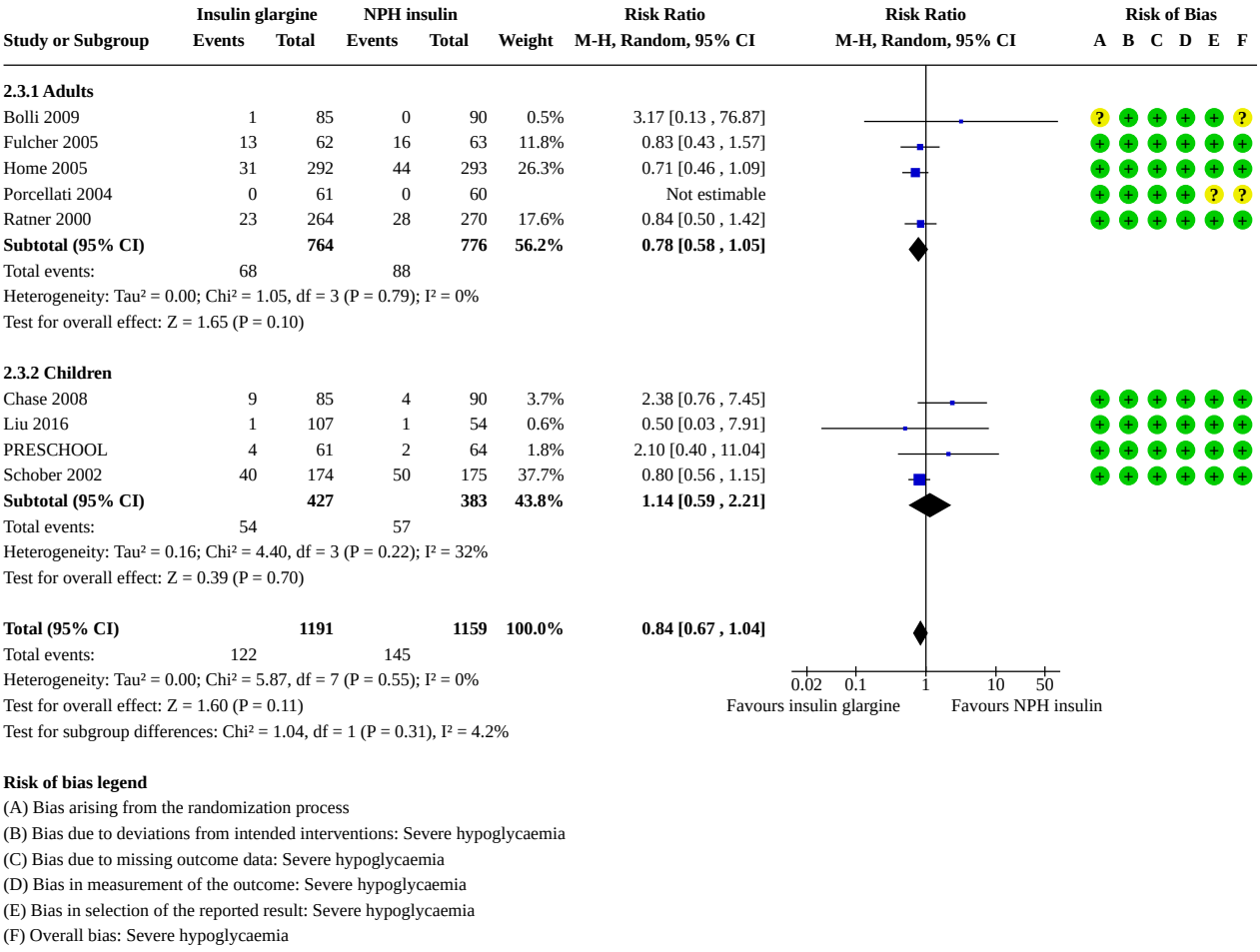
We did not perform subgroup and sensitivity analyses due to lack of data (Appendix 20).

Severe hypoglycaemia

Nine studies reported data on severe hypoglycaemia (Bolli 2009; Chase 2008; Fulcher 2005; Home 2005; Liu 2016; Porcellati 2004; PRESCHOOL; Ratner 2000; Schober 2002). All studies defined severe hypoglycaemia as hypoglycaemia requiring third party assistance. For two studies, we retrieved unpublished data from the CSRs (Fulcher 2005; Ratner 2000).

A total of 122/1191 participants (10.2%) in the insulin glargine group compared with 145/1159 participants (12.5%) in the NPH insulin group experienced severe hypoglycaemia. There was no evidence of a difference in severe hypoglycaemia (RR 0.84, 95% CI 0.67 to 1.04; P = 0.11; 9 studies, 2350 participants; moderate-certainty evidence; Analysis 2.3; Figure 4). The 95% prediction interval ranged between 0.65 and 1.09. We judged the overall risk of bias for this outcome as 'low'.

Figure 4. Severe hypoglycaemia



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Severe hypoglycaemia
(C) Bias due to missing outcome data: Severe hypoglycaemia
(D) Bias in measurement of the outcome: Severe hypoglycaemia
(E) Bias in selection of the reported result: Severe hypoglycaemia
(F) Overall bias: Severe hypoglycaemia

One study in the main publication defined severe hypoglycaemia as requiring third party assistance in the methods section of the main publication (Ratner 2000). However, the definition of severe hypoglycaemia reported in the results section in the main publication was severe hypoglycaemic event with blood glucose levels < 2.0 mmol/L. In the CSR, severe hypoglycaemia with and without confirmed blood glucose < 2.0 mmol/L was reported. With the definition of severe hypoglycaemia according to the methods section, 23/264 participants (8.7%) in the insulin glargine group compared with 28/270 participants (10.4%) in the NPH insulin group experienced severe hypoglycaemia. This number was used for the meta-analysis. Using severe hypoglycaemia applying the definition of blood glucose < 2.0 mmol/L showed that 7/264 participants (2.5%) in the insulin glargine group compared with 16/270 participants (5.9%) in the NPH insulin group experienced severe hypoglycaemia (Ratner 2000). From the CSR, it was also apparent, that during the screening phase no participants receiving insulin glargine during the study had an episode of severe hypoglycaemia compared with 6/270 participants (2.2%) receiving NPH insulin (Ratner 2000). One study stated in the FDA report that the participants receiving NPH insulin twice daily tended to have less hypoglycaemia than the participants receiving insulin glargine (FDA 2000; Home 2005). Schober 2002 reported the greatest number of events in children: in the CSR, 1/174 children (0.6%) in

the insulin glargine group compared with 1/175 children (0.6%) in the NPH insulin group experienced coma due to hypoglycaemia; 4/174 children (2.3%) in the insulin glargine group compared with 3/175 children (1.7%) in the NPH insulin group experienced convulsions due to hypoglycaemia; 6/174 children (3.4%) in the insulin glargine group compared with 1/175 children (0.6%) in the NPH insulin group experienced syncope due to hypoglycaemia. Home 2005 reported the greatest number of events in adults: in the CSR, 7/292 participants (2.4%) in the insulin glargine group compared with 12/293 participants (4.1%) in the NPH insulin group experienced coma, convulsions or syncope reported as associated symptoms from severe hypoglycaemia (Home 2005).

Subgroup analysis and sensitivity analysis

Analysing studies including only adults indicated an RR of 0.78, 95% CI 0.58 to 1.05; Analysis 2.3. Analysing studies including only children indicated an RR of 1.14, CI 95% CI 0.59 to 2.21; Analysis 2.3. The test for subgroup differences did not indicate interaction (P = 0.31).

Restricting the analysis to only published data indicated an RR of 0.87, 95% CI 0.63 to 1.22; Analysis 2.4. Restricting the analysis to only unpublished data indicated an RR of 0.83. 95% CI 0.56 to 1.25; Analysis 2.4. The test for subgroup differences did not indicate interaction (P = 0.87).

Sensitivity analysis excluding the largest study and the longest study indicated an RR of 0.88, 95% CI 0.68 to 1.14 (Home 2005).

All studies except one had received funding from the pharmaceutical industry (Porcellati 2004). Porcellati 2004 applied NPH insulin four times a day. Excluding this study from the analysis indicated an RR of 0.83, 95% CI 0.67 to 1.04.

We did not perform the remaining subgroup and sensitivity analyses due to lack of data (Appendix 20).

Hypoglycaemia reported as a serious adverse event

A total of 52/1131 participants (4.6%) in the insulin glargine group compared with 56/1098 participants (5.1%) in the NPH insulin group had a SAE due to hypoglycaemia. There was no evidence of a difference in hypoglycaemia reported as a SAE (RR 0.94, 95% CI 0.64 to 1.39; P = 0.76; 8 studies, 2229 participants; Analysis 2.5). The 95% prediction interval ranged between 0.52 and 1.71. We judged the overall risk of bias for this outcome as 'low' (data not shown).

The test for subgroup differences comparing adults with children did not indicate interaction (P = 0.90).

Secondary outcomes

Cardiovascular mortality

We could retrieve data on cardiovascular mortality from eight studies (Chase 2008; Fulcher 2005; Home 2005; Liu 2016; Porcellati 2004; PRESCHOOL; Ratner 2000; Schober 2002). Only one of these studies reported cardiovascular mortality in the full-text publication (Porcellati 2004). We retrieved the remaining data from unpublished sources.

Analysing all available data showed 0/1106 participants allocated to insulin glargine died compared with 1/1068 participants allocated to NPH insulin (Analysis 2.6). We judged the overall risk of bias for this outcome as 'low'.

Subgroup and sensitivity analyses

We did not perform subgroup and sensitivity analyses due to lack of data (Appendix 20).

Non-fatal myocardial infarction

None of the included studies reported non-fatal myocardial infarction in the publications. One study in adults had data on non-fatal myocardial infarction from the CSR (Home 2005). In this study, 0/292 participants in the insulin glargine group compared with 0/293 participants in the NPH insulin group experienced a non-fatal myocardial infarction (low-certainty evidence; Analysis 2.7). We judged the overall risk of bias for this outcome as 'low'.

Non-fatal stroke

None of the included studies reported non-fatal stroke in the publications. One study in adults had data on cerebral ischaemia from the CSR (Home 2005). In this study, 0/292 participants in the insulin glargine group compared with 1/293 participants in the NPH insulin group experienced cerebral ischaemia (low-certainty evidence; Analysis 2.8). We judged the overall risk of bias for this outcome as 'low'.

End-stage renal disease

None of the studies reported on end-stage renal disease.

Blindness

None of the studies reported on blindness.

Serious adverse events

Eight studies reported data on SAEs (Bolli 2009; Chase 2008; Fulcher 2005; Home 2005; Liu 2016; PRESCHOOL; Ratner 2000; Schober 2002).

A total of 109/1131 participants (9.6%) in the insulin glargine group compared with 110/1098 participants (10.0%) in the NPH insulin group experienced SAEs. There was no evidence of a difference in SAEs (RR 1.08, 95% CI 0.63 to 1.84; P = 0.79; 8 studies, 2229 participants; moderate-certainty evidence; Analysis 2.9). The 95% prediction interval ranged between 0.22 and 5.21. We judged the overall risk of bias for this outcome as 'low'.

One study did not mention SAEs in the publication (Porcellati 2004). One study reported SAEs other than hypoglycaemia in the main publication (Fulcher 2005): 5/62 participants (8.0%) in the insulin glargine group compared with 3/63 participants (4.7%) in the NPH insulin group experienced a SAE. From the CSR, the number of participants experiencing any SAE was reported and used in the meta-analysis (Fulcher 2005). Three other studies contributed with data from additional sources (Liu 2016; PRESCHOOL; Ratner 2000). Three studies reported SAEs in the main publication (Bolli 2009; Home 2005; Schober 2002).

Subgroup analysis and sensitivity analysis

Analysing studies including only adults indicated an RR of 0.99, 95% CI 0.72 to 1.35; Analysis 2.9. Analysing studies including only children indicated an RR of 1.02, CI 95% CI 0.28 to 3.64; Analysis 2.9. The test for subgroup differences did not indicate interaction (P = 0.96).

Restricting the analysis to only published data indicated an RR of 1.11, 95% CI 0.11 to 2.70; Analysis 2.10. Restricting the analysis to

only unpublished data indicated an RR of 1.10, 95% CI 0.46 to 2.60; Analysis 2.10. The test for subgroup differences did not indicate interaction (P = 0.99).

Sensitivity analysis excluding the largest study and the longest study indicated an RR of 1.15, 95% CI 0.58 to 2.30 (Home 2005).

We did not perform the remaining subgroup and sensitivity analyses due to lack of data (Appendix 20).

Diabetic ketoacidosis

We could retrieve data on diabetic ketoacidosis from seven studies (Chase 2008; Fulcher 2005; Home 2005; Liu 2016; PRESCHOOL; Ratner 2000; Schober 2002). Three studies reported ketoacidosis in their full-text publications (Chase 2008; Liu 2016; Schober 2002).

A total of 6/1046 participants (0.6%) had ketoacidosis in the insulin glargine group compared with 8/1008 participants (0.1%) in the NPH insulin group. There was no evidence of a difference in diabetic ketoacidosis (RR 0.53, 95% CI 0.19 to 1.44; P = 0.21; 7 studies, 2054 participants; Analysis 2.11). We judged the overall risk of bias for this outcome as 'low'.

Subgroup and sensitivity analyses

Analysing diabetic ketoacidosis in only adults indicated an RR of 1.00, 95% CI 0.11 to 9.58; Analysis 2.11. Analysing diabetic ketoacidosis in only children indicated an RR of 0.45, 95% CI 0.15 to 1.39, Analysis 2.11. The test for subgroup differences did not indicate interaction (P = 0.53).

Analysing only published data indicated that 4/366 participants (1.1%) in the insulin glargine group compared with 8/319 participants (2.5%) in the NPH insulin group experienced diabetic ketoacidosis. The RR was 0.39, 95% CI 0.11 to 1.31; Analysis 2.12. Analysing only unpublished data indicated that 2/680 participants (0.3%) in the insulin glargine group compared with 3/689 participants (0.4%) in the NPH insulin group experienced diabetic ketoacidosis. The RR was 1.01, 95% CI 0.18 to 5.77; Analysis 2.12. The test for subgroup differences did not indicate interaction (P = 0.38).

Sensitivity analysis excluding the largest study and the longest study indicated an RR of 0.43, 95% CI 0.16 to 1.17 (Home 2005).

We did not perform the remaining subgroup and sensitivity analyses due to lack of data (Appendix 20).

Non-serious adverse events

Eight studies reported data on non-serious adverse events (Bolli 2009; Chase 2008; Fulcher 2005; Home 2005; Liu 2016; PRESCHOOL; Ratner 2000; Schober 2002).

A total of 792/1131 participants (70.0%) in the insulin glargine group compared with 747/1098 (68.0%) participants in the NPH insulin group experienced a non-serious adverse event. There was no evidence of a difference in non-serious adverse events (RR 1.01, 95% CI 0.96 to 1.06; P = 0.72; 8 studies, 2229 participants; Analysis 2.13). The 95% prediction interval ranged between 0.95 and 1.07. We judged the overall risk of bias for this outcome as 'some concerns'.

One study did not mention adverse events in the publication (Porcellati 2004).

Subgroup analysis and sensitivity analysis

Analysing studies including only adults indicated an RR of 1.01, 95% CI 0.95 to 1.07; Analysis 2.13. Analysing studies including only children indicated an RR of 1.02, CI 95% CI 0.93 to 1.12; Analysis 2.13. The test for subgroup differences did not indicate interaction (P = 0.81).

Restricting the analysis to only published data indicated an RR of 1.00, 95% CI 0.94 to 1.05, Analysis 2.14. Restricting the analysis to only unpublished data indicated an RR of 1.03, 95% CI 0.94 to 1.14, Analysis 2.14. The test for subgroup differences did not indicate interaction (P = 0.53).

Sensitivity analysis excluding the largest study and the longest study indicated an RR of 1.00, 95% CI 0.95 to 1.06 (Home 2005).

We did not perform the remaining subgroup and sensitivity analyses due to lack of data (Appendix 20).

Withdrawals due to adverse events

A total of 11/1130 participants (1%) in the insulin glargine group compared with 9/1100 participants (0.8%) in the NPH insulin group withdrew because of adverse events. There was no evidence of a difference in withdrawals due to adverse events (RR 0.80, 95% CI 0.24 to 2.81; P = 0.76; 8 studies, 2130 participants; Analysis 2.15). The 95% prediction interval ranged between 0.07 and 10.27. We judged the overall risk of bias for this outcome as 'low' (data not shown).

Nocturnal hypoglycaemia

We could retrieve data on nocturnal hypoglycaemia from seven studies (Chase 2008; Fulcher 2005; Home 2005; Liu 2016; PRESCHOOL; Ratner 2000; Schober 2002).

Four studies reported **severe nocturnal hypoglycaemia** in the CSRs (Chase 2008; Fulcher 2005; Home 2005; Ratner 2000) and two studies reported severe nocturnal hypoglycaemia in the publications (PRESCHOOL; Schober 2002). A total of 69/938 participants (7.4%) in the insulin glargine group compared with 83/955 participants (8.7%) in the NPH insulin group experienced severe nocturnal hypoglycaemia. There was no evidence of a difference in severe nocturnal hypoglycaemia (RR 0.83, 95% CI 0.62 to 1.12; P = 0.23; 6 studies, 1893 participants; moderate-certainty evidence; Analysis 2.19). We judged the overall risk of bias for this outcome as 'low'.

One study only reported frequency of nocturnal hypoglycaemia for the last month of treatment and not for the whole intervention period (12 months): there were 1.2 (SD 0.2) episodes/patient-month in the insulin glargine group compared with 3.2 (SD 0.3) episodes/patient-month in the NPH insulin group (Porcellati 2004). One study reported that there was no statistically significant change in nocturnal hypoglycaemia between the intervention groups (Bolli 2009). Five of the studies reported the number of participants with nocturnal hypoglycaemia in the publications (Fulcher 2005; Home 2005; Liu 2016; PRESCHOOL; Schober 2002). For two studies, we retrieved data from other sources (Chase 2008; Ratner 2000). Chase 2008 reported that no statistically significant change between the intervention groups was identified. Ratner 2000 reported nocturnal hypoglycaemia with confirmed blood glucose < 2 mmol/L and not just hypoglycaemia occurring at night as defined in the method section of the publication. In the CSR of this study, two different definitions of nocturnal hypoglycaemia were stated:

hypoglycaemia at night and hypoglycaemia at night with blood glucose < 2 mmol/L. Nocturnal hypoglycaemia was reported for three different time periods in the CSR (after one month, from two months to the end of study, for the entire study period). From the tables in the CSR, it was apparent that the only analysis showing a statistically significant benefit of insulin glargine was nocturnal hypoglycaemia with confirmed blood glucose < 2 mmol/L from two months until the end of the study. This definition and time period were the ones reported in the full-text publication.

A total of 713/1045 participants (68.2%) in the insulin glargine group compared with 693/1009 participants (68.7%) in the NPH insulin group experienced any nocturnal hypoglycaemia. There was no evidence of a difference in any nocturnal hypoglycaemia (RR 1.00, 95% CI 0.96 to 1.05; P = 0.96; 7 studies, 1054 participants; Analysis 2.16). One study investigated mild nocturnal hypoglycaemia as reported in the CSR (Fulcher 2005): 39/62 participants (62.9%) in the insulin glargine group compared with 47/63 participants (74.6%) in the NPH insulin group experienced mild nocturnal hypoglycaemia (RR 0.84, 95% CI 0.66 to 1.07; Analysis 2.17). Symptomatic nocturnal hypoglycaemia with or without blood glucose validation was reported in four studies (Fulcher 2005; Home 2005; Liu 2016; PRESCHOOL). There was no evidence of a difference in symptomatic nocturnal hypoglycaemia (RR 0.93, 95% CI 0.82 to 1.05; P = 0.26; 4 studies, 996 participants; Analysis 2.18). No study reported on asymptomatic nocturnal hypoglycaemia. Home 2005 reported that the proportion of participants who experienced nocturnal hypoglycaemia confirmed by a blood glucose level < 2.8 mmol/L and < 2.0 mmol/L did not differ significantly between interventions. We judged the overall risk of bias for all these outcomes except for severe nocturnal hypoglycaemia as 'some concerns' (data not shown).

Subgroup analysis and sensitivity analysis

Analysing studies for any nocturnal hypoglycaemia including only adults indicated an RR of 0.99, 95% CI 0.92 to 1.06; Analysis 2.16. Analysing studies for any nocturnal hypoglycaemia including only children indicated an RR of 1.01, CI 95% CI 0.95 to 1.08; Analysis 2.16. The test for subgroup differences did not indicate interaction (P = 0.65).

Analysing studies for symptomatic nocturnal hypoglycaemia including only adults indicated an RR of 0.97, 95% CI 0.88 to 1.08; Analysis 2.18. Analysing studies for symptomatic nocturnal hypoglycaemia including only children indicated an RR of 0.74, 95% CI 0.55 to 1.00; Analysis 2.18. The test for subgroup differences did not indicate interaction (P = 0.09).

Analysing studies for severe nocturnal hypoglycaemia including only adults indicated an RR of 0.87, 95% CI 0.60 to 1.27; Analysis 2.19. Analysing studies for severe nocturnal hypoglycaemia including only children indicated an RR of 0.77, 95% CI 0.47 to 1.25; Analysis 2.19. The test for subgroup differences did not indicate interaction (P = 0.68).

Restricting the analysis to only published data for any nocturnal hypoglycaemia indicated an RR of 1.00, 95% CI 0.95 to 1.06; Analysis 2.20. Restricting the analysis to only unpublished data for any nocturnal hypoglycaemia indicated an RR of 1.00, 95% CI 0.91 to 1.08; Analysis 2.20. The test for subgroup differences did not indicate interaction (P = 0.86).

Sensitivity analysis of any nocturnal hypoglycaemia excluding the largest study and the longest study indicated an RR of 1.00, 95% CI 0.95 to 1.05 (Home 2005).

Restricting the analysis to only published data for symptomatic nocturnal hypoglycaemia indicated an RR of 0.87, 95% CI 0.67 to 1.12; Analysis 2.21. Analysing only unpublished data for symptomatic nocturnal hypoglycaemia indicated an RR of 0.94, 95% CI 0.80 to 1.10; Analysis 2.21.

We did not perform the remaining subgroup and sensitivity analyses due to lack of data (Appendix 20).

Mild/moderate hypoglycaemia

We could retrieve data on mild/moderate hypoglycaemia from seven studies (Chase 2008; Fulcher 2005; Home 2005; Liu 2016; PRESCHOOL; Ratner 2000; Schober 2002).

A total of 951/1045 participants (91.0%) in the insulin glargine group compared with 898/1009 participants (89.0%) in the NPH insulin group experienced mild/moderate hypoglycaemia. There was no evidence of a difference in mild/moderate hypoglycaemia (RR 1.02, 95% CI 1.00 to 1.04; P = 0.09; 7 studies, 2054 participants; Analysis 2.22). We judged the overall risk of bias for this outcome as 'some concerns'.

One study only reported frequency of mild hypoglycaemia for the last month of treatment and not for the whole intervention period (12 months): there were 7.2 (SD 0.5) episodes/patient-month in the insulin glargine group compared with 13.2 (SD 0.5) episodes/patient-month in the NPH insulin group (Porcellati 2004). One study reported that there was no statistically significant change in hypoglycaemia between the intervention groups (Bolli 2009). Five studies reported mild/moderate hypoglycaemia in a format making the data suitable for meta-analysis (Chase 2008; Home 2005; Liu 2016; PRESCHOOL; Schober 2002). For two studies, we retrieved the data from additional sources (Fulcher 2005; Ratner 2000).

Subgroup analysis and sensitivity analysis

Analysing studies including only adults indicated an RR of 1.02, 95% CI 0.99 to 1.06; Analysis 2.22. Analysing studies including only children indicated an RR of 1.01, CI 95% CI 0.99 to 1.04; Analysis 2.22. The test for subgroup differences did not indicate interaction (P = 0.68).

Restricting the analysis to only published data indicated an RR of 1.02, 95% CI 1.00 to 1.05; Analysis 2.23. Restricting the analysis to only unpublished data indicated an RR of 1.01, 95% CI 0.98 to 1.04; Analysis 2.23. The test for subgroup differences did not indicate interaction (P = 0.78).

Sensitivity analysis excluding the largest study and the longest study indicated an RR of 1.01, 95% CI 0.99 to 1.04 (Home 2005).

We did not perform the remaining subgroup and sensitivity analyses due to lack of data (Appendix 20).

Socioeconomic effects

We retrieved data for socioeconomic effects from CSRs of three studies (Fulcher 2005; Home 2005; Schober 2002). No studies reported an estimate of the costs of the intervention during the study period. One study had evaluated economic effects, but the supplemental CSR with these data could unfortunately

not be retrieved (Ratner 2000). In the CSR for Fulcher 2005, it was reported that very few participants (three in each group) reported a loss of income because of diabetes during the treatment period. Approximately 30 participants in each intervention group reported seeking medical advice (ambulatory care) once or more during the treatment period (Fulcher 2005). Home 2005 could not evaluate all participants for economic data: 6/275 participants (2.1%) changed from employment status to non-employment status during the study in the insulin glargine group compared with 7/265 participants (2.6%) in the NPH insulin group. Of the participants employed at baseline, 16/287 participants (7.5%) in the insulin glargine group compared with 23/283 participants (10.8%) in the NPH insulin group lost time for work during the study. Reasons for these changes during the study were not reported. Schober 2002 reported that nine of the caregivers (7.5%) employed at baseline had lost time for work during the study in the insulin glargine group compared with 12 of the caregivers (10.3%) in the NPH insulin group.

HbA1c

We retrieved data on HbA1c levels from all studies (Bolli 2009; Chase 2008; Fulcher 2005; Home 2005; Liu 2016; Porcellati 2004; PRESCHOOL; Ratner 2000; Schober 2002).

There was no evidence of a difference in HbA1c (MD 0.02%, 95% CI -0.1 to 0.1; P = 0.59; 9 studies, 2285 participants; moderate-certainty evidence; Analysis 2.24). The 95% prediction interval ranged between -0.5% and 0.5%. We judged the overall risk of bias for this outcome as 'low'.

One study reported HbA1c at the end of follow-up as adjusted least square means in the publication (Fulcher 2005). However, in this study, HbA1c at baseline was higher in the participants randomised to NPH insulin compared with insulin glargine (9.2% (SD 1.1) in the insulin glargine group compared with 9.7% (SD 1.3) in the NPH insulin group). In the CSR of this study, data with change from baseline were provided which we included in the meta-analysis. Chase 2008 reported HbA1c for completers of the study only. However, in the CSR, HbA1c was reported for completers and for the intention-to-treat population.

Subgroup and sensitivity analysis

Five studies reported HbA1c in adults with a MD of -0.01%, 95% CI -0.2 to 0.1; Analysis 2.24. Four studies including only children reported HbA1c with a MD of 0.03%, 95% CI -0.1 to 0.2; Analysis 2.24. The test for subgroup differences did not indicate interaction (P = 0.67).

Analysing only published data indicated HbA1c with a MD of 0.02%, 95% CI -0.1 to 0.1, Analysis 2.25. Analysing only unpublished data indicated HbA1c with a MD of -0.04%, 95% CI -0.3 to 0.2; Analysis 2.25. The test for subgroup differences did not indicate interaction (P = 0.60).

Sensitivity analysis excluding the largest study and the longest study indicated a MD in HbA1c of 0.0%, 95% CI -0.1 to 0.1 (Home 2005).

All studies, except one had received funding from the pharmaceutical industry (Porcellati 2004). Porcellati 2004 applied NPH four times a day. Excluding this study from the analysis indicated a MD in HbA1c of 0.02%, 95% CI -0.1 to 0.1.

We did not perform the remaining subgroup and sensitivity analyses due to lack of data (Appendix 20).

Combined HbA1c and severe hypoglycaemia

None of the studies reported on combined HbA1c and severe hypoglycaemia.

Insulin detemir compared with insulin glargine

For an overview of main results for this comparison, see Summary of findings 3.

Two studies compared insulin detemir with insulin glargine (Heller 2009; Pieber 2007). A total of 769 participants were randomised, 461 participants to insulin detemir and 308 participants to insulin glargine (Table 1). Both studies were published as full-text articles in English. However, we retrieved unpublished information on outcomes for both studies from additional sources. One study administered insulin detemir once daily (evening dose). If necessary, a second dose could be administered in the morning (Heller 2009). One study applied insulin detemir twice daily (Pieber 2007). Insulin glargine was given once daily (evening dose) in both studies. Fast-acting insulin was insulin aspart in both studies. Both studies included adults with T1DM. The duration of the intervention varied from 24 weeks to 52 weeks (see Table 1). Both studies were sponsored by Novo Nordisk.

Primary outcomes

All-cause mortality

We retrieved data on all-cause mortality from the clinical study synopsis of both studies. Heller 2009 reported that 0/299 participants died in the insulin detemir group compared with 1/144 participants (0.7%) in the insulin glargine group and Pieber 2007 reported that 0/161 participants died in the insulin detemir group compared with 0/159 participants in the insulin glargine group (low-certainty evidence; Analysis 3.1). We judged the overall risk of bias for this outcome as 'low'.

We did not perform subgroup and sensitivity analyses due to lack of data (Appendix 20).

Health-related quality of life

No study reported scales evaluating health-related quality of life. One study used the Diabetes Treatment Satisfaction Questionnaire and pain perception (Pieber 2007). One study used the Insulin Treatment Satisfaction Questionnaire (Heller 2009). Both treatment satisfaction questionnaires were reported in CSRs.

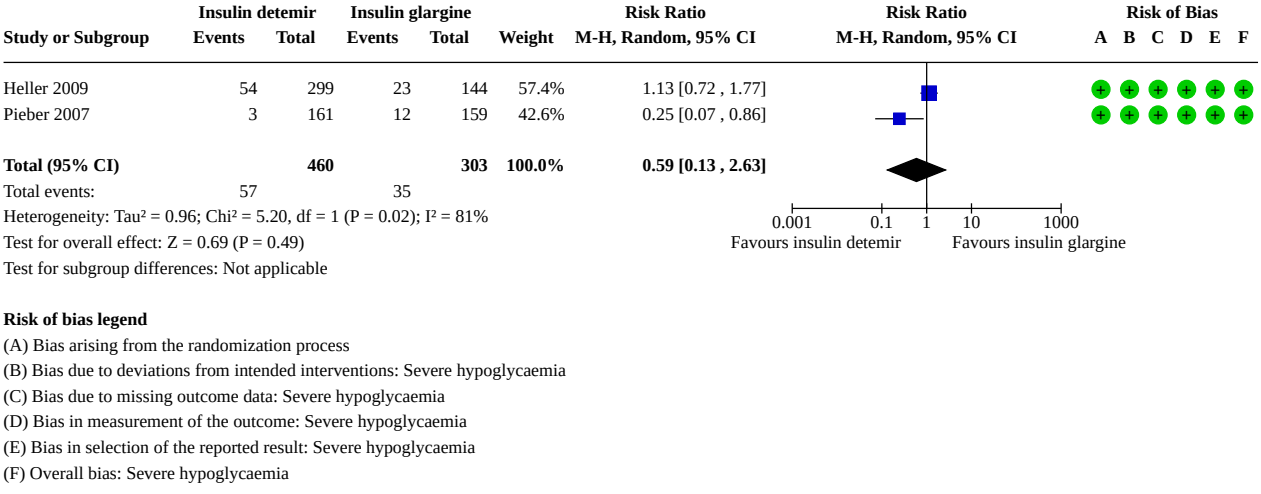
Severe hypoglycaemia

Heller 2009 reported the mean number of hypoglycaemic episodes in the insulin detemir group to be 146 in 299 participants in the insulin detemir group compared with 53 in 144 participants in the insulin glargine group. However, we could retrieve the number of participants experiencing one or more severe hypoglycaemic episodes from the associated CSR. Pieber 2007 reported severe hypoglycaemia in the publication.

A total of 57/460 participants (12.4%) in the insulin detemir group compared with 35/303 participants (11.6%) in the insulin glargine group experienced severe hypoglycaemia. There was no evidence of a difference in severe hypoglycaemia (RR 0.59, 95% CI 0.13 to 2.63; P = 0.49; 2 studies, 763 participants; very low-certainty

evidence; Analysis 3.2; Figure 5). We judged the overall risk of bias for this outcome as 'low'.

Figure 5. Severe hypoglycaemia



Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Severe hypoglycaemia
(C) Bias due to missing outcome data: Severe hypoglycaemia
(D) Bias in measurement of the outcome: Severe hypoglycaemia
(E) Bias in selection of the reported result: Severe hypoglycaemia
(F) Overall bias: Severe hypoglycaemia

We did not perform subgroup and sensitivity analyses due to lack of data (Appendix 20).

Hypoglycaemia reported as a serious adverse event

A total of 13/460 participants (2.8%) in the insulin detemir group compared with 5/303 participants (1.7%) in the insulin glargine group experienced hypoglycaemia as a SAE. There was no evidence of a difference in hypoglycaemia reported as a SAE (RR 1.16, 95% CI 0.14 to 9.48; P = 0.89; 2 studies, 763 participants; Analysis 3.4). We judged the overall risk of bias for this outcome as 'low' (data not shown).

Subgroup and sensitivity analysis

Analysis according to publication status indicated interaction (P = 0.02; Analysis 3.3). However, this has to be interpreted with caution because the 95% CIs slightly overlapped. The remaining subgroup and sensitivity analyses could not be performed due to lack of data (Appendix 20).

Secondary outcomes

Cardiovascular mortality

We could retrieve data on cardiovascular mortality from additional sources for both studies. Heller 2009 reported that 0/299 participants died due to cardiovascular disease in the insulin detemir group compared with 1/144 participants (0.7%) in the insulin glargine group and Pieber 2007 reported that 0/161 participants in the insulin detemir group compared with 0/159 participants in the insulin glargine group died (Analysis 3.5). We judged the overall risk of bias for this outcome as 'low'.

We did not perform subgroup and sensitivity analyses due to lack of data (Appendix 20).

Non-fatal myocardial infarction

Heller 2009 reported in the CSR that 1/299 participants (0.3%) in the insulin detemir group compared with 1/144 participants (0.7%) in the insulin glargine group experienced a non-fatal myocardial infarction (low-certainty evidence; Analysis 3.6). We judged the overall risk of bias for this outcome as 'low'.

Non-fatal stroke

Heller 2009 reported in the CSR that 2/299 participants (0.6%) in the insulin detemir group compared with 0/144 participants in the insulin glargine group experienced a non-fatal stroke (low-certainty evidence; Analysis 3.7). We judged the overall risk of bias for this outcome as 'low'.

End-stage renal disease

None of the studies for reported on end-stage renal disease.

Blindness

None of the studies reported on blindness.

Serious adverse events

Both studies reported SAEs in the publications. A total of 49/460 participants (10.7%) in the insulin detemir group compared with 18/303 participants (5.9%) in the insulin glargine group experienced a SAE. There was no evidence of a difference in SAEs (RR 1.72, 95% CI 0.91 to 3.23; P = 0.24; 2 studies, 763 participants; low-certainty evidence; Analysis 3.8). Analysing data in a fixed-effect model showed beneficial effects of insulin glargine (RR 1.79, 95% CI 1.04 to 3.08; P = 0.04). We judged the overall risk of bias for this outcome as 'low'.

We did not perform subgroup and sensitivity analyses due to lack of data (Appendix 20).

Diabetic ketoacidosis

Heller 2009 reported in the CSR that 1/299 participants (0.3%) in the insulin detemir group compared with 0/144 participants in the insulin glargine group experienced ketoacidosis (Analysis 3.9). We judged the overall risk of bias for this outcome as 'low'.

Non-serious adverse events

We could retrieve data on non-serious adverse events from both studies. Heller 2009 reported adverse events in the publication; we retrieved data for Pieber 2007 data from additional sources.

A total of 394/460 participants (85.7%) in the insulin detemir group compared with 250/303 participants (82.5%) in the insulin glargine group reported a non-serious adverse event. There was no evidence of a difference in non-serious adverse events (RR 1.01, 95% CI 0.93 to 1.09; 2 studies, 763 participants; Analysis 3.10). We judged the overall risk of bias for this outcome as 'some concerns'.

Subgroup and sensitivity analysis

Subgroup analysis according to published data compared with unpublished data did not indicate interaction (P = 0.28; Analysis 3.11). We did not perform the remaining subgroup and sensitivity analyses due to lack of data (Appendix 20).

Withdrawals due to adverse events

A total of 9/460 participants (2.0%) in the insulin detemir group compared with 5/303 participants (1.7%) in the insulin glargine group withdrew because of adverse events. There was no evidence of a difference in withdrawals due to adverse events (RR 1.06, 95% CI 0.31 to 3.67; P = 0.92; 2 studies, 763 participants; Analysis 3.12).

Nocturnal hypoglycaemia

We could retrieve data on nocturnal hypoglycaemia from both studies. Pieber 2007 reported nocturnal hypoglycaemia in the publication. We retrieved data for Heller 2009 from additional sources. Both studies defined nocturnal hypoglycaemia as an episode occurring between 23.00 and 06.00.

A total of 27/460 participants (5.9%) in the insulin detemir group compared with 15/303 participants (5.0%) in the insulin glargine group experienced **severe nocturnal hypoglycaemia**. There was no evidence of a difference in severe nocturnal hypoglycaemia (RR 0.55, 95% CI 0.06 to 5.12; P = 0.60; 2 studies, 763 participants; very low-certainty evidence; Analysis 3.16). We judged the overall risk of bias for this outcome as 'low'.

Pieber 2007 reported data on nocturnal hypoglycaemia according to different definitions in the publication. Heller 2009 reported there were no significant differences between the interventions in the risk of having a nocturnal hypoglycaemic episode, but the number of participants with an event in each intervention group was not provided in the publication. However, we could obtain these data from the CSR. Both studies had analysed nocturnal hypoglycaemia according to the same subclassifications: there was no evidence of a difference in any nocturnal hypoglycaemia (RR 1.01, 95% CI 0.93 to 1.09; P = 0.84; 2 studies, 763 participants; Analysis 3.13), in confirmed nocturnal hypoglycaemia (plasma glucose < 3.1 mmol/L and no assistance; RR 1.01, 95% CI 0.92 to 1.10; P = 0.90; 2 studies, 763 participants; Analysis 3.14); and in symptomatic nocturnal hypoglycaemia (plasma glucose ≤ 3.1 mmol/L or no plasma glucose, no assistance required; RR 1.02, 95% CI 0.81 to 1.29; P = 0.85; 2 studies, 763 participants; Analysis 3.15). We judged the overall risk of bias for all these outcomes except for severe nocturnal hypoglycaemia as 'some concerns' (data not shown).

Subgroup and sensitivity analysis

Analysis could only be performed according to published data compared with unpublished data: none of the definitions of nocturnal hypoglycaemia indicated interactions. We did not perform the remaining subgroup and sensitivity analyses due to lack of data (Appendix 20).

Mild/moderate hypoglycaemia

We could retrieve data on mild/moderate hypoglycaemia from both studies. Pieber 2007 reported mild/moderate hypoglycaemia in the publication. Heller 2009 reported that the overall risk of having a hypoglycaemic episode during the treatment period was similar between the insulin detemir and the insulin glargine group with a relative risk (insulin detemir/insulin glargine) of 0.94; P = 0.57. The number of participants with mild/moderate hypoglycaemia was not reported in this publication. However, we could retrieve data from the CSR.

A total of 404/460 participants (87.8%) in the insulin detemir group compared with 243/303 participants (80.2%) in the insulin glargine group experienced mild/moderate hypoglycaemia. There was no evidence of a difference in mild/moderate hypoglycaemia (RR 1.04, 95% CI 0.94 to 1.14; P = 0.44; 2 studies, 763 participants; Analysis 3.17). We judged the overall risk of bias for this outcome as 'some concerns'.

Subgroup and sensitivity analysis

Analysis according to published data compared with unpublished data did not indicate interaction. We did not perform the remaining subgroup and sensitivity analyses due to lack of data (Appendix 20).

Socioeconomic effects

No studies reported the costs of the intervention during the study period. One study published economic data based on simulation cohorts from a US healthcare system perspective (Pieber 2007).

HbA1c

We could retrieve data on HbA1c levels from both studies. There was no evidence of a difference in HbA1c (MD -0.01%, 95% CI -0.1 to 0.1; P = 0.89; 2 studies, 763 participants; low-certainty evidence; Analysis 3.18). We judged the overall risk of bias for this outcome as 'low'.

We did not perform subgroup and sensitivity analyses due to lack of data (Appendix 20).

Combined HbA1c and severe hypoglycaemia

Heller 2009 reported that HbA1c ≤ 7% was achieved without major hypoglycaemia during the last month of treatment for 91/285 participants (31.9%) in the insulin detemir group compared with 39/135 participants (28.9%) in the insulin glargine group (RR 1.11, 95% CI 0.81 to 1.51; P = 0.53; Analysis 3.19). Pieber 2007 did not report numerical data, but stated that the adjustment for HbA1c showed that the reduced risk of hypoglycaemia with insulin detemir was not due to differences in glycaemic control. We judged the overall risk of bias for this outcome as 'low' (data not shown).

We did not perform subgroup and sensitivity analyses due to lack of data (Appendix 20).

Insulin degludec compared with insulin detemir

For an overview of main results for this comparison, see Summary of findings 4.

Two studies compared insulin degludec with insulin detemir (BEGIN Young; Davies 2014). A total of 806 participants were randomised, 477 participants to insulin degludec and 329 participants to insulin detemir (see 'Overview of study populations' Table 1). One study included children (BEGIN Young). The mean age of the children was 10 years. Both studies were published as full-text articles in English. However, for both studies we could retrieve additional information on outcomes from additional sources. Both studies applied insulin degludec once daily and insulin detemir once or twice daily. Both studies applied insulin aspart as fast-acting insulin. The duration of the intervention was 26 weeks in both studies and both studies had an extension period of 26 weeks. Both studies were sponsored by the same pharmaceutical company (Novo Nordisk).

Primary outcomes

All-cause mortality

Both studies reported data on all-cause mortality (BEGIN Young; Davies 2014). No participant died (0/475 participants in the insulin degludec group compared with 0/327 participants in the insulin detemir group; low-certainty evidence; Analysis 4.1). We judged the overall risk of bias for this outcome as 'low'.

We did not perform subgroup and sensitivity analyses due to lack of data (Appendix 20).

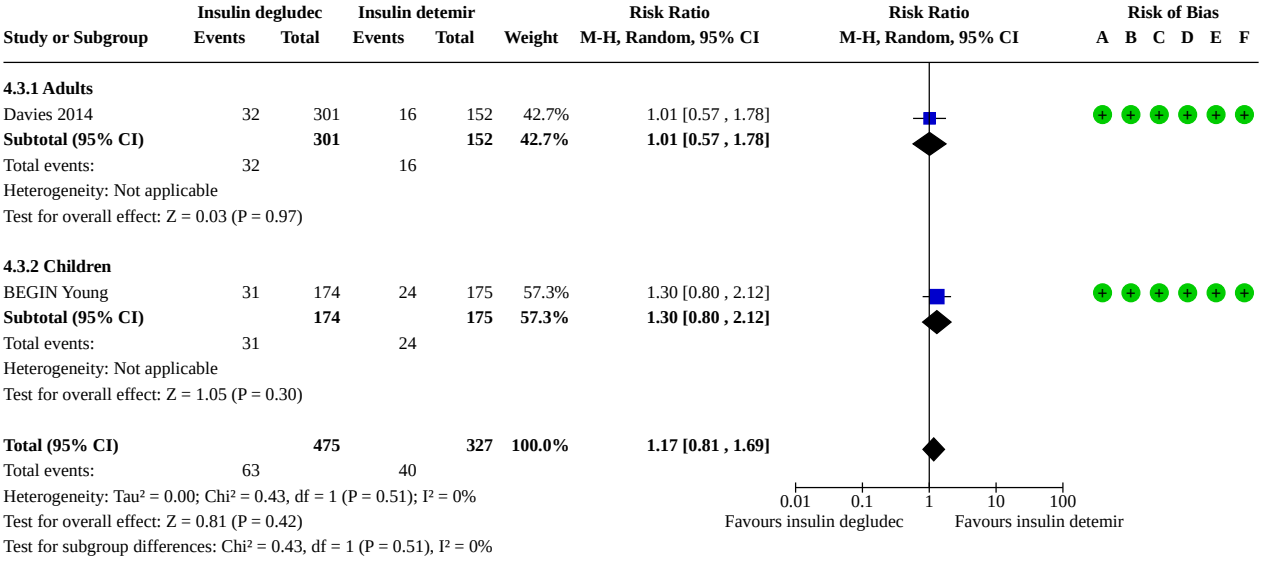
Health-related quality of life

We retrieved data on health-related quality of life from additional sources (Davies 2014). The applied questionnaire was the SF-36. There was no evidence of a difference in health-related quality of life for the physical health score (MD -0.60, 95% CI -1.83 to 0.63; P = 0.34; 1 study, 454 participants; low-certainty evidence; Analysis 4.2) The health-related quality of life for the mental health score favoured insulin detemir (MD -3.00, 95% CI -4.44 to -1.56; P < 0.001; 1 study, 454 participants; low-certainty evidence; Analysis 4.2). The minimal important difference for the physical component score is two to three points and for the mental component score three points. We judged the overall risk of bias for this outcome as 'some concerns'.

Severe hypoglycaemia

Both studies reported data on severe hypoglycaemia in the publications. In the insulin degludec group, 63/475 participants (13.3%) experienced severe hypoglycaemia compared with 40/327 participants (12.2%) in the insulin detemir group. There was no evidence of a difference in severe hypoglycaemia (RR 1.17, 95% CI 0.81 to 1.69; P = 0.42; 2 studies, 802 participants; low-certainty evidence; Analysis 4.3; Figure 6). We judged the overall risk of bias for this outcome as 'low'.

Figure 6. Severe hypoglycaemia



Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Severe hypoglycaemia
(C) Bias due to missing outcome data: Severe hypoglycaemia
(D) Bias in measurement of the outcome: Severe hypoglycaemia
(E) Bias in selection of the reported result: Severe hypoglycaemia
(F) Overall bias: Severe hypoglycaemia

Subgroup and sensitivity analysis

Subgroup analysis including only adults compared with studies including only children did not indicate interaction (P = 0.51; Analysis 4.3). We did not perform the remaining subgroup and sensitivity analyses due to lack of data (Appendix 20).

Hypoglycaemia reported as a serious adverse event

A total of 15/475 participants (3.2%) in the insulin degludec group compared with 10/327 participants (3.1%) in the insulin detemir group had a SAE due to hypoglycaemia. There was no evidence of a difference in SAEs (RR 0.92, 95% CI 0.37 to 2.32; P = 0.86; 2 studies, 802 participants; Analysis 4.4). We judged the overall risk of bias for this outcome as 'low' (data not shown).

The test for subgroup differences comparing adults with children did not indicate interaction (P = 0.27).

BEGIN Young in the SAE list of the CSR stated that 2/174 participants (1.1%) in the insulin degludec group compared with 4/175 participants (2.3%) in the insulin detemir experienced a hypoglycaemic seizure and 1/174 participants (0.6%) in the insulin degludec group compared with 1/175 participants (0.6%) in the insulin detemir group experienced hypoglycaemic unconsciousness. Davies 2014 in the SAE list of the CSR reported that 3/301 participants (1.0%) in the insulin degludec group compared with 1/152 participants (0.7%) in the insulin detemir group experienced a hypoglycaemic coma and 3/301 participants (1.0%) compared with 1/152 participants (0.7%) experienced hypoglycaemic unconsciousness.

Secondary outcomes

Cardiovascular mortality

Both studies reported data on cardiovascular mortality. No participant died (0/475 participants in the insulin degludec group compared with 0/327 participants in the insulin detemir group; Analysis 4.5). We judged the overall risk of bias for this outcome as 'low'.

We did not perform subgroup and sensitivity analyses due to lack of data (Appendix 20).

Non-fatal myocardial infarction

Davies 2014 reported that no participant experienced a non-fatal myocardial infarction (0/301 participants in the insulin degludec group compared with 0/152 participants in the insulin detemir group; ; low-certainty evidence; Analysis 4.6). We retrieved these data from additional sources. We judged the overall risk of bias for this outcome as 'low'.

Non-fatal stroke

Davies 2014 reported that no participant experienced a non-fatal stroke (0/301 participants in the insulin degludec group compared with 0/152 participants in the insulin detemir group; Analysis 4.7; low-certainty evidence). We retrieved these data from additional sources. We judged the overall risk of bias for this outcome as 'low'.

End-stage renal disease

Davies 2014 reported that 0/301 participants in the insulin degludec group compared with 0/152 participants in the insulin detemir group experienced end-stage renal disease (Analysis 4.8). We retrieved these data from additional sources. We judged the overall risk of bias for this outcome as 'low'.

Blindness

Davies 2014 reported that no participant experienced blindness (0/301 participants in the insulin degludec group compared with 0/152 participants in the insulin detemir group; Analysis 4.9). These data were retrieved from additional sources. We judged the overall risk of bias for this outcome as 'low'.

Serious adverse events

Both studies reported SAEs. In the insulin degludec group, 41/475 participants (8.6%) compared with 24/327 participants (7.3%) in the insulin detemir group experienced a SAE. There was no evidence of a difference in SAEs (RR 1.25, 95% CI 0.76 to 2.05; P = 0.38; 2 studies, 802 participants; low-certainty evidence; Analysis 4.10). We judged the overall risk of bias for this outcome as 'low'.

Subgroup and sensitivity analysis

Subgroup analysis including only adults compared with studies including only children did not indicate interaction (P = 0.63; Analysis 4.10). We did not perform the remaining subgroup and sensitivity analyses due to lack of data (Appendix 20).

Diabetic ketoacidosis

None of the studies reported on ketoacidosis in the publications. However, we retrieved data on diabetic ketoacidosis from additional sources. A total of 2/475 participants (0.4%) in the insulin degludec group compared with 0/327 participants in the insulin detemir group experienced diabetic ketoacidosis (Analysis 4.11). Both participants experiencing diabetic ketoacidosis were children (BEGIN Young). We judged the overall risk of bias for this outcome as 'low'.

We did not perform the remaining subgroup and sensitivity analyses due to lack of data (Appendix 20).

Non-serious adverse events

BEGIN Young reported the number of children with non-serious adverse events in the publication. For Davies 2014, we retrieved this information from additional sources. A total of 380/475 participants (80%) in the insulin degludec group compared with 269/327 participants (82.3%) in the insulin detemir group experienced a non-serious adverse event. There was no evidence of a difference in non-serious adverse events (RR 1.02, 95% CI 0.96 to 1.08; P = 0.48; 2 studies, 802 participants; Analysis 4.12). We judged the overall risk of bias for this outcome as 'some concerns'.

Subgroup and sensitivity analysis

Analyses including only adults compared with studies including only children and analyses comparing only published data with only unpublished data did not indicate interaction (P = 0.53; Analysis 4.12). We did not perform the remaining subgroup and sensitivity analyses due to lack of data (Appendix 20).

Withdrawals due to adverse events

A total of 5/475 participants (1.1%) in the insulin degludec group compared with 1/327 participants (0.3%) in the insulin detemir group withdrew because of adverse events. There was no evidence of a difference in withdrawals due to adverse events (RR 2.32, 95% CI 0.38 to 14.18; P = 0.36; 2 studies, 802 participants; Analysis 4.13). We judged the overall risk of bias for this outcome as 'low' (data not shown).

Nocturnal hypoglycaemia

Both studies reported data on nocturnal hypoglycaemia. None of the studies reported on any nocturnal hypoglycaemia.

Severe nocturnal hypoglycaemia was reported in the CSRs of both studies. A total of 17/475 participants in the insulin degludec group (3.6%) compared with 10/327 participants (3.1%) in the insulin detemir group experienced severe nocturnal hypoglycaemia. There was no evidence of a difference in severe nocturnal hypoglycaemia (RR 1.12, 95% CI 0.51 to 2.46; P = 0.77; 2 studies, 802 participants; low-certainty evidence; Analysis 4.18). We judged the overall risk of bias for this outcome as 'low'.

We retrieved data on nocturnal hypoglycaemia confirmed with blood glucose measurements. There was no evidence of a difference in confirmed nocturnal hypoglycaemia (RR 1.04, 95% CI 0.94 to 1.15; P = 0.40; 2 studies, 802 participants; Analysis 4.14). From the CSRs of both studies, data for mild documented nocturnal hypoglycaemia (plasma glucose ≤ 3.9 mmol/L, able to self-treat) were available. There was no evidence of a difference in mild documented nocturnal hypoglycaemia (RR 0.97, 95% CI 0.86 to 1.10; P = 0.67; 2 studies, 802 participants; Analysis 4.15). There was no evidence of a difference in symptomatic nocturnal hypoglycaemia without blood glucose measurements (RR of 0.72, 95% CI 0.15 to 3.59; P = 0.69; 2 studies, 802 participants; Analysis 4.16). There was no evidence of a difference in asymptomatic nocturnal hypoglycaemia (RR 0.91, 95% CI 0.80 to 1.03; P = 0.13; 2 studies, 802 participants; Analysis 4.17). We judged the overall risk of bias for all these outcomes except for severe nocturnal hypoglycaemia as 'some concerns' (data not shown).

Subgroup and sensitivity analysis

Subgroup analysis including only adults only compared with studies including only children did not indicate subgroup interaction (P = 0.82; Analysis 4.18). We did not perform the remaining subgroup and sensitivity analyses due to lack of data (Appendix 20).

Mild/moderate hypoglycaemia

Both studies reported data on mild/moderate hypoglycaemia in the publications. There was no evidence of a difference in mild/moderate hypoglycaemia (RR 1.02, 95% CI 0.99 to 1.05; P = 0.17; 2 studies, 802 participants; Analysis 4.19). We judged the overall risk of bias for this outcome as 'some concerns'.

Subgroup and sensitivity analysis

Subgroup analysis including only adults compared with studies including only children did not indicate interaction (P = 0.85; Analysis 4.19). We did not perform the remaining subgroup and sensitivity analyses due to lack of data (Appendix 20).

Socioeconomic effects

No studies reported the costs of the intervention during the study period. One study reported economic predictions of the interventions based on simulation cohorts in an UK setting of children and adolescents (BEGIN Young).

HbA1c

Both studies had data for HbA1c. BEGIN Young reported data until the end of the extension period in the publication and not until the end of the intervention period. However, we could retrieve these data from ClinicalTrials.gov. There was no evidence of a difference in HbA1c (MD 0.05%, 95% CI -0.1 to 0.2; P = 0.44; 2 studies, 804 participants; low-certainty evidence; Analysis 4.20). We judged the overall risk of bias for this outcome as 'low'.

Subgroup and sensitivity analysis

Subgroup analyses including only adults only compared with studies including only children and only published data compared with only unpublished data did not indicate interactions (P = 0.42; Analysis 4.20). We did not perform the remaining subgroup and sensitivity analyses due to lack of data (Appendix 20).

Combined HbA1c and severe hypoglycaemia

Davies 2014 reported the combined outcome HbA1c and severe hypoglycaemia in the CSR. At the end of the intervention period, a total of 116/292 participants (39.7%) in the insulin degludec group compared with 53/145 participants (36.6%) in the insulin detemir group achieved an HbA1c < 7% without severe hypoglycaemia during the last 12 weeks of treatment (RR 1.09, 95% CI 0.84 to 1.41; P = 0.53; Analysis 4.21). We judged the overall risk of bias for this outcome as 'low' (data not shown).

Insulin degludec compared with insulin glargine

For an overview of main results for this comparison, see Summary of findings 5.

Four studies compared insulin degludec with insulin glargine (BEGIN Basal-Bolus Type 1; BEGIN Flex T1; SWITCH 1; Urakami 2017). A total of 1477 participants were randomised, 895 participants to insulin degludec and 582 participants to insulin glargine (see Table 1). One study included children (Urakami 2017). The mean age of the children was 10.5 years. All studies were published in full text in English. However, for all studies, we could retrieve additional information on outcomes from additional sources. All studies applied insulin degludec once daily and insulin glargine once daily. Urakami 2017 applied insulin aspart or insulin lispro before meals. The remaining studies applied insulin aspart before meals. The duration of the intervention ranged from 26 weeks to 52 weeks. SWITCH 1 and Urakami 2017 had a cross-over design; the remaining studies were parallel-group RCTs. Because of carryover effects, we evaluated outcomes before cross-over. In SWITCH 1, each of the two treatment periods consisted of a 16-week titration period and a 16-week maintenance period; only data for health-related quality of life and HbA1c were available before cross-over. Three of the studies were sponsored by Novo Nordisk (BEGIN Basal-Bolus Type 1; BEGIN Flex T1; SWITCH 1); one study did not report the funding source (Urakami 2017).

All-cause mortality

Two studies reported on all-cause mortality (BEGIN Basal-Bolus Type 1; BEGIN Flex T1). For one study, we retrieved this information from additional sources (BEGIN Flex T1). SWITCH 1 reported that four deaths occurred. However, these data could not be included in the meta-analysis because it was not reported if the deaths occurred before or after cross-over.

All studies reporting all-cause mortality were performed in adults. A total of 3/646 participants (0.5%) in the insulin degludec group compared with 1/327 participants (0.3%) in the insulin glargine group died. There was no evidence of a difference in all-cause mortality (Peto OR 1.34, 95% CI 0.15 to 11.93; P = 0.79; 2 studies, 955 participants; very low-certainty evidence; Analysis 5.1). We judged the overall risk of bias for this outcome as 'low'.

Subgroup analysis and sensitivity analysis

Analysis according to only published data compared with only unpublished data did not indicate interaction (P = 0.46; Analysis 5.2). The remaining subgroup and sensitivity analyses could not be performed due to lack of data (Appendix 20).

Health-related quality of life

SWITCH 1 reported health-related quality of life before cross-over in the CSR. BEGIN Basal-Bolus Type 1 reported health-related quality of life in an appendix to the publication. Both studies applied the SF-36 questionnaire. There was no evidence of a difference in health-related quality of life (MD for physical health score -0.04 points, 95% CI -1.21 to 1.13; P = 0.94; 2 studies, 1042 participants; very low-certainty evidence; Analysis 5.3; and MD of mental health score -0.09 points, 95% CI -1.03 to 0.85; P = 0.85; 2 studies, 1042 participants; very low-certainty evidence; Analysis 5.4). The minimal important difference for the physical component score is two to three points and for the mental component score three points. We judged the overall risk of bias for this outcome as 'some concerns'.

Subgroup analysis and sensitivity analysis

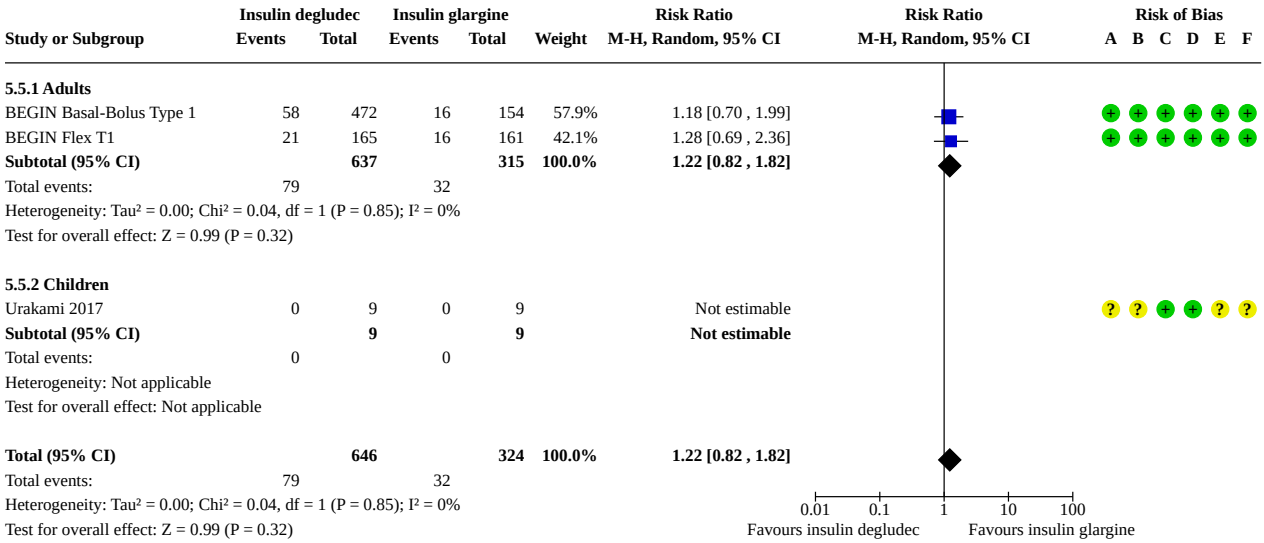
Analysis according to only published data compared with only unpublished data did not indicate subgroup interaction. The remaining subgroup and sensitivity analyses could not be performed due to lack of data (Appendix 20).

Severe hypoglycaemia

We could evaluate severe hypoglycaemia for three studies (BEGIN Basal-Bolus Type 1; BEGIN Flex T1; Urakami 2017). Two studies reported severe hypoglycaemia in the main publication (BEGIN Basal-Bolus Type 1; Urakami 2017) and for one study we retrieved data from an appendix to the publication (BEGIN Flex T1).

A total of 79/646 participants (12.3%) in the insulin degludec group compared with 32/324 participants (9.9%) in the insulin glargine group reported severe hypoglycaemia. There was no evidence of a difference in severe hypoglycaemia (RR 1.22, 95% CI 0.82 to 1.82; P = 0.32; 3 studies, 970 participants; low-certainty evidence; Analysis 5.5; Figure 7). We judged the overall risk of bias for this outcome as 'low'.

Figure 7. Severe hypoglycaemia



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Severe hypoglycaemia
(C) Bias due to missing outcome data: Severe hypoglycaemia
(D) Bias in measurement of the outcome: Severe hypoglycaemia
(E) Bias in selection of the reported result: Severe hypoglycaemia
(F) Overall bias: Severe hypoglycaemia

Subgroup analysis and sensitivity analysis

We did not perform subgroup and sensitivity analyses due to lack of data (Appendix 20).

Hypoglycaemia reported as a serious adverse event

A total of 49/1100 participants (4.5%) in the insulin degludec group compared with 44/784 participants (5.6%) in the insulin glargine group had a SAE due to hypoglycaemia. There was no evidence of a difference in hypoglycaemia reported as a SAE (RR 0.81, 95% CI 0.40 to 1.66; P = 0.57; 4 studies, 1884 participants; Analysis 5.6). We judged the overall risk of bias for this outcome as 'low' (data not shown).

Cardiovascular mortality

We could retrieve data on cardiovascular mortality from two studies through additional sources (BEGIN Flex T1; Urakami 2017). One study reported the cause of death in the main publication (BEGIN Basal-Bolus Type 1). Only BEGIN Basal-Bolus Type 1 reported

any deaths due to cardiovascular disease. In this study, 2/472 participants (0.4%) in the insulin degludec group compared with 1/154 participants (0.6%) in the insulin glargine group died due to cardiovascular disease (Analysis 5.7). We judged the overall risk of bias for this outcome as 'low'.

We did not perform subgroup and sensitivity analyses due to lack of data (Appendix 20).

Non-fatal myocardial infarction

We could retrieve data on non-fatal myocardial infarction for three studies from additional sources (BEGIN Basal-Bolus Type 1; BEGIN Flex T1; Urakami 2017). However, only one study reported any participant experiencing a non-fatal myocardial infarction. In this study, 1/472 participants (0.2%) in the insulin degludec group compared with 0/154 participants in the insulin glargine group experienced a non-fatal myocardial infarction (low-certainty evidence; Analysis 5.8). We judged the overall risk of bias for this outcome as 'low'.

We did not perform subgroup and sensitivity analyses due to lack of data (Appendix 20).

Non-fatal stroke

We could retrieve data on non-fatal stroke for two studies from CSRs (BEGIN Basal-Bolus Type 1; BEGIN Flex T1). For one study, data were provided by the study author (Urakami 2017). BEGIN Flex T1 reported no event (0/165 participants in the insulin degludec group compared with 0/161 participants in the insulin glargine group). Urakami 2017 also reported no event (0/9 participants in both intervention groups). BEGIN Basal-Bolus Type 1 reported that 1/472 participants (0.2%) in the insulin degludec group compared with 0/154 participants in the insulin glargine group experienced cerebral ischaemia (low-certainty evidence; Analysis 5.9). We judged the overall risk of bias for this outcome as 'low'.

We did not perform subgroup and sensitivity analyses due to lack of data (Appendix 20).

End-stage renal disease

For one study, the study author provided information that no participant developed end-stage renal disease (Urakami 2017). None of the other studies reported on end-stage renal disease. We judged the overall risk of bias for this outcome as 'low' (data not shown).

Blindness

For one study, the study author provided information that no participant developed blindness (Urakami 2017). None of the other studies reported on blindness. We judged the overall risk of bias for this outcome as 'low' (data not shown).

Serious adverse events

Three studies reported SAEs (BEGIN Basal-Bolus Type 1; BEGIN Flex T1; Urakami 2017). Two studies reported data in the publications (BEGIN Basal-Bolus Type 1; BEGIN Flex T1). For one study, the investigator reported that no participant experienced a SAE (Urakami 2017).

A total of 56/646 participants (8.7%) in the insulin degludec group compared with 25/324 participants (7.7%) in the insulin glargine group experienced serious adverse events. There was no evidence of a difference in SAEs (RR 0.92, 95% CI 0.58 to 1.46; P = 0.73; 3 studies, 970 participants; low-certainty evidence; Analysis 5.10). We judged the overall risk of bias for this outcome as 'low'.

We did not perform subgroup and sensitivity analyses due to lack of data (Appendix 20).

Diabetic ketoacidosis

Three studies reported diabetic ketoacidosis (BEGIN Basal-Bolus Type 1; BEGIN Flex T1; Urakami 2017). One study reported data in the publication (BEGIN Basal-Bolus Type 1). For two studies, we retrieved data from additional sources (BEGIN Flex T1; Urakami 2017).

A total of 3/646 participants (0.5%) in the insulin degludec group compared with 3/324 participants (0.9%) in the insulin glargine group experienced diabetic ketoacidosis. There was no evidence of a difference in diabetic ketoacidosis (RR 0.57, 95% CI 0.05 to 6.89; P = 0.66; 3 studies, 970 participants; Analysis 5.11). We judged the overall risk of bias for this outcome as 'low'.

Subgroup analysis and sensitivity analysis

Analysis according to only published data compared with only unpublished data did not indicate subgroup interaction.

We could not perform the remaining subgroup and sensitivity analyses due to lack of data (Appendix 20).

Non-serious adverse events

Three studies reported non-serious adverse events (BEGIN Basal-Bolus Type 1; BEGIN Flex T1; Urakami 2017). Two studies reported data in the publications (BEGIN Basal-Bolus Type 1; BEGIN Flex T1). For one study, the investigator reported that no participant experienced a non-serious adverse event (Urakami 2017).

A total of 522/646 participants (80.8%) in the insulin degludec group compared with 244/324 participants (75.3%) in the insulin glargine group experienced a non-serious adverse event. There was no evidence of a difference in non-serious adverse events (RR 1.02, 95% CI 0.95 to 1.10; P = 0.52; 3 studies, 970 participants; Analysis 5.13). We judged the overall risk of bias for this outcome as 'some concerns'.

We did not perform subgroup and sensitivity analyses due to lack of data (Appendix 20).

Nocturnal hypoglycaemia

Three studies reported nocturnal hypoglycaemia (BEGIN Basal-Bolus Type 1; BEGIN Flex T1; Urakami 2017). Two studies reported data for one or more nocturnal hypoglycaemic outcomes in the publications (BEGIN Basal-Bolus Type 1; BEGIN Flex T1). For one study, the investigator reported that no participant experienced nocturnal hypoglycaemia (Urakami 2017).

A total of 23/646 participants (3.6%) in the insulin degludec group compared with 8/324 participants (2.5%) in the insulin glargine group experienced **severe nocturnal hypoglycaemia**. There was no evidence of a difference in severe hypoglycaemia (RR 1.39, 95% CI 0.59 to 3.27; P = 0.46; 3 studies, 970 participants; low-certainty evidence; Analysis 5.19). We judged the overall risk of bias for this outcome as 'low'.

A total of 464/646 participants (71.8%) in the insulin degludec group compared with 235/324 participants (72.5%) in the insulin glargine group experienced nocturnal hypoglycaemia. There was no evidence of a difference in nocturnal hypoglycaemia (RR 0.99, 95% CI 0.91 to 1.07; P = 0.76; 3 studies, 970 participants; Analysis 5.15). We retrieved data on mild nocturnal hypoglycaemia from additional sources. There was no evidence of a difference in mild nocturnal hypoglycaemia (RR 0.98, 95% CI 0.90 to 1.07; P = 0.63; 2 studies, 952 participants; Analysis 5.16). Asymptomatic nocturnal hypoglycaemia was reported in the CSRs of two studies. There was no evidence of a difference in asymptomatic nocturnal hypoglycaemia (RR 0.84, 95% CI 0.71 to 1.00; P = 0.05; 2 studies, 952 participants; Analysis 5.17). There was no evidence of a difference in symptomatic nocturnal hypoglycaemia (RR 1.22, 95% CI 0.72 to 2.07; P = 0.46; 2 studies, 952 participants; Analysis 5.18). We judged the overall risk of bias for all these outcomes except for severe nocturnal hypoglycaemia as 'some concerns' (data not shown).

We did not perform subgroup and sensitivity analyses due to lack of data (Appendix 20).

Mild/moderate hypoglycaemia

Three studies reported on mild/moderate hypoglycaemia (BEGIN Basal-Bolus Type 1; BEGIN Flex T1; Urakami 2017). Two studies reported data in the publications (BEGIN Basal-Bolus Type 1; BEGIN Flex T1). For one study, the investigator reported that no participant experienced mild/moderate hypoglycaemia (Urakami 2017).

A total of 624/646 participants (96.6%) in the insulin degludec group compared with 312/324 participants (96.3%) in the insulin glargine group experienced mild/moderate hypoglycaemia. There was no evidence of a difference in mild/moderate hypoglycaemia (RR 1.02, 95% CI 0.99 to 1.04; P = 0.18; 3 studies, 970 participants; Analysis 5.20). We judged the overall risk of bias for this outcome as 'some concerns'.

We did not perform subgroup and sensitivity analyses due to lack of data (Appendix 20).

Socioeconomic effects

No studies reported the costs of the intervention during the study period. One co-publication analysed the cost-effectiveness based on applying assumptions from two studies to a UK National Health Service perspective (BEGIN Basal-Bolus Type 1; BEGIN Flex T1).

HbA1c

Four studies reported HbA1c levels (BEGIN Basal-Bolus Type 1; BEGIN Flex T1; SWITCH 1; Urakami 2017). Three studies reported data in the publications (BEGIN Flex T1; SWITCH 1; Urakami 2017). BEGIN Basal-Bolus Type 1 only reported HbA1c after the extension period and not after the end of the regular intervention in the publication. However, we could retrieve these data from the CSR.

There was a reduction in HbA1c in favour of insulin glargine (MD 0.1%, 95% CI 0.0 to 0.2; P = 0.05; 1388 participants; 4 studies; Analysis 5.21; low-certainty evidence). We judged the overall risk of bias for this outcome as 'low'.

Subgroup and sensitivity analyses

Three studies reported HbA1c in adults with a MD of 0.1%, 95% CI 0.0 to 0.2; Analysis 5.21. One study reported HbA1c in children with a MD of 0%, 95% CI -0.6 to 0.6; Analysis 5.21. The test for subgroup differences did not indicate interaction (P = 0.71).

Analysing only published data indicated a MD in HbA1c of 0.1%, 95% 0.02 to 0.3; Analysis 5.22. Analysing only unpublished data indicated a MD in HbA1c of 0.0%, 95% CI -0.2 to 0.2; Analysis 5.22. The test for subgroup differences did not indicate interaction (P = 0.26).

Sensitivity analysis excluding the largest study and the longest study indicated a MD in HbA1c of 0.1%, 95% CI 0.02 to 0.3 (BEGIN Basal-Bolus Type 1).

The remaining subgroup analyses could not be performed due to lack of data (Appendix 20).

Combined HbA1c and severe hypoglycaemia

A combined measure of HbA1c and severe hypoglycaemia was available from two studies through the CSRs (BEGIN Basal-Bolus Type 1; BEGIN Flex T1). BEGIN Basal-Bolus Type 1 reported that 174/453 participants (38.4%) in the insulin degludec group compared with 63/149 participants (42.3%) in the insulin glargine group achieved the HbA1c target < 7% without severe hypoglycaemia during the last 12 weeks of treatment. BEGIN Flex T1 reported that 56/153 participants (36.6%) in the insulin degludec group compared with 60/156 participants (38.5%) in the insulin glargine group achieved the HbA1c target < 7% without severe hypoglycaemia during the last 12 weeks of treatment.

There was no evidence of a difference in people achieving HbA1c < 7% without severe hypoglycaemia (RR 0.92, 95% CI 0.78 to 1.10; 2 studies, 911 participants; Analysis 5.23). We judged the overall risk of bias for this outcome as 'low' (data not shown).

Assessment of reporting bias

We did not draw funnel plots due to limited number of studies per outcome included in the analyses.

Ongoing studies

We did not identify ongoing trials of interest for this review.

Studies awaiting assessment

We identified 13 studies with 20 records which we classified as awaiting classification (Agesen 2019; Basal Analog Study; ChiCTR2000032703; EudraCT 2007-004144-74; EudraCT 2009-012317-22; INEOX; IRCT201203079224N1; J-Collection; Mianowska 2007; NCT00564018; Sherif 2014; UMIN000020521; UMIN000021046); for details please see 'Studies awaiting classification'.

Three studies randomising 474 participants compared insulin degludec with insulin glargine (Agesen 2019; ChiCTR2000032703; INEOX). Four studies randomising 253 participants compared insulin detemir with insulin glargine (Basal Analog Study; EudraCT 2007-004144-74; EudraCT 2009-012317-22; J-Collection). Three studies randomising 154 participants compared insulin glargine with NPH insulin (IRCT201203079224N1; Mianowska 2007; Sherif 2014).

Two studies had more than two intervention groups: one study randomising 33 participants had three intervention groups comparing insulin glargine with insulin detemir with NPH insulin

(NCT00564018), one study randomising 100 participants compared insulin degludec with insulin glargine and with continuing existing basal insulin treatment (UMIN000020521).

One study compared insulin degludec with another unspecified long-acting insulin analogue (UMIN000021046). This study randomising 200 participants included people with T1DM and T2DM.

Seven studies were marked as awaiting classification, as they were listed as completed, but no publications were yet available (Agesen 2019; EudraCT 2007-004144-74; EudraCT 2009-012317-22; INEOX; IRCT201203079224N1; UMIN000020521; UMIN000021046).

Two studies were published as abstracts (Basal Analog Study; Sherif 2014). One study had results available in the trials register – however, it was stated in the trials register that the trial was ended prematurely. It was not possible through correspondence with authors to clarify how long the trial continued (EudraCT 2007-004144-74). One study was listed as completed and prematurely ended with no study data (NCT00564018).

One cross-over study had a full-text publication available. No data could be retrieved before cross-over from the publication (Mianowska 2007).

Investigators were contacted, if this was possible, in order to get the status of the studies clarified (See Appendix 19).

DISCUSSION

Summary of main results

This Cochrane Review is the first systematic review investigating the effects of (ultra-)long acting insulin analogues in people with T1DM with substantial amounts of information from CSRs and clinical study synopses. We included 26 studies with 8784 participants: 2428 participants were randomised to NPH insulin, 2889 participants to insulin detemir, 2095 participants to insulin glargine and 1372 participants to insulin degludec. Eight studies contributing 21% of all participants included children.

The amount of evidence on patient-important outcomes was limited from full-text publications. However, we could retrieve substantial data on patient-important outcomes from the CSRs. There was moderate-certainty evidence comparing insulin detemir with NPH insulin for T1DM showing a lower risk of severe hypoglycaemia in favour of insulin detemir. However, the 95% prediction interval indicated inconsistency of this result. Insulin detemir or insulin glargine compared with NPH insulin did not show benefits or harms for severe nocturnal hypoglycaemia. For all other main outcomes, with overall low risk of bias and comparing insulin analogues with each other, there were no clear differences. Data on patient-important outcomes such as health-related quality of life, macrovascular and microvascular diabetic complications were sparse or missing.

Comparing the insulin analogues detemir and glargine with NPH insulin, we are moderately confident about the results for all-cause mortality, severe (nocturnal) hypoglycaemia, SAEs and HbA1c. We are uncertain about the effects on non-fatal myocardial infarction, non-fatal stroke and health-related quality of life, mainly because data were sparse or there were only a few studies which did not last long enough to investigate these outcomes.

There was no evidence of a difference in any outcome between children and adults.

Overall completeness and applicability of evidence

We conducted an extensive search for studies, included publications in all languages, and tried to obtain additional data on all studies. We identified two unpublished studies (NCT00595374; NCT00605137). We managed to retrieve additional unpublished information on all studies, except for three studies which were only available as full-text publications (Bolli 2009; Porcellati 2004; Urakami 2017). Two study authors provided personal information on their studies (Home 2005; Urakami 2017), One unpublished study did not have a CSR but some data could be retrieved from a clinical study synopsis (NCT00595374). Two Japanese studies had CSRs, but we were unable to obtain the complete version of these (Kobayashi 2007; NCT00605137). Two studies had a cross-over design and not all data could be analysed or were reported before cross-over which we needed because of potential carryover effects (SWITCH 1; Urakami 2017). We looked for additional studies and cross-checked our data with the data from other meta-analyses of relevance (Laranjeira 2018; Tricco 2014; Tricco 2018). The information obtained from CSRs was clearly the best to establish an adequate 'Risk of bias assessment' and to maximise the yield of information for our prespecified outcomes (Appendix 22; Appendix 23; Appendix 24; Appendix 25; Appendix 26; Appendix 27; Appendix 28; Appendix 29; Appendix 30; Appendix 31; Appendix 32; Appendix 33; Appendix 34; Appendix 35; Appendix 36; Appendix 37; Appendix 38; Appendix 39; Appendix 40; Appendix 41; Appendix 42). We noticed major differences between reported outcomes in publications and CSRs, e.g. all-cause mortality was documented in 25% of publications compared to 91% in CSRs (Appendix 41). SAEs and non-serious adverse events were documented in 54% of publications compared to 91% in CSRs (Appendix 41). However, the amount of information within the CSRs varied substantially and we probably did not have access to a single full CSR (Appendix 7).

We investigated a broad spectrum of people with T1DM as both children and adults were included. However, we did not include pregnant women with T1DM, as we anticipated these women would have pronounced fluctuating insulin requirements and a specific hypoglycaemia risk profile. All studies were performed in white or Asian people. Data on people of African origin were lacking. None of the studies was performed in low- or middle-income settings.

Quality of the evidence

Depending on the outcome measures, we judged the certainty of the evidence as moderate for all-cause mortality, severe hypoglycaemia, severe nocturnal hypoglycaemia, SAEs and HbA1c. For most comparisons, we judged the certainty of the evidence as low for non-fatal myocardial infarction, non-fatal stroke and health-related quality of life. No information or only few data were available for blindness, end-stage renal disease, combined HbA1c with severe hypoglycaemia and socioeconomic effects.

For all studies, we contacted one or more study authors to obtain supplemental information on baseline data, 'Risk of bias' domains and outcomes (see Appendix 19). However, several investigators advised us to contact the pharmaceutical company of the study, as they did not have access to the full dataset.

All studies but six had a non-inferiority RCT design which is often required for regulatory approval (Bolli 2009; Home 2005; Porcellati 2004; Ratner 2000; Schober 2002; Urakami 2017). The usual primary endpoint was change in HbA1c which does not minimise the reliability of analysing other outcomes such as hypoglycaemia by means of meta-analysis, because with a potential benefit of newer compounds in reducing HbA1c, a benefit of the number of hypoglycaemic episodes could be expected. Adjustments of hypoglycaemic events for HbA1c levels or achievement of certain HbA1c thresholds without hypoglycaemia would provide important information. Unfortunately, only a few of our included studies reported on this combined endpoint, and, if done, no clear differences were recorded.

All studies except one had an open-label design (SWITCH 1). This could have influenced some of the subjective outcome measures, especially health-related quality of life, non-serious adverse events, mild/moderate hypoglycaemia and some measures of nocturnal hypoglycaemia. Another factor influencing findings could have been investigators being more careful when adjusting the newer insulin analogues due to less clinical experience with these compounds. Also, some participants might have been more prone to measure blood glucose as they might have anticipated experiencing more hypoglycaemic episodes with human insulin preparations, thereby even affecting hypoglycaemia confirmed with blood glucose measurements.

Improving and maintaining glycaemic control in T1DM is a key objective. However, hypoglycaemia is a serious problem affecting health-related quality of life and treatment satisfaction of people with diabetes, making it difficult to achieve near-normal glucose levels in T1DM. Therefore, for any proclaimed benefit of an intervention on hypoglycaemia, it is vital to evaluate the risk of bias in order to establish reliable results. 'Risk of bias' assessment depends considerably on the definition of hypoglycaemia. It appears low if severe hypoglycaemia is also reported as a serious adverse event (SAE) because there is a standard definition of SAEs, or if the combined endpoint of HbA1c levels with severe hypoglycaemia is reported. Unfortunately, no data were available for the combined endpoint HbA1c with severe hypoglycaemia for the comparisons insulin detemir versus NPH insulin and insulin glargine versus NPH insulin. Of note, only about one third of participants being treated with insulin glargine, insulin detemir or insulin degludec achieved an HbA1c < 7% without severe hypoglycaemia. Other definitions of severe hypoglycaemia like hypoglycaemia-induced coma or convulsions, necessity for intubation or intensive-care unit stay also reflect hard clinical endpoints. However, the included studies most often defined severe hypoglycaemia as a hypoglycaemic event which needed "third party assistance". This is prone to bias because third party assistance might encompass a broad range of interventions, e.g. giving food or a drink by a relative or friend, subcutaneous glucagon injection or intravenous glucose administration. Only Thalange 2013 made an effort to define third party assistance in a way that minimised risk of bias (the child had to be semiconscious or unconscious or in coma with or without convulsions and may have required parenteral treatment with glucagon or intravenous glucose). A Cochrane Review associated to this systematic review will establish an in-depth analysis of the definitions and reporting of hypoglycaemia in trials of long-acting insulin analogues in people with type 1 diabetes mellitus (Ørskov Ipsen 2020).

An overview of the reported definitions of hypoglycaemic episodes in our included studies found no evidence of differences between the various interventions on these outcomes with the exception of insulin detemir compared with NPH insulin, demonstrating a benefit for severe hypoglycaemia, any/mild/symptomatic nocturnal hypoglycaemia and mild/moderate hypoglycaemia (Appendix 42). With the exception of severe hypoglycaemia, we judged the risk of bias as 'some concerns' for measurement of these outcomes. There was no benefit or risk of insulin detemir for hypoglycaemia reported as a SAE or severe nocturnal hypoglycaemia event (Appendix 42).

Long-term complications of diabetes were sparsely reported. Long-term complications of diabetes develop over years, and therefore the duration of the included studies might have been too short to identify if an intervention had beneficial or harmful effects. Data on all-cause mortality were most often retrieved from CSRs and few deaths were observed in the studies. However, to our knowledge, no data from long-term observational studies indicate that the type of intermediate or (ultra-)long-acting insulin influences the risk of death or macrovascular and microvascular complications of diabetes. However, long-term follow-up from interventional studies has shown that good glycaemic control in people with T1DM is an important factor for preventing complications (DCCT/EDIC 2016).

No studies reported the direct costs of insulin treatment during the study period. Several studies had co-publications with economic analyses in different country settings based on assumptions derived from the clinical study (Bartley 2008; BEGIN Basal-Bolus Type 1; BEGIN Flex T1; BEGIN Young; Pieber 2007). However, these assumptions do not seem to be supported by our meta-analyses of the clinical trial data. Furthermore, other studies have shown that the direct costs of the long-acting insulin analogues often are substantially higher than the costs of NPH insulin (Ewen 2019).

Only one study had not received free drugs or financial funding from the pharmaceutical industry (Porcellati 2004). It is known that studies receiving funding or provision of free drugs or devices from a pharmaceutical company lead to more favourable results and conclusions compared to studies sponsored by other sources (Lundh 2017).

Potential biases in the review process

We were unable to draw funnel plots to assess small-study bias due to lack of data. We tried to explore inconsistency of results and the reasons for it through subgroup and sensitivity analyses. The only factor, comparing insulin detemir with NPH insulin, that indicated an influence on the effect estimate for the sensitivity analysis of one outcome (severe hypoglycaemia) was publication status. This has to be interpreted with caution because the subgroup of studies with unpublished data consisted of two studies only.

We identified 13 studies as 'awaiting classification'. Data from these studies would have added information on an additional 1194 participants. Most of the studies were listed as completed in trials registers, but data, publications or both were not available. For some of the studies, these data might not yet have been analysed, but other studies were completed years ago and are still not published (Basal Analog Study; EudraCT 2007-004144-74; J-Collection; NCT00564018; UMIN000021046). For

most studies awaiting classification, we contacted the investigators for clarification.

We were dealing with a heterogeneous group of studies. Our meta-analyses, when performed, were limited by the inability to use individual participant data to assess whether distinct clinical characteristics may have influenced the effect estimates of the interventions. Many of the included studies were designed and powered to detect changes in HbA1c but, for all studies, we were able to extract most of our predefined outcomes.

Several studies were published in more than one publication which, for some studies, made it difficult to separate the primary publication from companion papers (for details, see Included studies).

Two review authors carried out data extraction. However, the review authors extracting the data were not blinded as to from which study they were extracting data.

We only included studies with a duration of 24 weeks or more to get some information on patient-relevant outcomes; by not including studies with a shorter duration, we might have underestimated the short-term risks of the interventions.

A potential selection bias exists as more healthy and motivated people may participate in a clinical study. However, a Cochrane Review observed that clinical outcomes in people participating in RCTs are not substantially different to outcomes in comparable individuals outside the RCT context (Vist 2008).

We requested CSRs and other information from EMA. EMA replied that it "is currently operating within the fourth phase of its business continuity plan to ensure operational continuity during its relocation to Amsterdam. Whilst every effort is being made to process all requests as soon as possible, you should be aware that due to these exceptional circumstances from October 2019 requests cannot be processed immediately and will be dealt in a chronological order from the time they were received". At the moment of publication of this Cochrane Review, the first pieces of information from EMA are arriving. Because we do not know when the last information package of EMA will be available, we plan to make full use of EMA data in a future update of our review. In case of very important EMA data, we will publish an interim updated version of our review as soon as possible.

Agreements and disagreements with other studies or reviews

Other reviews of insulin analogues in people with T1DM have been published. The most recent systematic review was performed for refinement of the WHO Essential Medicine List (EML), which was an update of a systematic review published in 2014 (Tricco 2018). The review for WHO EML included adults with T1DM, but also included pregnant women with T1DM. We did not chose to include the latter cohort as pregnancy causes considerable changes in insulin sensitivity. Tricco 2018 included studies irrespective of study duration. We required a minimum duration of 24 weeks to get more reliable information on patient-relevant outcome measures. Short-term studies usually evaluate surrogate markers and often have shorter intervention periods than the titration periods of the longer-term studies. Tricco 2018 analysed insulin glargine and insulin detemir together; we chose to perform separate analyses. Tricco 2018 included 62 RCTs according to the abstract. However, they missed identifying co-publications of primary publications. Therefore, several studies were included more than once and handled as independent studies. Another difference to our review is the lack of identification of unpublished data, especially CSRs which provided substantial information to all our analyses including 'Risk of bias' assessment. Tricco 2018 reported a statistically significant decrease in HbA1c with insulin analogues compared with NPH insulin and a statistically significant lower risk of severe hypoglycaemia, which we could not verify in our analyses. One umbrella review of reviews compared long-acting insulin analogues with NPH insulin (Laranjeira 2018). Eleven systematic reviews were identified and a total of 25 RCTs were included irrespective of age of participants or duration of the intervention. The conclusion of this overview, based on data for all systematic reviews, was that long-acting insulin analogues were more effective than NPH insulin concerning lowering HbA1c. No statistically significant differences were found for severe hypoglycaemia (Laranjeira 2018).

AUTHORS' CONCLUSIONS

Implications for practice

We analysed randomised controlled trials (RCTs) with a duration of 24 weeks or more comparing (ultra-)long-acting insulin with neutral protamine Hagedorn (NPH) insulin or another (ultra-)long-acting insulin in people with type 1 diabetes mellitus. Nine RCTs compared NPH insulin with insulin detemir or insulin glargine, respectively. Two RCTs each compared insulin detemir with insulin glargine or insulin degludec, respectively. Four RCTs compared insulin degludec with insulin glargine. No studies compared insulin degludec with NPH insulin. There was moderate-certainty evidence that insulin detemir reduces severe hypoglycaemia compared with NPH insulin. However, the 95% prediction interval indicated inconsistency which means that if we performed an additional study comparing insulin detemir with NPH insulin there may not be a clear difference in the risk of severe hypoglycaemia for this comparison.

There were no clear differences for severe nocturnal hypoglycaemia comparing insulin detemir or insulin glargine with NPH insulin. For all other main outcomes, with overall low risk of bias and comparing (ultra-)long-acting insulin analogues with each other, there were also no clear differences.

Definitions of hypoglycaemia varied substantially among the studies. Health-related quality of life was inconsistently reported and did not show clear benefits or harms for any insulin analogue or NPH insulin. Data on macrovascular and microvascular diabetic complications were sparse or missing.

It remains unclear whether the risk of hypoglycaemia, especially severe and severe nocturnal hypoglycaemia, is associated with clinically relevant differences regarding the type of (ultra-)long-acting or intermediate-acting insulin.

Implications for research

All studies investigating insulin use in diabetes should report hypoglycaemic episodes in a standard way. 'Risk of bias' assessment depends considerably on the definition of hypoglycaemia. It appears low if severe hypoglycaemia is also reported as a serious adverse event (SAE) because there is a

standard definition of SAEs or if the combined endpoint of HbA1c levels with associated hypoglycaemia is reported. Other definitions of severe hypoglycaemia like hypoglycaemia-induced coma or convulsions, necessity for intubation or intensive-care unit stay also reflect hard clinical endpoints. However, the included studies most often defined severe hypoglycaemia as a hypoglycaemic event which needed "third party assistance". This is prone to bias because third party assistance encompasses a broad range of interventions, e.g. giving food or a drink by a relative or friend, subcutaneous glucagon injection or intravenous glucose administration. Therefore, any proclaimed benefit of (ultra-)long-acting insulin analogues compared with NPH insulin especially for (nocturnal) hypoglycaemia has to demonstrate clinically relevant differences for these outcomes which should be measured in an identical manner to achieve fair comparisons within and between studies.

There is a gap in research on patient-important outcomes such as health-related quality of life, macrovascular and microvascular diabetic complications which were rarely reported or missing. Furthermore, studies including people from a wide range of ethnicities and studies in low-and middle-income countries are needed.

The availability of clinical study reports (CSRs) provided a substantially improved body of evidence, for both data extraction and 'Risk of bias' analysis. Pharmaceutical companies, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) should facilitate full access to CSRs to better enable systematic reviewers to establish high-quality systematic reviews.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Bartley 2008

Study characteristics	
Methods	**Design**: parallel-group RCT; non-inferiority design; randomisation ratio: 2:1
Participants	**Inclusion criteria**: ≥ 18 years; with an HbA1c ≤ 11.0% and BMI ≤ 35.0 kg/m^2 with a history of T1DM ≥ 1 year treated on a basal–bolus insulin regimen for ≥ 3 months and able and willing to SMPG **Exclusion criteria**: proliferative retinopathy or maculopathy, other significant medical disorders, recurrent major hypoglycaemia, allergy to insulin and pregnant or breast feeding **Diagnostic criteria**: — **Number of study centres**: 33
Interventions	**Intervention(s)**: detemir **Comparator(s)**: NPH **Duration of intervention**: 24 months **Duration of follow-up**: 24 months (plus 4 to 8 days) **Run-in period**: none
Outcomes	**Reported outcome(s) in full text of publication**: glycaemic control, hypoglycaemia, safety
Study registration	**Trial identifier**: NCT00184665; NN304-1595 **Study terminated early**: no
Publication details	**Language of publication**: English **Funding**: commercial funding (Novo Nordisk) **Publication status**: peer-reviewed journal and conference abstract
Stated aim of study	**Quote**: "This 24-month, multi-national, open-label, parallel group trial investigated the long-term efficacy and safety of insulin detemir and Neutral Protamine Hagedorn insulin in combination with meal-time insulin aspart in patients with Type 1 diabetes using a treat-to-target concept"
Notes	**Quote**: "Six months into the trial, blinded review of the pre-breakfast and pre-evening meal PG concentrations revealed that PG targets were not achieved in a substantial proportion of patients and a protocol amendment was implemented to ensure more frequent contact between patients and investigators during the last year of the trial".CSR identified: from CSR data from hypoglycaemia combined with HbA1c, adverse events, serious adverse events, ketoacidosis and myocardial infarction

BEGIN Basal-Bolus Type 1

Study characteristics	
Methods	**Design**: parallel-group RCT; non-inferiority design; randomisation ratio: 3:1
Participants	**Inclusion criteria**: T1DM for at least 12 months; current treatment with any basal bolus insulin for at least 12 months; HbA1c below or equal to 10.0%, BMI below or equal to 35.0 kg/m^2; for the extension study only: completion of the 52-week treatment period in study **Exclusion criteria**: use within the last 3 months of any other antidiabetic glucose-lowering drug than insulin; anticipated change in concomitant medication known to interfere significantly with glucose metabolism, such as systemic corticosteroids, beta-blockers, monoamine oxidase (MAO) inhibitors; cardiovascular disease, within the last 6 months defined as: stroke, decompensated heart failure NYHA Class III or IV, myocardial infarction, unstable angina pectoris or coronary arterial bypass graft or angioplasty; uncontrolled treated/untreated severe hypertension (systolic BP ≥ 180 mmHg and/or diastolic BP ≥ 100 mmHg); impaired liver function, defined as ALAT ≥ 2.5 times upper limit of normal (one re-test analysed at the central laboratory within a week from receipt of the result was permitted with the result of the last sample being conclusive); impaired renal function defined as serum creatinine ≥ 180 µmol/L (≥ 2.0 mg/dL); recurrent severe hypoglycaemia (more than 1 severe hypoglycaemic event during the last 12 months) or hypoglycaemic unawareness or hospitalisation for diabetic ketoacidosis during the previous 6 months; proliferative retinopathy or maculopathy requiring treatment as determined by the investigator; pregnancy, breastfeeding, the intention of becoming pregnant or not using adequate contraceptive measures according to local requirements (for Germany: implants, injectables, combined oral contraceptives, hormonal intrauterine device, sexual abstinence or vasectomised partner) (for United Kingdom: adequate contraceptive measures were defined as established use of oral, injected or implanted hormonal methods of contraception, sterilisation, intrauterine device or intrauterine system, or consistent use of barrier methods); cancer and medical history of cancer (except basal cell skin cancer or squamous cell skin cancer); any clinically significant disease or disorder, except for conditions associated with T1DM, which in the investigator's opinion could interfere with the results of the study; mental incapacity, psychiatric disorder, unwillingness or language barriers precluding adequate understanding or co-operation, including not able to read or write; previous participation in this study; receipt of any investigational drug within 1 month prior to screening visit; donation of blood or participation in other trials within 1 month prior to screening visit; known or suspected abuse of alcohol, narcotics or illicit drugs **Diagnostic criteria**: — **Number of study centres**: 79
Interventions	**Intervention(s)**: degludec **Comparator(s)**: glargine **Duration of intervention**: 52 weeks **Duration of follow-up**: 52 weeks (104 weeks) **Run-in period**: none
Outcomes	**Reported outcome(s) in full text of publication**: mortality, cardiovascular outcomes, safety, glycaemic measures
Study registration	**Trial identifier**: main study: NCT00982228, obsolete identifier: NCT0119804, NN1250-3583, EudraCT number 2008-005774-13; WHO identifier U1111-1116-1578; extension study: NN1250-3644, EudraCT Number 2009-015755-24; NCT01198041; WHO identifier U1111-1111-8789 **Study terminated early**: no
Publication details	**Language of publication**: English **Funding**: commercial funding (Novo Nordisk)

BEGIN Basal-Bolus Type 1 *(Continued)*

	Publication status: peer-reviewed journal and conference abstract
Stated aim of study	**Quote**: "We therefore compared the efficacy and safety of insulin degludec and insulin glargine, both administered once daily with mealtime insulin aspart, in basal-bolus therapy for type 1 diabetes".
Notes	BEGIN Basal–Bolus Type 1 refers to the first 52 weeks, thereafter there was the extension study BEGIN Conference abstract did not reveal any additional data At selected study sites (25), participants underwent assessment of their 24-hour interstitial glucose profile with a CGM device for 3 consecutive days at baseline (72 hours before visit 2), and at visits 28 and 41 (weeks 26 and 52, respectively) CSR and trial synopsis available. Provided outcome data on severe hypoglycaemia/HbA1c combined Study also reported in FDA 2015 (FDA 2015) - 2 deaths in each intervention arm - but unknown whether this was before or after extension period. No additional data from EMA 2012 (EMA 2012)

BEGIN Flex T1

Study characteristics	
Methods	**Design**: parallel-group RCT; non-inferiority design; randomisation ratio: 1:1
Participants	**Inclusion criteria**: informed consent; males or females 18 years or more; T1DM for ≥ 12 months, the last 3 months with injection-based therapies; current treatment with any basal insulin using one or two daily injections and no fewer than three injections with bolus insulin as mealtime bolus insulin therapy; HbA1c ≤ 10.0% by central laboratory analysis; BMI ≤ 35.0 kg/m^2; ability to self-manage insulin therapy as assessed by confirmation (verbal confirmation at screening visit) of a changed bolus insulin dose the preceding 2 months prior to screening; ability and willingness to adhere to the protocol, including performance of SMPG readings and self-adjustment of insulin doses according to protocol **Exclusion criteria**: use within the last 3 months of any glucose-lowering drug other than insulin; initiation or significant change of any systemic treatment which, in the investigator's opinion, could interfere with glucose metabolism, such as systemic corticosteroids, beta-blockers or monoamine oxidase inhibitors (inhaled corticosteroids were allowed); cardiovascular disease, within the last 6 months (defined as: stroke; decompensated heart failure NYHA class III or IV; myocardial infarction; unstable angina pectoris; or coronary arterial bypass graft or angioplasty); uncontrolled treated/untreated severe hypertension (systolic BP ≥ 180 mmHg and/or diastolic BP ≥ 100 mmHg); impaired liver function, defined as ALAT ≥ 2.5 times upper limit of normal; impaired renal function defined as serum-creatinine ≥ 180 µmol/L or 2.0 mg/dL; recurrent severe hypoglycaemia (more than 1 severe hypoglycaemic event during the last 12 months) or hypoglycaemic unawareness as judged by the investigator or hospitalisations for diabetic ketoacidosis during the previous 6 months; proliferative retinopathy or maculopathy requiring treatment, according to the investigator; pregnancy, breastfeeding, the intention of becoming pregnant or not using adequate contraceptive measures according to local requirements; cancer and medical history of cancer (except basal cell skin cancer or squamous cell skin cancer); any clinically significant disease or disorder, except for conditions associated with T1DM, which in the investigator's opinion could interfere with the results of the study; mental incapacity, psychiatric disorder, unwillingness or language barriers precluding adequate understanding or co-operation, including participants not able to read or write; previous participation in this study; known or suspected allergy to any of the study products or related products; receipt of any investigational drug within 1 month; donation of blood or participation in other trials within 1 month prior; known or suspected abuse of alcohol, narcotics, or illicit drugs **Diagnostic criteria**: clinically diagnosed (from CSR) **Number of study centres**: 71
Interventions	**Intervention(s)**: degludec

BEGIN Flex T1 *(Continued)*

	Comparator(s): glargine **Duration of intervention**: 26 weeks (52 weeks) **Duration of follow-up**: 26 weeks (26 weeks) **Run-in period**: none
Outcomes	**Reported outcome(s) in full text of publication**: adverse events, hypoglycaemia, glycaemic variables
Study registration	**Trial identifier**: NCT01079234, NN1250-3770, WHO U1111-1112-8813, EudraCT Number 2009-012923-27 **Study terminated early**: no
Publication details	**Language of publication**: English **Funding**: commercial funding (Novo Nordisk) **Publication status**: peer-reviewed journal
Stated aim of study	**Quote**: "The aim of this trial is to investigate the efficacy and safety of NN1250 (insulin degludec) in participants with type 1 diabetes".
Notes	The participants were randomised to three intervention arms - insulin degludec forced-Flex, insulin degludec and insulin glargine. We have only included data from the insulin degludec and insulin glargine groups as they had identical titration regimens. The study consisted of a 26-week main period and 26-week extension period. Only data from the main period were included, as the two degludec groups were combined into one group in the extension period. Abstract revealed no additional data CSR and synopsis available. Data provided for all-cause mortality, cardiovascular mortality, myocardial infarction, stroke, ketoacidosis, severe hypo/HbA1c combined Study also reported in FDA 2015 (FDA 2015) - no additional data. No additional data from EMA 2012 (EMA 2012)

BEGIN Young

Study characteristics	
Methods	**Design**: parallel-group RCT; non-inferiority design; randomisation ratio: 1:1
Participants	**Inclusion criteria**: informed consent, 1–17 years of age, T1DM, ongoing daily treatment with insulin (any regimen) for at least 3 months prior to screening. No oral anti-diabetic drugs, HbA1c maximum 11% **Exclusion criteria**: known or suspected hypersensitivity to study product(s) or related products, previous participation in this study, pregnancy, breastfeeding or intend to become pregnant, menarche and are not using adequate contraceptive, known hypoglycaemic unawareness or recurrent severe hypoglycaemic events, more than 1 diabetic ketoacidosis requiring hospitalisation within the last 3 months prior to screening, significant concomitant disease (except for conditions associated with T1DM) which in the investigator's opinion could interfere with the study, receipt of any investigational drug within 1 month prior to screening **Diagnostic criteria**: based on clinical judgement and supported by laboratory analysis as per local guidelines **Number of study centres**: 72

BEGIN Young *(Continued)*

Interventions	**Intervention(s)**: degludec **Comparator(s)**: detemir **Duration of intervention**: 26 weeks (plus 26 weeks of extension) **Duration of follow-up**: 26 weeks (plus 26 weeks of extension) **Run-in period**: —
Outcomes	**Reported outcome(s) in full text of publication**: mortality, adverse events, hypoglycaemia, HbA1c
Study registration	**Trial identifier**: NCT01513473, NN1250-3561, EudraCT 2011-003148-39; EMA (ODCO) P/44/2010; WHO U1111-1122-4758; JapicCTI-121824 **Study terminated early**: no
Publication details	**Language of publication**: English **Funding**: commercial funding (Novo Nordisk) **Publication status**: peer-reviewed journal and abstract
Stated aim of study	**Quote**: "The objective of this trial was to investigate the efficacy and safety of IDeg vs. IDet, both in combination with bolus insulin aspart (IAsp), in children and adolescents with T1D"
Notes	All participants who completed 26 weeks of treatment (main period) were encouraged to continue in an extension of the study under similar conditions, for an additional 6 months (extension period). The South African sites did not participate in the 26 weeks of extension. Socioeconomic effects were reported in the abstract (Thalange 2017). Selected countries/sites participants underwent assessment of their 24-hour interstitial glucose levels with a continuous glucose monitoring (CGM) device. CSR available - in there data on diabetic ketoacidosis were available Study also reported in FDA 2015 and EMA 2014 and EMA 2015 reports - no additional data (FDA 2015; EMA 2014; EMA 2015). In FDA, medical review data for adverse events (including ketoacidosis) in table 36 (page 77)

Bolli 2009

Study characteristics	
Methods	**Design**: parallel-group RCT; non-inferiority design; randomisation ratio: 1:1
Participants	**Inclusion criteria**: 18 to 60 years with T1DM (> 3 years duration), with fasting plasma C-peptide < 0.1 nmol/L and HbA1c 7-9%, and who were on intensive insulin therapy (NPH twice or more daily and lispro or regular human insulin at mealtimes), no micro- or macro-angiopathic complications and BMI 18-26 kg/m^2 **Exclusion criteria**: — **Diagnostic criteria**: fasting plasma C-peptide < 0.1 nmol/L (not directly described, but is an inclusion criterion) **Number of study centres**: 21
Interventions	**Intervention(s)**: glargine **Comparator(s)**: NPH

Bolli 2009 *(Continued)*

	Duration of intervention: 28 weeks (4-week run-in phase, 24-week treatment period) **Duration of follow-up**: 30 weeks (4-week run-in phase, 24-week treatment period and 2-week safety assessment) **Run-in period**: 4 weeks
Outcomes	**Reported outcome(s) in full text of publication**: glycaemic control, safety, quality of life
Study registration	**Trial identifier**: — **Study terminated early**: no
Publication details	**Language of publication**: English **Funding**: commercial funding (Sanofi-Aventis) **Publication status**: peer-reviewed journal
Stated aim of study	**Quote**: "To compare switching from NPH insulin (NPH) to insulin glargine (glargine) with continuing NPH for changes in fasting blood glucose (FBG) in patients with Type 1 diabetes on basal bolus therapy with insulin lispro as bolus insulin."
Notes	

Chase 2008

Study characteristics	
Methods	**Design**: parallel-group RCT; non-inferiority design; randomisation ratio: 1:1
Participants	**Inclusion criteria**: ≥ 9 to ≤ 17 years; Tanner stage ≥ 2; HbA1c ≥ 7.0% to ≤ 9.5%) who had a diagnosis of T1DM for at least 1 year and were receiving any daily insulin regimen consisting of 2 or more injections or a continuous subcutaneous insulin infusion, ability and willingness to count carbohydrates and perform SMBG testing at least 4 times per day **Exclusion criteria**: clinically relevant cardiovascular, hepatic, renal, neurologic, endocrine, or other major systemic diseases; psychiatric problems; laboratory test abnormalities; a history of 2 or more episodes of severe hypoglycaemia within the past 12 months or diabetic ketoacidosis in the past 3 months; or hypersensitivity to the investigational product or treatment; lipohypertrophy, a history of drug or alcohol abuse, current use of systemic corticosteroids or large doses of inhaled corticosteroids, and pregnancy **Diagnostic criteria**: fasting C-peptide concentration of ≤ 0.5 nmol/L **Number of study centres**: 40
Interventions	**Intervention(s)**: glargine **Comparator(s)**: NPH/Lente **Duration of intervention**: 24 weeks **Duration of follow-up**: 25 weeks (the treatment period was followed by a 1-week follow-up) **Run-in period**: 4 weeks (during the educational run-in period, patients received instruction from a certified diabetes educator on carbohydrate counting and basal/bolus insulin regimens)
Outcomes	**Reported outcome(s) in full text of publication**: serious adverse events, hypoglycaemia, HbA1c

Chase 2008 *(Continued)*

Study registration	**Trial identifier**: HOE901/4030; NCT00046501 **Study terminated early**: no
Publication details	**Language of publication**: English **Funding**: commercial funding (Sanofi) **Publication status**: peer-reviewed journal
Stated aim of study	**Quote**: "To compare long-acting insulin glargine (Lantus) with intermediate-acting insulin (neutral protamine Hagedorn [NPH]/Lente) when used as the basal component of a multiple daily injection (MDI) regimen with prandial insulin lispro (Humalog) in adolescents with type 1 diabetes mellitus (T1DM)"
Notes	Only three participants in the NPH/Lente group received Lente Subset of participants had CGM Clinical study summary available from Sanofis web page. This stated that The Diabetes Quality of Life for Youth questionnaire was applied. In the study summary, it was mentioned that more reported treatment emergent adverse events were observed in the glargine group compared with the NPH group From CSR, data for mortality and adverse events were retrieved

Davies 2014

Study characteristics	
Methods	**Design**: parallel-group RCT; non-inferiority design; randomisation ratio: 1:1
Participants	**Inclusion criteria**: adults (≥ 18 years or ≥ 20 years for Japan) diagnosed with T1DM for ≥ 12 months, currently treated with any basal–bolus insulin regimen for ≥ 12 months prior to screening and with HbA1c ≤ 10.0% (85.8 mmol/mol) and BMI ≤ 35.0 kg/m^2, For Japan only: minimum age was 20 years For the extension study only: completed the six-month treatment period in study NN1250-3585 (NCT01074268) **Exclusion criteria**: clinically significant concomitant diseases, including impaired renal and hepatic function; recurrent severe hypoglycaemia or hypoglycaemic unawareness or hospitalisation for diabetic ketoacidosis during the previous 6 months; and cardiovascular disease within the previous 6 months prior to the study, use of any other antidiabetic drug than insulin within the last 3 months, uncontrolled treated/untreated severe hypertension, pregnancy, breast-feeding, the intention of becoming pregnant or not using adequate contraceptive measures, cancer and medical history of cancer **Diagnostic criteria**: — **Number of study centres**: 55 sites (in 7 countries)
Interventions	**Intervention(s)**: degludec **Comparator(s)**: detemir **Duration of intervention**: 26 weeks **Duration of follow-up**: 26 weeks (52 weeks) **Run-in period**: none **Number of study centres**: 55 sites (in 7 countries)

Davies 2014 *(Continued)*

Outcomes	**Reported outcome(s) in full text of publication**: glycaemic control, hypoglycaemia, safety
Study registration	**Trial identifier**: NCT01074268; NN1250-3585 (26 weeks); NCT01190956; obsolete identifiers: NCT01190956; EudraCT number: 2009-011672-29 and 2009-015721-36; WHO identifier: U1111-1111-7249 and U1111-1114-9479; JAPIC Identifier: JapicCTI-10106 and JapicCTI-22-0677; extension study: NN1250-3725; main study: CTRI/2010/091/000145; extension study: CTRI/2010/091/001097 **Study terminated early**: no
Publication details	**Language of publication**: English **Funding**: commercial funding (Novo Nordisk) **Publication status**: peer-reviewed journal
Stated aim of study	**Quote**: "The primary outcome was non-inferiority of IDeg to IDet in glycated haemoglobin (HbA1c) reduction after 26 weeks"
Notes	Participants who completed the core study were invited to participate in a 26-week extension study Data were entered after 26 weeks of intervention DiabMedSat (Diabetes Medication Satisfaction), DPM (Diabetes Productivity Measure), TRIM-D (Treatment Related Impact Measure for Diabetes) and SF-36 v2 were reported by the investigators and CSR CSR and synopsis available - added information in combined HbA1c and severe hypoglycaemia Study also reported in FDA 2015 document (FDA 2015)- no additional data. No additional data from EMA 2012 (EMA 2012)

Fulcher 2005

Study characteristics	
Methods	**Design**: parallel-group RCT; non-inferiority design; randomisation ratio: 1:1
Participants	**Inclusion criteria**: T1DM, 18-80 years, treated with insulin for 1 year or more, HbA1c 8% or more, Additional from CSR: BMI < 35 kg/m^2, Ability and willingness to perform frequent SMBG using a blood glucose meter and to perform continuous blood glucose measurements on numerous occasions **Exclusion criteria**: nightshift workers, patients with known sensitivity to the study drug or related drugs, and patients with impaired hepatic function or any other clinically relevant physiological or psychological medical conditions were excluded, Additional from CSR: treatment with any blood glucose altering drugs other than insulin in the last 4 weeks before study entry e.g. corticosteroids; pregnancy, breastfeeding; treatment with any investigational drug in the last 2 months before study entry **Diagnostic criteria**: post-prandial C-peptide level ≤ 0.5 nmol/L (≤ 1.5 ng/mL) in the presence of a blood glucose level ≥ 5.5 mmol/L **Number of study centres**: 9
Interventions	**Intervention(s)**: glargine **Comparator(s)**: NPH **Duration of intervention**: 30 weeks (6-week forced titration phase + 24-week phase) **Duration of follow-up**: 30 weeks

Fulcher 2005 *(Continued)*

	Run-in period: — (but had a one- to two-week screening phase before the treatment phase)
Outcomes	**Reported outcome(s) in full text of publication**: glycaemic control, hypoglycaemia, weight, lipid status, safety
Study registration	**Trial identifier**: HOE901/4010 **Study terminated early**: no
Publication details	**Language of publication**: English **Funding**: commercial funding (Aventis) **Publication status**: peer-reviewed journal and conference abstract
Stated aim of study	**Quote**: "To compare glycaemic control and symptomatic hypoglycaemia rates with glargine versus neutral protamine Hagedorn (NPH) in poorly controlled type 1 diabetes patients."
Notes	Conference abstract added no additional information CSR was provided by Sanofi. CSR provided protocol, diagnostic criteria for T1DM, additional outcome data (e.g. mortality, ketoacidosis, hypoglycaemia) and information on bias.

Heller 2009

Study characteristics	
Methods	**Design**: parallel-group RCT; non-inferiority design; randomisation ratio: 1:1
Participants	**Inclusion criteria**: ≥ 18 years who had T1DM for at least 12 months, had been taking a basal–bolus insulin regimen for at least 3 months, and had a HbA1c value ≤ 11.0% **Exclusion criteria**: proliferative retinopathy or maculopathy requiring acute treatment within 6 months before the study; any recurrent major hypoglycaemia; an anticipated change in any medication known to interfere with glucose metabolism; impaired hepatic or renal function; cardiac problems or uncontrolled hypertension believed to affect study participation **Diagnostic criteria**: — **Number of study centres**: 38 (number from synopsis/CSR)
Interventions	**Intervention(s)**: detemir **Comparator(s)**: glargine **Duration of intervention**: 52 weeks **Duration of follow-up**: 52 weeks **Run-in period**: — (but there might have been one based on the following sentence: "All patients were asked to record a 10-point self-monitored PG (SMPG) profile on a typical day during the weeks before the randomization visit")
Outcomes	**Reported outcome(s) in full text of publication**: glycaemic measures, safety, hypoglycaemia
Study registration	**Trial identifier**: NN304-1430; EUDRACT 2004-000086-35; NCT00095082 **Study terminated early**: no

Heller 2009 *(Continued)*

Publication details	**Language of publication**: English **Funding**: commercial funding (Novo Nordisk) **Publication status**: peer-reviewed journal
Stated aim of study	**Quote**: "The primary study objective was to determine whether insulin detemir (detemir) was noninferior to insulin glargine (glargine) as the basal insulin in a basal–bolus regimen, with insulin aspart as the mealtime insulin, in terms of glycemic control at the end of 52 weeks in patients with type 1 diabetes mellitus (T1DM)."
Notes	Each participant attended 13 study visits and received 16 scheduled telephone calls from the study site From the clinical study synopsis: "The risk of having a nocturnal hypoglycaemic episode during the treatment period was similar in the two groups with a relative risk of 1.12 (P = 0.375)." and "The overall risk of having a hypoglycaemic episode during the treatment period was similar between the insulin detemir and the insulin glargine groups with a relative risk (insulin detemir/insulin glargine) of 0.94 (P = 0.571)." Data for mortality extracted from synopsis. From CSR, data on mortality, severe hypoglycaemia, nocturnal hypoglycaemia, mild hypoglycaemia, acute myocardial infarction, stroke and diabetic ketoacidosis could be retrieved

Home 2005

Study characteristics	
Methods	**Design**: parallel-group RCT; non-inferiority design; randomisation ratio: 1:1
Participants	**Inclusion criteria**: T1DM and post-prandial serum C-peptide levels of < 0.50 nmol/L or < 1.50 µg/L when the capillary blood glucose level was ≥ 5.5 mmol/L (≥ 100 mg/dL) at the first visit. All had been treated with insulin for at least 1 year, aged 17–77 years **Exclusion criteria**: from FDA document (FDA 2000): pregnancy, surgical treatment for diabetic retinopathy, other glucose-lowering drugs within 4 weeks, impaired renal function, abnormal liver tests **Diagnostic criteria**: C-peptide < 0.05 nmol/L **Number of study centres**: 63
Interventions	**Intervention(s)**: glargine **Comparator(s)**: NPH **Duration of intervention**: 28 weeks **Duration of follow-up**: 28 weeks **Run-in period**: 4 weeks
Outcomes	**Reported outcome(s) in full text of publication**: glycaemic variables, adverse events, safety
Study registration	**Trial identifier**: HOE 901/3001 **Study terminated early**: no
Publication details	**Language of publication**: English **Funding**: commercial funding (Aventis Pharma)

Home 2005 *(Continued)*

	Publication status: peer-reviewed journal and conference abstract
Stated aim of study	**Quote**: "To compare insulin glargine with NPH human insulin for basal insulin supply in adults with type 1 diabetes"
Notes	Of the 655 people entering the screening phase, 602 were randomised and 585 were treated with study medication - 292 with insulin glargine and 293 with NPH insulin (147 people received once-daily NPH insulin and 146 received twice-daily NPH insulin) - not reported how the 602 were randomised The corresponding author, Dr. Home, assumed that no participants died, as otherwise it would have been stated in the published paper. Dr. Home made us aware that the publication Witthaus et al. 2001 included the same population. No additional data from conference abstract Study included in FDA 2000 document (FDA 2000)- no additional outcome data

Kobayashi 2007

Study characteristics	
Methods	**Design**: parallel-group RCT; non-inferiority design; randomisation ratio: 2:1
Participants	**Inclusion criteria**: duration of diabetes mellitus for at least 2 years; current treatment of basal-bolus regimen for at least 12 weeks using an intermediate/long-acting human insulin and insulin aspart; HbA1c < 11.0%; BMI < 30 kg/m^2 **Exclusion criteria**: impaired renal function; impaired hepatic function; serious heart diseases; known hypoglycaemia unawareness or recurrent major hypoglycaemia; proliferative retinopathy or maculopathy requiring acute treatment; uncontrolled treated/untreated hypertension; current treatment with total insulin dose of more than 100 IU/day; current treatment or expected at the screening to start treatment with systemic corticosteroids **Diagnostic criteria**: — **Number of study centres**: 52
Interventions	**Intervention(s)**: detemir **Comparator(s)**: NPH **Duration of intervention**: 48 weeks **Duration of follow-up**: 48 weeks (plus 2 to 9 days) **Run-in period**: none
Outcomes	**Reported outcome(s) in full text of publication**: all-cause mortality, hypoglycaemia, adverse events, HbA1c
Study registration	**Trial identifier**: NN304-1476; JapicCTI-R070008; NCT00604344 **Study terminated early**: no
Publication details	**Language of publication**: Japanese **Funding**: commercial funding (Novo Nordisk)

Kobayashi 2007 *(Continued)*

	Publication status: peer-reviewed journal, conference abstracts and clinical study synopsis, 3 pages from CSR
Stated aim of study	**Quote**: "A 48-week, randomised, multi-centre, open-labelled, parallel-group trial to compare the efficacy and the safety of NN304 (insulin detemir) and NPH human insulin in participants with insulin requiring diabetes mellitus on a basal-bolus regimen"
Notes	Included both people with T1DM and T2DM, but separate data provided CSR provided data on diabetic ketoacidosis

Liu 2016

Study characteristics	
Methods	**Design**: parallel-group RCT; non-inferiority design; randomisation ratio: 2:1
Participants	**Inclusion criteria**: T1DM, aged at least 6 years to less than 18 years **Exclusion criteria**: treatment with other glucose-lowering medications other than insulin, HbA1c < 7% or > 12 %; Added from CSR: treated with insulin pump during the two months prior to screening; had undergone pancreas or islet cell transplantation; pancreatectomised; anticipated duration of life < 1 year for parents; history of primary seizure disorder; history of severe hypoglycaemic episode accompanied by seizure and/or coma, or diabetic ketoacidosis leading to hospitalisations or to care in the emergency ward, in the 2 months prior to the screening visit; known history of eating disorder such as anorexia or bulimia; known history of drug or alcohol abuse within 6 months prior to screening; treatment with systemic glucocorticoids within the month prior to screening; history of treatment for diabetic retinopathy (laser photocoagulation or vitrectomy) in the 6 months prior to screening, or diabetic retinopathy that may require treatment (e.g. laser photocoagulation) during the year following screening; treatment with any non-insulin anti-hyperglycaemic medication during the 3 months prior to screening; serum creatinine > 177 µmol/L; ALAT/ASAT greater than 3 times upper limit of normal); pregnancy, lactation **Diagnostic criteria**: — **Number of study centres**: 10
Interventions	**Intervention(s)**: glargine **Comparator(s)**: NPH **Duration of intervention**: 24 weeks **Duration of follow-up**: 28 weeks (up to 2 weeks screening + 1-week run-in + 24 week-treatment + 1-week follow-up) **Run-in period**: 1 week
Outcomes	**Reported outcome(s) in full text of publication**: hypoglycaemia, ketoacidosis, HbA1c
Study registration	**Trial identifier**: NCT01223131; EFC11681; U1111-1116-3661; EudraCT 2014-004640-35 **Study terminated early**: no
Publication details	**Language of publication**: English **Funding**: commercial funding (Sanofi) **Publication status**: peer-reviewed journal and abstract

Liu 2016 *(Continued)*

Stated aim of study	**Quote**: "Therefore, the purpose of the present study was to describe the safety and efficacy of once-daily insulin glargine over a period of 24 weeks in Chinese paediatric patients with T1DM"
Notes	Clinic consultations occurred at screening/run-in (week –3 to – 2 and week –1), randomisation (week 0), weeks 1, 2, 4, 6, 8, 10, 12, 16, 20, 24 (end of treatment) and week 25 (follow-up) Two years after enrolment of the first patient, a total of 108 patients were screened and 93 randomised, which constituted only 25% of the original enrolment target. Therefore, the study protocol was amended to reduce the planned number of enrolled patients to 150, with 100 patients randomised to insulin glargine and 50 to NPH insulin CSR synopsis did not report new outcome compared with clinical trials registers. EMA documents did not add additional outcomes (EMA 2015a; EMA 2015b)

NCT00595374

Study characteristics	
Methods	**Design**: parallel-group RCT; non-inferiority design; randomisation ratio: 2:1
Participants	**Inclusion criteria**: duration of T1DM > 12 months, > 18 years; BMI below 35 kg/m^2, HbA1c between 7.0-12.0%; current treatment with pre-prandial short-acting insulin and insulin NPH once or twice daily for at least 6 months **Exclusion criteria**: known or suspected allergy to study product or related products, receipt of any investigational products within the last 2 months prior to this study; drug or alcohol dependence, pregnancy, breastfeeding or intention of becoming pregnant **Diagnostic criteria**: — **Number of study centres**: 17
Interventions	**Intervention(s)**: detemir **Comparator(s)**: NPH **Duration of intervention**: 26 weeks **Duration of follow-up**: 26 weeks (+ 7 days) **Run-in period**: 2 weeks
Outcomes	**Reported outcome(s) in full text of publication**: no full text available
Study registration	**Trial identifier**: NCT00595374; NN304-1582 **Study terminated early**: no
Publication details	**Language of publication**: not published **Funding**: commercial funding (Novo Nordisk) **Publication status**: unpublished study. Data extraction based on ClinicalTrials.gov and clinical study synopsis
Stated aim of study	**Quote**: "The aim of this trial is to compare the efficacy and safety of insulin detemir and insulin NPH in adults with type 1 diabetes on blood glucose control"

NCT00595374 *(Continued)*

Notes	"The primary efficacy variable, the HbA1c showed no statistically significant difference between NPH insulin and insulin detemir for both the Full Analysis Set (FAS) and the Per-Protocol-Set (PPS)" and "Both overall and nocturnal analyses show no statistically significant difference in incidence of hypoglycaemic episodes." and "The results indicate that the mean class level of nocturnal hypoglycaemic episode shows no statistically significant difference between NPH insulin and insulin detemir for the FAS (P = 0.2119)" and "Seven patients experienced a total of 10 serious adverse events" Novo Nordisk replied that no CSR was available for this study

NCT00605137

Study characteristics	
Methods	**Design**: parallel-group RCT; non-inferiority design; randomisation ratio: 2:1
Participants	**Inclusion criteria**: T1DM for at least one year; current treatment of basal-bolus regimen for at least 12 weeks using an intermediate/long-acting human insulin and insulin aspart and/or soluble human insulin; HbA1c below 11.0%; able and willing to perform self-monitoring of capillary blood glucose and to take measures in case of hypoglycaemia **Exclusion criteria**: impaired renal function; impaired hepatic function; known hypoglycaemia unawareness or recurrent major hypoglycaemia; proliferative retinopathy or maculopathy requiring acute treatment; uncontrolled treated/untreated hypertension; current treatment with total daily insulin dose of more than 2.00 IU/kg; current treatment or expected at the screening to start treatment with systemic corticosteroids; history of serious allergy or serious anaphylactic reaction **Diagnostic criteria**: — **Number of study centres**: 17
Interventions	**Intervention(s)**: detemir **Comparator(s)**: NPH **Duration of intervention**: 24 weeks **Duration of follow-up**: 24 weeks **Run-in period**: the participants were randomised 6 weeks after the screening visit
Outcomes	**Reported outcome(s) in full text of publication**: no full text available (outcomes reported in synopsis: mortality, adverse events, hypoglycaemia, HbA1c)
Study registration	**Trial identifier**: NCT00605137; NN304-1604; JapicCTI-R070014 **Study terminated early**: no
Publication details	**Language of publication**: not published **Funding**: commercial funding (Novo Nordisk) **Publication status**: unpublished study. Data extraction based on ClinicalTrials.gov, clinical study synopsis, CSR (Novo Nordisk provided 4 pages of the CSR) and the trial protocol
Stated aim of study	**Quote**: "To investigate the safety profile of NN304 compared to NPH human insulin during a 24-week treatment period in children with type 1 diabetes on a basal-bolus regimen"
Notes	The maintenance period was defined as the interval from 6 weeks after the first day on the study product to the last day on study product (including the last day)

NCT00605137 *(Continued)*

	"The same trend was seen in nocturnal hypoglycaemic episodes."

Pieber 2007

Study characteristics	
Methods	**Design**: parallel-group RCT; non-inferiority design; randomisation ratio: 1:1
Participants	**Inclusion criteria**: 18 years or more, T1DM ≥ 1 year, BMI ≤ 35 kg/m^2, HbA1c between 7.5 and 12.0%, Prior to the study, treated with either intermediate-/long-acting insulin twice daily and three to four pre-meal human soluble insulin injections for ≥ 6 months, or biphasic insulin morning and evening and pre-lunch human soluble insulin injection for ≥ 6 months; total daily insulin dose was < 1.4 units/kg **Exclusion criteria**: significant medical problems, including proliferative retinopathy or maculopathy requiring acute treatment; recurrent severe hypoglycaemia; hypoglycaemic unawareness; impaired hepatic or renal function, or uncontrolled cardiovascular problems; pregnant or breastfeeding women **Diagnostic criteria**: — **Number of study centres**: 39 (from synopsis)
Interventions	**Intervention(s)**: detemir **Comparator(s)**: glargine **Duration of intervention**: 26 weeks **Duration of follow-up**: 26 weeks **Run-in period**: —
Outcomes	**Reported outcome(s) in full text of publication**: severe adverse events, hypoglycaemia, HbA1c
Study registration	**Trial identifier**: NCT00312104; NN304-1372 **Study terminated early**: no
Publication details	**Language of publication**: English **Funding**: commercial funding (Novo Nordisk) **Publication status**: peer-reviewed journal
Stated aim of study	**Quote**: "To compare glycaemic control and risk of hypoglycaemia of twice-daily insulin detemir with once-daily insulin glargine in participants with Type 1 diabetes"
Notes	At end of study, higher dose of insulin in the detemir group vs. the glargine group. From synopsis: "The mean daily dose of basal insulin was 34% higher for insulin detemir than for insulin glargine". Data on mortality and adverse events were extracted from synopsis/CSR. FDA medical review (FDA 2002) did not provide additional data

Porcellati 2004

Study characteristics

Porcellati 2004 *(Continued)*

Methods	**Design**: parallel-group RCT; superiority design; randomisation ratio: 1:1
Participants	**Inclusion criteria**: T1DM; C-peptide ≤ 0.15 nmol/L; on intensified treatment with multiple daily combinations of lispro and NPH insulin at each meal, and NPH at bedtime for at least 2 years **Exclusion criteria**: microangiopathy; autonomic neuropathy **Diagnostic criteria**: based on inclusion criteria, it is anticipated to be C-peptide ≤ 0.15 nmol/L **Number of study centres**: 1
Interventions	**Intervention(s)**: glargine **Comparator(s)**: NPH **Duration of intervention**: 1 year **Duration of follow-up**: 1 year **Run-in period**: 1 month
Outcomes	**Reported outcome(s) in full text of publication**: glycaemic control, hypoglycaemia
Study registration	**Trial identifier**: — **Study terminated early**: no
Publication details	**Language of publication**: English **Funding**: non-commercial funding (National Ministery of Scientific Research and University of Perugia) **Publication status**: peer-reviewed journal and conference abstract
Stated aim of study	**Quote**: "The aim of this study was to test superiority of glargine on long-term blood glucose (BG) as well as on responses to hypoglycaemia vs. NPH."
Notes	Conference abstract did not report any additional data

PRESCHOOL

Study characteristics	
Methods	**Design**: parallel-group RCT; non-inferiority design; randomisation ratio: 1:1
Participants	**Inclusion criteria**: paediatric patients with T1DM aged at least one year to less than 6 years at screening **Exclusion criteria:** T1DM for less than one year; HbA1c at screening > 12% or < 6%; diabetes other than T1DM; parents and patients not willing to undergo all study assessments and treatments; treated with insulin pump therapy during the two months prior to screening; history of primary seizure disorder; history of severe hypoglycaemic episode accompanied by seizure and/or coma, or diabetic ketoacidosis leading to hospitalisation or to care in the emergency ward in the 2 months prior to the screening; need for chronic treatment with acetaminophen (paracetamol)-containing medications; serum creatinine > 2.0 mg/dL at screening; serum ALAT or ASAT greater than 3x upper limit of normal for the patient's age and gender; haemoglobin < 10 g/dL, or platelet count less than 100,000/cu mm; treatment with any pharmacologic anti-hyperglycaemic oral agent for more than 3 months at any time; treatment with any non-insulin antihyperglycaemic medication for the 3 months prior to screening; treatment with systemic glucocorticoids within the month prior to screening

PRESCHOOL *(Continued)*

	Diagnostic criteria: —
	Number of study centres: 61
Interventions	**Intervention(s)**: glargine
	Comparator(s): NPH
	Duration of intervention: 24 weeks
	Duration of follow-up: 28 to 30 weeks (screening period 2 to 4 weeks, treatment period 24 weeks, and post-treatment observation period 2 weeks)
	Run-in period: 2 weeks
Outcomes	**Reported outcome(s) in full text of publication**: HbA1c, hypoglycaemia
Study registration	**Trial identifier**: NCT00993473; Eudra CT: 2009-011231-12; EFC11202; CTRI/2009/091/000912
	Study terminated early: no
Publication details	**Language of publication**: English
	Funding: commercial funding (Sanofi)
	Publication status: peer-reviewed journal
Stated aim of study	**Quote**: "To evaluate hypoglycemia with insulin glargine vs. neutral protamine Hagedorn (NPH) insulin in young children, using continuous glucose monitoring (CGM)"
Notes	Additional data from trials registers on serious adverse events, adverse events, ketoacidosis and mortality. CSR did not report any new data but reported HbA1c in more analyses - most appropriate was HbA1c change from baseline, which was used for the analysis and retrieved from the CSR

Ratner 2000

Study characteristics	
Methods	**Design**: parallel-group RCT; non-inferiority design; randomisation ratio: 1:1
Participants	**Inclusion criteria**: 18-80 years; T1DM for at least 1 year; HbA1c ≤ 12%; ability and willingness to perform SMBG using a blood glucose meter at home, as evidenced by 7 consecutive daily FBG values during the screening phase
	Exclusion criteria: treatment with other glucose-lowering drugs than insulin within 1 month of study entry, pregnancy, impaired hepatic function, impaired renal function, night shift, glucocorticoids
	Diagnostic criteria: post-prandial C-peptide levels ≤ 0.5 nmol/L
	Number of study centres: 49
Interventions	**Intervention(s)**: glargine
	Comparator(s): NPH
	Duration of intervention: 28 weeks
	Duration of follow-up: 28 weeks
	Run-in period: none

Ratner 2000 *(Continued)*

Outcomes	**Reported outcome(s) in full text of publication**: HbA1c, hypoglycaemia, safety
Study registration	**Trial identifier**: HOE 901/3004 **Study terminated early**: no
Publication details	**Language of publication**: English **Funding**: commercial funding (Hoechst Marion Roussel, Aventis) **Publication status**: peer-reviewed journal and conference abstract
Stated aim of study	**Quote**: "This study compared insulin glargine with NPH human insulin in participants with type 1 diabetes who had been previously treated with multiple daily injections of NPH insulin and regular insulin"
Notes	Herschon 2004 reported on a subgroup of participants (394 out of 534). Part of the study was published in an abstract - this abstract was not retrieved Sanofi provided a CSR. From CSR: amendment 1 (21 May 1997) shortened the treatment period from 52 to 28 weeks; this was achieved by omitting 3 visits, but the interval between visits was not affected. The decision to shorten the treatment period from 52 weeks to 28 weeks was based on the outcome of a meeting with representatives of the US Food and Drug Administration (FDA). The conclusion of this meeting was that a 6-month treatment period would be sufficient to demonstrate the efficacy and safety of HOE 901 in a Phase III study for regulatory purposes From CSR: additional mortality, hypoglycaemia data, serious adverse events, cost, quality of life Study included in FDA 2000 (FDA 2000) - data on hypoglycaemia and serious adverse events could be retrieved (but these data were also available from CSR)

Robertson 2007

Study characteristics	
Methods	**Design**: parallel-group RCT; non-inferiority design; randomisation ratio: 2:1
Participants	**Inclusion criteria**: T1DM for at least 12 months; age 6-17 years; 6-7 years: BMI less than or equal to 19 kg/m^2, 8-9 years: BMI less than or equal to 20 kg/m^2, 10-11 years: BMI less than or equal to 22 kg/m^2, 12-13 years: BMI less than or equal to 24 kg/m^2 and 14-17 years: BMI less than or equal to 27 kg/m^2; HbA1c equal to or less than 12.0% **Exclusion criteria**: proliferate retinopathy or maculopathy; total daily insulin dose greater than 2.00 IU/kg; any condition or disease that ruled out study participation according to the judgement of the investigator; mental incapacity, unwillingness or language barriers precluding understanding or co-operation; life-style incompatible with study participation **Diagnostic criteria**: — **Number of study centres**: 44
Interventions	**Intervention(s)**: detemir **Comparator(s)**: NPH **Duration of intervention**: 26 weeks **Duration of follow-up**: 26 weeks

Robertson 2007 *(Continued)*

	Run-in period: none
Outcomes	**Reported outcome(s) in full text of publication**: adverse events, hypoglycaemia, HbA1c
Study registration	**Trial identifier**: NCT00312156; NN304-1379 **Study terminated early**: no
Publication details	**Language of publication**: English **Funding**: commercial funding (Novo Nordisk) **Publication status**: peer-reviewed journal
Stated aim of study	**Quote**: "This study compared the effect of insulin detemir on glycaemic control (HbA1c, fasting plasma glucose and variability thereof) with that of Neutral Protamine Hagedorn human isophane (NPH) insulin, both combined with insulin aspart, in children with Type 1 diabetes mellitus, and compared the safety of these treatments."
Notes	Trial synopsis - this provided additional information on serious adverse events A post-treatment follow-up visit was performed 2-4 days after the last visit FDA Medical review 2005 provided information on mortality (FDA 2005)

Russell-Jones 2004

Study characteristics	
Methods	**Design**: parallel-group RCT; non-inferiority design; randomisation ratio: 2:1
Participants	**Inclusion criteria**: ≥ 18 years with T1DM for ≥ 1 year who were already using basal or premixed insulin once daily in the evening (between 5 PM and 11 PM) and human insulin before meals for ≥ 2 months **Exclusion criteria**: very poorly controlled diabetes using the current once daily therapy (as determined by HbA1c > 12% and/or a total basal insulin dose > 100 IU/d); pregnant or breastfeeding; significant medical problems including proliferative retinopathy, impaired hepatic or renal function, recurrent major hypoglycaemia, uncontrolled hypertension, or severe cardiac problems; concomitant use of medications known to interfere with glucose metabolism was not permitted **Diagnostic criteria**: — **Number of study centres**: 92
Interventions	**Intervention(s)**: detemir **Comparator(s)**: NPH **Duration of intervention**: 6 months **Duration of follow-up**: 6 months **Run-in period**: — (3 weeks screening period, not further specified)
Outcomes	**Reported outcome(s) in full text of publication**: HbA1c, safety, hypoglycaemia
Study registration	**Trial identifier**: NCT03220425; NN304-1335 **Study terminated early**: no

Russell-Jones 2004 *(Continued)*

Publication details	**Language of publication**: English **Funding**: commercial funding (Novo Nordisk) **Publication status**: peer-reviewed journal/conference abstract
Stated aim of study	**Quote**: "The purpose of this trial was to compare the effects of QD basal insulin replacement using insulin detemir versus neutral protamine Hagedorn (NPH) insulin in basal-bolus therapy in combination with regular human insulin (HI) in patients with type 1 diabetes mellitus (DM)."
Notes	The study consisted of an initial 1-month titration period (2 visits and telephone contact), during which dosing was optimised to meet individual requirements, and a 5-month maintenance period (4 visits) Twenty-four–hour continuous blood glucose profiles were measured in a subgroup of patients from both treatment groups during the last month of treatment. Patients from 18 selected investigational sites were asked (but not required) to wear the Continuous Glucose Monitoring System (CGMS; Medtronic MiniMed, Northridge, California) for 72 hours. For logistic reasons, as well as for optimising compliance, investigational sites were selected based on previous experience with the device and willingness to participate The relative risk of hypoglycaemia was estimated from the incidence of all hypoglycaemic episodes occurring during the maintenance period (i.e. 5 months) (the interval from 30 days after first dose to last day on study product). Conference abstract did not provide any new information CSR provided data on mortality, serious adverse events and adverse events. Study described in FDA medical review (FDA 2002) which provided data on mortality. EMA provided no additional data (EMA 2004)

Schober 2002

Study characteristics	
Methods	**Design**: parallel-group RCT; non-inferiority design; randomisation ratio: 1:1
Participants	**Inclusion criteria**: T1DM; age 5-16 years; treated with insulin for at least one year; using at least three daily injections; HbA1c < 12% **Exclusion criteria**: other glucose-lowering treatment than insulin within the last month; postmenarchal, sexually active girls not using adequate contraception; treatment with hyperglycaemic drugs; impaired liver function; impaired renal function **Diagnostic criteria**: — **Number of study centres**: 30
Interventions	**Intervention(s)**: glargine **Comparator(s)**: NPH **Duration of intervention**: 28 weeks **Duration of follow-up**: 28 weeks (run-in period included) **Run-in period**: 4 weeks
Outcomes	**Reported outcome(s) in full text of publication**: hypoglycaemia, adverse events, HbA1c
Study registration	**Trial identifier**: HOE901/3003

Schober 2002 *(Continued)*

	Study terminated early: no
Publication details	**Language of publication**: English **Funding**: not reported in main publication, but co-publication reported funding from Sanofi **Publication status**: peer-reviewed journal
Stated aim of study	**Quote**: "The objective of this 28-week, multicenter, centrally randomized and controlled study was to compare the effects of insulin glargine and NPH insulin on glycosylated hemoglobin (HbA1c) in children and adolescents with T1DM."
Notes	From Herwig 2007: "This study included those patients from the previous study who continued with insulin glargine treatment." Study in reference is Schober 2002. Herwig and colleagues reported funding from Sanofi CSR provided by Sanofi: added mortality data and a trial protocol. FDA 2000 did not provide additional data (FDA 2000) CSR provided data on economics

Standl 2004

Study characteristics	
Methods	**Design**: parallel-group RCT; non-inferiority design; randomisation ratio: 1:1
Participants	**Inclusion criteria**: adults (aged 18–74 years); T1DM of 12 months or more; treated with twice-daily basal insulin in combination with meal-related bolus insulin for at least 2 months; BMI ≤ 35.0 kg/m^2; HbA1c ≤ 12%; total basal insulin dosage ≤ 100 IU/day **Exclusion criteria**: proliferative retinopathy; impaired hepatic or renal function; severe cardiac disease; uncontrolled hypertension; recurrent major hypoglycaemia; insulin allergy; pregnant or breast-feeding women **Diagnostic criteria**: — **Number of study centres**: 47
Interventions	**Intervention(s)**: detemir **Comparator(s)**: NPH **Duration of intervention**: 6 months **Duration of follow-up**: 6 months (12 months) **Run-in period**: none
Outcomes	**Reported outcomes in full text of publication:** glycaemic control, hypoglycaemia, weight, safety
Study registration	**Trial identifier**: NN304-1181 (extension NN304-1243) **Study terminated early:** no
Publication details	**Language of publication**: English **Funding**: commercial funding (Novo Nordisk) **Publication status**: peer-reviewed journal

Standl 2004 *(Continued)*

Stated aim of study	**Quote**: "This trial compared the long-term safety and efficacy of the basal insulin preparations, insulin detemir and NPH insulin, in basal-bolus therapy for patients with type 1 diabetes".
Notes	After an initial 6-month treatment period, patients were invited to participate in a 6-month extension period Data were entered after the 6-month main period Additional data on this study were available from the FDA Medical Review of Levemir (FDA 2002) for severe hypoglycaemia after 6 months and mortality. EMA document provided no additional data (EMA 2004). CSR provided by Novo Nordisk. From this, it was apparent that quality of life had been evaluated. A trial protocol was provided as well. Data for adverse events could be added as well as exact values for people included in the analysis of the study

SWITCH 1

Study characteristics	
Methods	**Design**: cross-over RCT; non-inferiority design; randomisation ratio: 1:1
Participants	**Inclusion criteria**: fulfilling at least one of the below criteria: experienced at least one severe hypoglycaemic episode within the last year (according to the ADA definition, April 2013); moderate chronic renal failure, defined as glomerular filtration rate 30 - 59 mL/min/1.73 m^2 per chronic kidney disease epidemiology collaboration; hypoglycaemic symptom unawareness; diabetes mellitus duration for more than 15 years; recent episode of hypoglycaemia within the last 12 weeks: male or female; age at least 18 years at the time of signing informed consent; T1DM (diagnosed clinically) for at least 52 weeks; current treatment with a basal-bolus regimen consisting of NPH insulin once daily/twice daily or insulin detemir once daily/twice daily plus 2-4 daily injections of any rapid-acting meal time insulin or continuous subcutaneous insulin infusion (with rapid-acting insulin) for at least 26 weeks; HbA1c below or equal to 10%; BMI below or equal to 45 kg/m^2 **Exclusion criteria**: known or suspected hypersensitivity to study product(s) or related products; previous participation in this study; female who is pregnant, breastfeeding or intends to become pregnant or is of child-bearing potential and not using adequate contraceptive methods; treatment with glargine or degludec within the last 26 weeks; use of any other glucose-lowering drug than those stated in the inclusion criteria within the last 26 weeks; receipt of any investigational medicinal product within 4 weeks prior to screening; any chronic disorder or severe disease which, in the opinion of the investigator, might jeopardise the safety or compliance with the protocol: current or past (within the last 5 years) malignant neoplasms (except basal cell and squamous cell carcinoma); stroke, decompensated NYHA class III or IV, myocardial infarction, unstable angina pectoris, or coronary arterial bypass graft or angioplasty, all within the last 26 weeks; uncontrolled or untreated severe hypertension defined as systolic BP ≥ 180 mmHg and/or diastolic BP ≥ 100 mmHg; impaired liver function defined as ALAT or ASAT ≥ 2.5 times upper limit of normal; severe renal impairment defined as glomerular filtration rate < 30 mL/min/1.73 m^2; proliferative retinopathy or maculopathy requiring acute treatment according to the investigator verification by fundoscopy or fundus photography performed within 12 weeks **Diagnostic criteria**: clinically diagnosed **Number of study centres**: 90
Interventions	**Intervention(s)**: degludec **Comparator(s)**: glargine **Duration of intervention**: 32 weeks **Duration of follow-up**: 32 weeks

SWITCH 1 *(Continued)*

	Run-in period: none
Outcomes	**Reported outcome(s) in full text of publication**: hypoglycaemia, safety, at cross-over: HbA1c and quality of life
Study registration	**Trial identifier**: NCT02034513; NN1250-3995; WHO ID: U1111-1129-9668; EudraCT number: 2012-001930-32 **Study terminated early**: no
Publication details	**Language of publication**: English **Funding**: commercial funding (Novo Nordisk) **Publication status**: peer-reviewed journal
Stated aim of study	**Quote**: "To determine whether insulin degludec is noninferior or superior to insulin glargine U100 in reducing the rate of symptomatic hypoglycemic episodes"
Notes	The study had a cross-over design - each intervention period was 32 weeks before cross-over. Main analyses of the study were performed in the last 16 weeks of each cross-over period: weeks during the maintenance period (weeks 16-32 and 48-64) Study also reported in FDA 2015 report; this trial is described as ongoing and no additional data could be retrieved (FDA 2015)

Thalange 2013

Study characteristics	
Methods	**Design**: parallel-group RCT; non-inferiority design; randomisation ratio: 1:1
Participants	**Inclusion criteria**: T1DM for at least 12 months; age 2-16 years; total daily insulin dose ≤ 2.0 U/kg; insulin detemir naive; HbA1c less or equal to 11%; BMI ≤ 27 kg/m^2 **Exclusion criteria**: significant concomitant disease **Diagnostic criteria**: — **Number of study centres**: 35
Interventions	**Intervention(s)**: detemir **Comparator(s)**: NPH **Duration of intervention**: 52 weeks **Duration of follow-up**: 104 weeks (only for the detemir group) **Run-in period**: none
Outcomes	**Reported outcome(s) in full text of publication**: adverse events, ketoacidosis, HbA1c, hypoglycaemia
Study registration	**Trial identifier**: NN304-1689; EudraCT 2006-000051-18; NCT00435019 (main study); NCT00623194 (extension study); NN304-1690 (extension study) **Study terminated early**: no
Publication details	**Language of publication**: English

Thalange 2013 *(Continued)*

	Funding: commercial funding (Novo Nordisk) **Publication status**: peer-reviewed journal
Stated aim of study	**Quote**: "This 52-week, randomized, multinational, open-label, parallel-group, non-inferiority trial investigated the efficacy and safety of basal–bolus treatment with insulin detemir vs. NPH (neutral protamine Hagedorn) insulin, in combination with insulin aspart, in participants aged 2–16 years with Type 1 diabetes mellitus"
Notes	A total of 10 scheduled visits to the clinical study sites and 8 telephone contacts. Only participants in the detemir group were invited to extended follow-up Quote: "Children in the IDet arm who completed this study were offered the option to continue treatment with IDet (once or twice daily) together with IAsp (2–4 times daily with meals) for a further 52 weeks (extension study), for a total of 104 weeks of treatment (total treatment period)" The CSR did not add any additional information on outcomes. Additional information on baseline variables were identified Described in EMA 2011 report, but no additional outcomes provided (EMA 2011)

Urakami 2017

Study characteristics	
Methods	**Design**: cross-over RCT; randomisation ratio: 1:1
Participants	**Inclusion criteria**: T1DM; children; Tanner stage 1-3; previously received a once-daily injection of glargine at bedtime as a basal insulin regimen **Exclusion criteria**: — **Diagnostic criteria**: — **Number of study centres**: 1
Interventions	**Intervention(s)**: degludec **Comparator(s)**: glargine **Duration of intervention**: 24 weeks **Duration of follow-up**: 24 weeks **Run-in period**: —
Outcomes	**Reported outcome(s) in full text of publication**: hypoglycaemia, HbA1c
Study registration	**Trial identifier**: — **Study terminated early**: no
Publication details	**Language of publication**: English **Funding**: not reported **Publication status**: peer-reviewed journal

Urakami 2017 *(Continued)*

Stated aim of study	**Quote**: "In the present study, we have compared the efficacy and safety of IGlar vs. IDeg as a basal-bolus therapy during sequential 24-week periods in a randomized crossover study of Japanese children with type 1 diabetes".
Notes	Study authors provided outcomes on request. No study protocol provided

Vague 2003

Study characteristics	
Methods	**Design**: parallel-group RCT; non-inferiority design; randomisation ratio: 1:1
Participants	**Inclusion criteria**: T1DM for at least 1 year; received basal (once or multiple times daily) bolus insulin treatment for at least 2 months; HbA1c level ≤ 12%, BMI ≤ 35kg/m^2; total basal insulin dosage of ≤ 100 IU/day **Exclusion criteria**: proliferative retinopathy; impaired hepatic or renal function; severe cardiac problems; uncontrolled hypertension; recurrent major hypoglycaemia; allergy to insulin; pregnancy and breastfeeding **Diagnostic criteria**: — **Number of study centres**: 46
Interventions	**Intervention(s)**: detemir **Comparator(s)**: NPH **Duration of intervention**: 6 months **Duration of follow-up**: 6 months (12 months) **Run-in period**: none
Outcomes	**Reported outcome(s) in full text of publication**: HbA1c, safety, hypoglycaemia
Study registration	**Trial identifier**: NN304-1205; extension trial: NN304-1316 **Study terminated early**: no
Publication details	**Language of publication**: English **Funding**: commercial funding (Novo Nordisk) **Publication status**: peer-reviewed journal
Stated aim of study	**Quote**: "The aim of this trial was to evaluate the metabolic control, risk of hypoglycemia, and other potential effects of treatment with insulin detemir in patients with type 1 diabetes on such a basal-bolus regimen"
Notes	Patients completing the initial 6-month trial were invited to participate in the extension phase, with 316 of 425 accepting CSR reported mortality, serious adverse events and ketoacidosis Additional information available from FDA review (mortality) (FDA 2002). EMA document provided no additional data (EMA 2004)

—: denotes not reported
ADA: American Diabetes Association
ALAT: alanine aminotransferase
ASAT: aspartate-aminotransferase
BG: blood glucose
BMI: body mass index
BP: blood pressure
FBG: fasting blood glucose
CGM: continuous glucose monitoring
CGMS: continuous glucose monitoring system
CSR: clinical study report
DM: diabetes mellitus
DiabMedSat: diabetes medication satisfaction
DPM: diabetes productivity measure
EMA: European Medicine Agency
EudraCT: European Union Drug Regulating Authorities Clinical Trials Database
FAS: full analysis set
FDA: Food and Drug Administration
HbA1c: glycosylated haemoglobin A1c
HI: human insulin
IAsp: insulin aspart
IDeg: insulin degludec
IDet: insulin detemir
IGlar: insulin glargine
IU: international units
MAO: monoamine oxidase
MDI: multiple daily injection
NPH: neutral protamine Hagedorn
NYHA: New York Heart Association
PG: plasma glucose
PM: post meridiem
PPS: per-protocol set
QD: quaque die (daily)
SF-36: short-form 36
SMBG: self-monitoring of blood glucose
SMPG: self-measured plasma glucose
RCT: randomised controlled trial
T1DM: type 1 diabetes mellitus
T2DM: type 2 diabetes mellitus
Trim-D: treatment related impact measure for diabetes

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

Study	Reason for exclusion
21st Brazilian Diabetes Society Congressa	Congress report containing no studies of relevance
Bin-Abbas 2006	Wrong study design: not a randomised clinical trial
Bolli 2016	Wrong study design: pooled data from four randomised clinical trials
Chacra 2010	Wrong intervention (applied basal insulin no longer available)
Hirsch 2012	Wrong study drug: compared insulin degludec/aspart combined with detemir + aspart (NCT00978627; NN5401-3645; NN5401-3645; Eudra: 2008-005769-71; U1111-1111-8943; 2009-013412-13; U1111-1113-2475)
HypoANA	Wrong study drug: applied different type of rapid-acting insulin analogue in the intervention arms

Study	Reason for exclusion
Iga 2017	Short duration of the intervention
Kiess 2004	Wrong study design: letter
Manini 2007	Wrong study design: not a randomised clinical trial
NCT00788840	Wrong population: people with T2DM
NCT01854723	Wrong population: people with insulin resistance
Orchard 2014	Wrong intervention: different co-intervention
Ota 2017	Trial combined outcomes of people with T1DM and T2DM. No separate data available for the 12 people with T1DM included in the trial
Perez-Maraver 2013	Applied different type of rapid-acting insulin analogue in the intervention arms
Polonsky 2014	Wrong study design: not a randomised clinical trial
Prikhodina 2007	Wrong study design: not a randomised clinical trial
Tentolouris 2018	Wrong study design: not a randomised clinical trial
UMIN000001562	Wrong study design: one intervention arm
UMIN000009965	Study protocol for a study with short duration
UMIN000013817	Study protocol for a study with short duration
Yamada 2014	Short duration of the intervention
Ziemen 2015	Wrong intervention: comparing insulin glargine in different concentrations

T1DM: type 1 diabetes mellitus
T2DM: type 2 diabetes mellitus

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

Agesen 2019

Methods	**Allocation**: randomised **Intervention model**: cross-over **Masking**: open-label **Primary purpose**: treatment
Participants	**Condition**: T1DM **Estimated number of participants:** 154 **Inclusion criteria**: T1DM for more than five years, one or more episodes of nocturnal severe hypoglycaemia in the previous two years (defined as need for third party assistance to restore blood glucose level), age > 18 years, treatment with multiple dose insulin injection (more than 2) or insulin pump allowing for both human insulin and insulin analogues, a negative pregnancy test,

Agesen 2019 *(Continued)*

	willingness to a once-daily regimen concerning basal insulin, willingness to do self-monitoring of blood glucose and keep a diary **Exclusion criteria**: history of primary or secondary adrenal or growth hormone insufficiency, untreated hypothyroidism, history of unstable angina or major cardiovascular events, heart failure (NYHA class IV), history of malignancy unless a disease-free period exceeding five years, history of alcohol or drug abuse, pregnancy or lactation, and women of childbearing potential who are not using chemical or mechanical contraception, HbA1c > 86 mmol/mol (10%), and shifting working hours
Interventions	**Intervention(s)**: degludec **Comparator(s)**: glargine **Duration of the intervention:** 12 months before cross-over (24 months in total)
Outcomes	**Primary outcome(s)**: symptomatic nocturnal hypoglycaemia **Secondary outcome(s)**: hypoglycaemia (severe, any nocturnal, CGM recorded, any in hospital), HbA1c, insulin dose, quality of life, change in glycaemic variability **Other outcome(s)**: — **Relevant proposed outcome measures for SoF table**: health-related quality of life, hypoglycaemia
Reason for awaiting classification	Marked as 'completed' in Clinicaltrials.gov but no publication was available
Study details	**Study identifier:** NCT02192450; 2014-001942-24 **Study start date**: July 2014 **Study completion date**: June 2019 **Responsible party/principal investigator**: Ulrik Pedersen-Bjergaard, Nordsjaellands Hospital, Denmark
Official title and purpose of study	Insulin Degludec and Symptomatic Nocturnal Hypoglycaemia (HypoDeg) **Quote**: "The purpose of this study is to determine whether insulin degludec compared to insulin glargine can reduce the risk of symptomatic nocturnal hypoglycaemia in participants with the greatest potential benefit from optimised insulin treatment, which are patients with type 1 diabetes and high risk of nocturnal severe hypoglycaemia"
Notes	

Basal Analog Study

Methods	**Allocation**: randomised **Intervention model**: parallel-group assignment **Masking**: open-label **Primary purpose**: treatment
Participants	**Condition**: newly diagnosed T1DM **Estimated number of participants:** 120

Basal Analog Study *(Continued)*

	Inclusion criteria: diagnosis of T1DM and novel to insulin therapy, age 7 to 17 years **Exclusion criteria**: moderate to severe ketoacidosis (pH < 7.2 and/or standard bicarbonate < 10 mmol/L); suspected non-type 1 IA2 and GAD65: all antibody negative; celiac disease or other chronic disease; hypothyroidism, if not well controlled syndromes; previous anorexia nervosa; neuro-psychiatric disease; malignancy
Interventions	**Intervention(1)**: glargine **Comparator(1)**: detemir **Comparator (2)**: NPH **Duration of the intervention:** 12 months
Outcomes	**Primary outcome(s)**: HbA1c **Secondary outcome(s)**: stimulated C-peptide, IGF-1 (from EudraCT: quality of life, hypoglycaemia) **Other outcome(s)**: — **Relevant proposed outcome measures for SoF table**: health-related quality of life, hypoglycaemia
Reason for awaiting classification	Marked as 'completed' in Clinicaltrials.gov and conference abstract available. No publication available. HbA1c reported in a format making it unsuitable for meta-analysis
Study details	**Study identifier:** EudraCT-number 2005-001726-80; NCT01271517 **Study start date**: September 2005 **Study completion date**: March 2005 **Responsible party/principal investigator**: Peter Bang, Karolinska Institutet, Sweden
Official title and purpose of study	Basal Analog Study - Comparison of lantus or levemir with NPH insulin from T1DM diagnosis (BAS) **Quote**: "To study if the use of long acting insulin analog treatment from diagnosis of pediatric type 1 diabetes mellitus (T1DM) improves metabolic control and IGF-I levels"
Notes	Corresponding author contacted. No full-text publication was available. Published as conference abstract

ChiCTR2000032703

Methods	**Allocation**: randomised **Intervention model**: cross-over study **Masking**: not stated **Primary purpose**: treatment
Participants	**Condition**: T1DM **Estimated number of participants:** 20 **Inclusion criteria**:

ChiCTR2000032703 *(Continued)*

	1. At the time of screening, the age of patients >= 18 years old; both male and female considered; 2. Participants who were all type 1 diabetic patients, with the serum C-peptide concentration confirmed as low level (< 0.07 nmol/L) at least twice; 3. Participants who had been continuously using the basic plus meal insulin treatment scheme in the past 3 months; 4. Patients with HbA1c meeting the standard: 6.9% <= HbAlc <= 10.0%; 5. Body mass index (BMI) of 18.0-35.0kg/m^2; 6. Patients who could understand and abide by the test process, voluntarily participate in the test and provide informed consent. **Exclusion criteria**: 1. Patients with diabetic ketoacidosis or diabetic hyperosmotic nonketotic coma in the past 6 months; 2. Patients with severe infection, surgery or severe trauma in the past month; 3. Patients with any of the following history and conditions of heart disease in the past 6 months: (1) Decompensated cardiac insufficiency (NYHA grade III or IV) (2) Unstable angina, myocardial infarction, coronary artery bypass grafting or coronary stent implantation (3) Uncontrolled or serious arrhythmias (such as long QT interval syndrome) according to the evaluation of researchers; 4. Patients with haemorrhagic stroke or ischaemic stroke in the past 6 months as assessed by the researchers; 5. At present, patients with any disease that may cause haemolysis or red blood cell instability and affect the detection of glycosylated haemoglobin; 6. Patients with a history of acute or chronic pancreatitis; 7. Liver function damaged, AST/ALT > 3 times of the upper limit of reference range, total bilirubin > 1.5 times of the upper limit of reference range; 8. Renal insufficiency, glomerular filtration rate (EGFR) < 60 mL/min/1.73m^2 9. Patients with diseases that may cause tissue hypoxia (especially the deterioration of acute disease or chronic respiratory disease); 10. Patients with severe chronic gastrointestinal diseases with malnutrition, hunger or weakness; 11. Patients with adrenal dysfunction; 12. Patients that were habitual heavy drinkers; 13. Patients with dehydration or gastrointestinal symptoms, such as diarrhoea or vomiting related to dehydration risk; 14. Patients with malignant tumours requiring treatment in the past 5 years; 15. Patients who had received or were receiving any other investigational drug in the past 3 months; 16. Patients with serious mental illness or language disorder who were unwilling or unable to fully understand co-operation; 17. Patients who were or might be allergic to insulin or similar drugs; 18. Pregnant or lactating women; 19. Patients who had used CGMS system in the past 6 months; 20. Patients who were receiving systemic glucocorticoid treatment (oral and intravenous) due to any disease; 21. Patients taking vitamin C and aspirin with daily dose greater than 60 mg; 22. Honeymoon patients with type 1 diabetes; 23. Patients known to be allergic to medical grade glue; 24. Where the researchers believed that the participants had other important diseases that were not suitable for the study.
Interventions	**Intervention**: glargine **Comparator**: degludec **Duration of the intervention**: unclear
Outcomes	**Primary outcome(s)**: 24-h mean glucose levels (SD, coefficient of variation), mean (largest) amplitude of glycaemic excursions, mean of daily difference, time in hypoglycaemia (< 2.8/3.9 mmol/L) during a 24-h period, time in hyperglycaemia (> 7.8/10.0/13.9 mmol/L) during a 24-h period;

ChiCTR2000032703 *(Continued)*

	Secondary outcome(s): HbA1c, insulin dose, nocturnal hypoglycaemia, self-perceived satisfaction rating scale **Other outcome(s)**: — **Relevant proposed outcome measures for SoF table**: HbA1c, nocturnal hypoglycaemia
Reason for awaiting classification	No publication available. Unclear duration of intervention/follow-up
Study details	**Study identifier:** ChiCTR2000032703 **Study start date**: May 2020 **Study completion date**: unclear **Responsible party/principal investigator**: Kuang Hongyu, The First Affiliated Hospital of Harbin Medical University, 23 Post Street, Nangang District, Harbin, Heilongjiang, China
Official title and purpose of study	Comparision of insulin degludec and insulin glargine on blood glucose variability in northern Chinese patients with type 1 diabetes **Quote**: "To compare blood glucose variability in northern Chinese patients with type 1 diabetes treated with insulin glargine (IGla) versus insulin degludec (IDeg) using flash glucose monitoring (FGM)"
Notes	

EudraCT 2007-004144-74

Methods	**Allocation**: randomised **Intervention model**: parallel-group assignment **Masking**: open-label **Primary purpose**: treatment
Participants	**Condition**: T1DM **Estimated number of participants:** 97 **Inclusion criteria**: T1DM, female, 13-20 years, diagnosed over 1 year or C-peptide negative, post-menarchal or in late puberty, HbA1c < 12%, BMI less than or equal to +2.5 for age, no active or untreated concurrent disease **Exclusion criteria:** non-T1DM including those secondary to an existing pathology, any other physical or psychological disease likely to interfere with the normal conduct of the study and interpretation of the results, pregnant or breastfeeding women, females of reproductive age who are unwilling to take appropriate measures of contraception, taking medication likely to affect glucose metabolism
Interventions	**Intervention**: glargine **Comparator**: detemir **Duration of the intervention:** 1 year according to protocol, but study ended prematurely, therefore, unknown how long the study duration was
Outcomes	**Primary outcome(s)**: BMI

EudraCT 2007-004144-74 *(Continued)*

	Secondary outcome(s): (results available for adverse events at EudraCT) **Other outcome(s)**: — **Relevant proposed outcome measures for SoF table**: serious adverse events
Reason for awaiting classification	The trial is listed as prematurely ended, but duration of trial unknown
Study details	**Study identifier:** EudraCT 2007-004144-74; ISRCTN49492872 **Study start date**: October 2007 **Study completion date**: December 2016 **Responsible party/principal investigator**: David Dunger, University of Cambridge, United Kingdom
Official title and purpose of study	A comparison of the effects of insulin detemir with insulin glargine on weight gain in female adolescents and young adults with Type 1 Diabetes (T1D) on a basal bolus regimen **Quote**: "To explore the hypothesis that use of insulin Detemir vs. insulin Glargine will lead to reduced weight gain in young women with Type 1 Diabetes"
Notes	ISRCTN49492872; EudraCT 2007-004144-74 Results are available on https://www.clinicaltrialsregister.eu/ctr-search/trial/2007-004144-74/results

EudraCT 2009-012317-22

Methods	**Allocation**: randomised **Intervention model**: parallel-group assignment **Masking**: open-label **Primary purpose**: treatment
Participants	**Condition**: T1DM **Estimated number of participants:** 16 **Inclusion criteria**: aged >= 6 and < 11 years; HbA1c < 7.5%; basal C-peptide < 0.1 nmol/L **Exclusion criteria**: clinical signs of puberty illness associated with T1DM, using any drug except insulin, clinically relevant microalbuminuria, non-availability of blood samples
Interventions	**Intervention(s)**: glargine **Comparator(s)**: detemir **Duration of the intervention:** 1 year (not explicitly stated - could also be 4 months)
Outcomes	**Primary outcome(s)**: GH and IGF-1 levels **Secondary outcome(s)**: — **Other outcome(s)**: — **Relevant proposed outcome measures for SoF table**: —

EudraCT 2009-012317-22 *(Continued)*

Reason for awaiting classification	Marked as 'completed' in EU Clinical Trial Register but no publication available
Study details	**Study identifier:** EudraCT 2009-012317-22 **Study start date**: June 2009 **Study completion date**: — (listed as completed) **Responsible party/principal investigator**: GM Lancise, Azienda Ospedaliero Universitaria Ospedali Ruinti Umberte, Italy
Official title and purpose of study	Pediatric basal bolus therapy - Basal-bolus regimen in the treatment of children with type 1 diabetes **Quote**: "...to study the difference of GH/IGF1 axis in children treated with glargine or detemir"
Notes	Primary investigator contacted. No reply

INEOX

Methods	**Allocation**: randomised **Intervention model**: parallel-group assignment **Masking**: open-label **Primary purpose**: treatment
Participants	**Condition**: T1DM **Estimated number of participants:** 300 **Inclusion criteria:** 18 to 65 years; T1DM of more than two years; HbA1c ≤ 10%; intensive treatment with basal multiple doses of insulin **Exclusion criteria**: chronic kidney disease, liver disease, thyroid dysfunction (except hypothyroidism correctly treated and controlled); pregnancy or pregnancy planning; T2DM; hyperuricaemia
Interventions	**Intervention(s)**: degludec **Comparator(s)**: glargine **Duration of the intervention:** 6 months
Outcomes	**Primary outcome(s)**: oxidative stress markers **Secondary outcome(s)**: glycaemic measures, hypoglycaemia, ketosis, quality of life, treatment satisfaction **Other outcome(s)**: — **Relevant proposed outcome measures for SoF table**: hypoglycaemia, health-related quality of life
Reason for awaiting classification	Marked as expected to be completed December 2019 in ClinicalTrials.gov. No data available
Study details	**Study identifier:** FIM-EOX-2016-01; EudraCT 2016-002915-17; NCT03328845

INEOX *(Continued)*

	Study start date: January 2017 **Study completion date**: December 2019 **Responsible party/principal investigator**: Maria Soledad Ruiz de Adana, Regional University Hospital of Málaga, Spain
Official title and purpose of study	Impact on the oxidative stress of the different analogues of insulin in people with type 1 diabetes (Ineox Study) (INEOX) **Quote:** "This study evaluates in a group of people with DM 1 the influence in parameters of oxidative stress of the treatments with the different current analogs of insulin"
Notes	

IRCT201203079224N1

Methods	**Allocation**: randomised **Intervention model**: parallel-group assignment **Masking**: open-label **Primary purpose**: treatment
Participants	**Condition**: T1DM **Estimated number of participants:** 40 **Inclusion criteria**: age 6 to 11 years; T1DM under treatment of insulin at least 6 months; BMI below the 90th percentile at baseline and having the desire and ability to measure blood glucose self-monitoring using glucometer devices **Exclusion criteria**: mental and physical disorders; patients who did not complete the study period and patients with diabetes who were not suitable for regular tracking and checking
Interventions	**Intervention(s)**: glargine **Comparator(s)**: NPH **Duration of the intervention:** 6 months
Outcomes	**Primary outcome(s)**: fasting blood glucose, HbA1c, lipid profile **Secondary outcome(s)**: — **Other outcome(s)**: — **Relevant proposed outcome measures for SoF table**: none
Reason for awaiting classification	Marked as 'completed' in Clinicaltrials.gov but no publication available
Study details	**Study identifier:** IRCT201203079224N1 **Study start date**: May 2012 **Study completion date**: not reported, but marked as complete

IRCT201203079224N1 *(Continued)*	
	Responsible party/principal investigator: Dr. Aria Setoodeh, Tehran University of Medical Sciences
Official title and purpose of study	Insulin glargine + insulin aspart vs NPH insulin + regular insulin for people with type 1 diabetes
Notes	Primary investigator contacted. No reply

J-Collection	
Methods	**Allocation**: randomised **Intervention model**: cross-over **Masking**: open-label **Primary purpose**: treatment
Participants	**Condition**: T1DM **Estimated number of participants:** 20 **Inclusion criteria**: 18 years or more, T1DM, receiving basal-bolus insulin therapy **Exclusion criteria**: T2DM
Interventions	**Intervention(s)**: glargine **Comparator(s)**: detemir **Duration of the intervention:** unknown
Outcomes	**Primary outcome(s)**: continuous glucose value of 24 hours by CGM **Secondary outcome(s)**: — **Other outcome(s)**: — **Relevant proposed outcome measures for SoF table**: none
Reason for awaiting classification	Marked as 'completed' in UMIN-CTR Clinical Trial but no publication available
Study details	**Study identifier:** UMIN000001402 **Study start date**: May 2008 **Study completion date**: December 2012 **Responsible party/principal investigator:** Daisuke Tsujino, The Jikei University School of Medicine, Division of Diabetes, Metabolism and Endocrinology, Department of Internal Medicine, Japan
Official title and purpose of study	**Quote**: "We compare glucose control of Detemir to Glargine in Japanese patient with type 1 diabetes".
Notes	

Mianowska 2007

Methods	**Allocation**: randomised **Intervention model**: cross-over assignment **Masking**: open-label **Primary purpose**: treatment
Participants	**Condition**: T1DM **Estimated number of participants:** 14 **Inclusion criteria**: T1DM, 6 to 12 years, unsatisfactory glycaemic control defined as the presence of at least one of the following: (i) mean HbA1c from the preceding 6 months > 7.5% or (ii) large daily blood glucose excursions (from < 3.1 mmol/L to > 13.9 mmol/L) or (iii) strong dawn phenomenon (without an extra insulin injection at 3.00-4.00 a.m. and most blood glucose measurements before breakfast > 8.9 mmol/L) **Exclusion criteria**: inadequate results of baseline laboratory tests and clinical remission (total daily insulin dose < 0.3 U/kg/day with HbA1c < 6.5%)
Interventions	**Intervention(s)**: glargine **Comparator(s)**: NPH **Duration of the intervention:** 6 months
Outcomes	**Primary outcome(s)**: — **Secondary outcome(s)**: — **Other outcome(s)**: HbA1c, hypoglycaemia, ketoacidosis, glucose, weight, insulin dose **Relevant proposed outcome measures for SoF table**: hypoglycaemia
Reason for awaiting classification	Study was published - no data before cross-over reported
Study details	**Study identifier:** — **Study start date**: — **Study completion date**: — (but publication from 2007) **Responsible party/principal investigator**: Dr. Mianowska, Klinika Chorób Dzieci, Katedry Pediatrii UM, Poland
Official title and purpose of study	**Quote**: "The aim of this prospective cross-over study was to compare glycemic control on NPH insulin (NPH) and on glargine in unsatisfactorily controlled type 1 diabetic prepubertal children."
Notes	No severe hypoglycaemia or ketoacidosis occurred during the trial.

NCT00564018

Methods	**Allocation**: randomised **Intervention model**: parallel-group assignment **Masking**: open-label

NCT00564018 *(Continued)*

	Primary purpose: treatment
Participants	**Condition**: T1DM **Estimated number of participants:** 33 **Inclusion criteria:** newly diagnosed T1DM within 1 week of diagnosis; age 6 to 18 years **Exclusion criteria**: actual treatment with oral drugs influencing beta cell function or blood glucose levels (e.g. oral hypoglycaemic agents); actual treatment with drugs influencing insulin sensitivity (e.g. metformin or systemic steroids); significant concomitant disease likely to interfere with glucose metabolism (children with active bacterial infections at the time of diagnosis must be cured prior to entry); expected poor compliance; pregnancy; any other condition that by the judgement of the investigator may be potentially harmful to the patients
Interventions	**Intervention(s)**: detemir **Comparator (1)**: glargine **Comparator (2)**: NPH **Duration of the intervention:** planned to 1 year (but terminated early - unknown when)
Outcomes	**Primary outcome(s)**: C-peptide **Secondary outcome(s)**: HbA1c **Other outcome(s)**: adverse events **Relevant proposed outcome measures for SoF table**: serious adverse events
Reason for awaiting classification	Marked as terminated early - the duration of the trial was not reported prior to termination
Study details	**Study identifier:** NCT00564018; UTSW-052006-056 **Study start date**: September 2006 **Study completion date**: April 2011 **Responsible party/principal investigator**: Soumya Adhikari, University of Texas Southwestern Medical Center, USA
Official title and purpose of study	**Quote**: "To determine whether using a long-acting insulin analog at the time of diagnosis, instead of intermediate-acting insulin, affects the rate of loss of the body's ability to make insulin in children with newly diagnosed type 1 diabetes."
Notes	

Sherif 2014

Methods	**Allocation**:randomised **Intervention model**: parallel-group assignment **Masking**:open-label **Primary purpose**: treatment
Participants	**Condition**: T1DM

Sherif 2014 *(Continued)*

	Estimated number of participants: 100 **Inclusion criteria**: T1DM, age 3 to 8 years **Exclusion criteria**: —
Interventions	**Intervention(s)**: glargine **Comparator(s)**: NPH **Duration of the intervention:** 6 months
Outcomes	**Primary outcome(s)**: — **Secondary outcome(s)**: — **Other outcome(s)**: glycaemic control, frequency of hypoglycaemia, quality of life and serum level of C-reactive protein as an inflammatory marker **Relevant proposed outcome measures for SoF table**: hypoglycaemia, health-related quality of life
Reason for awaiting classification	Abstract of trial available from ISPAD 2014 conference. No full text identified
Study details	**Study identifier:** — **Study start date**: — **Study completion date**: — **Responsible party/principal investigator**: — (first author of abstract is EM Sherif, Ain Shams University, Pediatric Department, Cairo, Egypt)
Official title and purpose of study	**Quote**: "To compare the efficacy and safety of insulin glargine with NPH insulin in children with type 1 diabetes mellitus (T1DM) below years old regarding glycemic control, frequency of hypoglycemia, quality of life and serum level of hsC-reactive protein (C-RP) as an inflammatory marker"
Notes	No contact information could be retrieved. Published as conference abstract. Performed in Egypt. Reported in abstract that quality of life improved in all children receiving insulin glargine but not with NPH insulin (no other data provided). Frequency of severe and nocturnal hypoglycaemia was lower with insulin glargine (no other data provided). HbA1c at the end of the study was 6.6% (SD 0.5) for the insulin glargine group versus 7.4% (SD 0.7) for the NPH insulin group

UMIN000020521

Methods	**Allocation**: randomised **Intervention model**: parallel-group **Masking**: open-label **Primary purpose**: treatment
Participants	**Condition**: diabetes (not specified if T1DM or T2DM) **Estimated number of participants:** 100 **Inclusion criteria**: T1DM, HbA1c more than 8.0%, already using insulin

UMIN000020521 *(Continued)*

	Exclusion criteria: hypoglycaemic risk, serious heart trouble, severe hepatic dysfunction, severe renal dysfunction, internal secretion disease, steroids
Interventions	**Intervention(s)**: degludec **Comparator(1)**: glargine **Comparator (2):** continuing basal insulin treatment **Duration of the intervention:** 24 weeks
Outcomes	**Primary outcome(s)**: change in HbA1c, body weight, the custom-built Diabetes Treatment Satisfaction questionnaire result and adverse events including hypoglycaemia **Secondary outcome(s)**: achievement rate of HbA1c < 7.0% and < 8.0%; fasting blood glucose; glycaemic variability by SMBG; change in insulin dose **Other outcome(s)**: — **Relevant proposed outcome measures for SoF table**: hypoglycaemia, adverse events
Reason for awaiting classification	Marked as 'completed' in UMIN000020521 but no publication or results available
Study details	**Study identifier:** UMIN000020521 **Study start date**: January 2016 **Study completion date**: July 2019 **Responsible party/principal investigator**: Koichiro Yasuda, Osaka Saiseikai Noe Hospital, Japan
Official title and purpose of study	The efficacy and the safety of the new long-acting insulin in patient with diabetes **Quote**: "To compare a new long-acting insulin with existing diabetes therapeutic drug for efficacy and safety in diabetes"
Notes	

UMIN000021046

Methods	**Allocation**: cluster-randomised **Intervention model**: parallel-group assignment **Masking**: open-label **Primary purpose**: treatment
Participants	**Condition**: T1DM and T2DM **Estimated number of participants:** 200 **Inclusion criteria**: 20 years or more, diabetes receiving basal-bolus insulin therapy in outpatients for > 4 months prior to screening; if T2DM then a duration of a disease more than 12 months; available for self-monitoring of blood glucose **Exclusion criteria**: hypersensitivity to insulin; severe ketosis, diabetic coma or formerly comatose; severe renal dysfunction including patients needing haemodialysis or peritoneal dialysis; pre or

UMIN000021046 *(Continued)*	
	proliferative retinopathy, including vitreous haemorrhage risk; serious infection; perioperative period; serious trauma; pregnancy or possible pregnancy
Interventions	**Intervention(s)**: degludec **Comparator(s)**: another long acting insulin analogue **Duration of the intervention:** 24 weeks
Outcomes	**Primary outcome(s)**: change in HbA1c **Secondary outcome(s)**: hypoglycaemia, glucose levels, diabetes treatment satisfaction **Other outcome(s)**: — **Relevant proposed outcome measures for SoF table**: hypoglycaemia
Reason for awaiting classification	Marked as 'completed' in UMIN-CTR Clinical Trial but no publication available
Study details	**Study identifier:** UMIN000021046 **Study start date**: April 2013 **Study completion date**: February 2015 **Responsible party/principal investigator**: Tomoyasu Fukui, Department of Medicine, Division of Diabetes, Metabolism and Endocrinology, Showa University School of Medicine, Japan
Official title and purpose of study	Showa University examines the effects of insulin degludec **Quote**: "To compare glucose lowering effect of insulin degludec to conventional basal insulin analogue in Japanese patients with type 1 and type 2 diabetes in basal-bolus treatment"
Notes	Combines people with T1DM and T2DM - unknown if separate data might be available. Not specified which other long-acting insulin analogue was applied in the comparator arm

— denotes not reported
a.m.: ante meridiem
BAS: basal analog study
BMI: body mass index
CGM: continuous glucose monitoring
CGMS: continuous glucose monitoring system
DM: diabetes mellitus
EudraCT: European Union Drug Regulating Authorities Clinical Trials Database
FGM: flash glucose monitoring
GAD: glutamic acid decarboxylase
GH: growth hormone
HbA1c: glycosylated haemoglobin A1c
HypoDeg: insulin degludec and symptomatic nocturnal hypoglycaemia study
IA2: islet tyrosine phosphatase 2
IDeg: insulin degludec
IGF-1: insulin-Like Growth Factor 1
IGla: insulin glargine
INEOX: impact on the oxidative stress of the different analogues of insulin in people with type 1 diabetes study
ISPAD: International Society for Pediatric and Adolescent Diabetes
NPH: neutral protamine Hagedorn
NYHA: New York Heart Association
pH: potentia hydrogenii
QT: time from the start of the Q wave to the end of the T wave (recorded by electrocardiogram)
SD: standard deviation

SMBG: self-monitoring of blood glucose
SoF: Summary of Findings
T1DM: type 1 diabetes mellitus
T2DM: type 2 diabetes mellitus
USA: United States of America

RISK OF BIAS

Legend: Low risk of bias | High risk of bias | Some concerns

Risk of bias for analysis 1.1 All-cause mortality

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.1.1 Adults						
Bartley 2008	✓	✓	✓	✓	✓	✓
Kobayashi 2007	✓	✓	✓	✓	✓	✓
NCT00595374	✓	✓	✓	✓	✓	✓
Russell-Jones 2004	✓	✓	✓	✓	✓	✓
Standl 2004	✓	✓	✓	✓	✓	✓
Vague 2003	✓	✓	✓	✓	✓	✓
Subgroup 1.1.2 Children						
NCT00605137	✓	✓	✓	✓	✓	✓
Robertson 2007	✓	✓	✓	✓	✓	✓
Thalange 2013	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.3 Severe hypoglycaemia

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.3.1 Adults						
Bartley 2008	✓	✓	✓	✓	✓	✓
Kobayashi 2007	✓	✓	✓	✓	✓	✓
Russell-Jones 2004	✓	✓	✓	✓	✓	✓
Standl 2004	✓	✓	✓	✓	✓	✓
Vague 2003	✓	✓	✓	✓	✓	✓
Subgroup 1.3.2 Children						
NCT00605137	✓	✓	✓	✓	✓	✓
Robertson 2007	✓	✓	✓	✓	✓	✓
Thalange 2013	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.6 Cardiovascular mortality

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.6.1 Adults						
Bartley 2008	✓	✓	✓	✓	✓	✓
Kobayashi 2007	✓	✓	✓	✓	✓	✓
NCT00595374	✓	✓	✓	✓	✓	✓
Russell-Jones 2004	✓	✓	✓	✓	✓	✓

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Standl 2004	✓	✓	✓	✓	✓	✓
Vague 2003	✓	✓	✓	✓	✓	✓
Subgroup 1.6.2 Children						
NCT00605137	✓	✓	✓	✓	✓	✓
Robertson 2007	✓	✓	✓	✓	✓	✓
Thalange 2013	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.7 Non-fatal myocardial infarction

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Bartley 2008	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.8 Serious adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.8.1 Adults						
Bartley 2008	✓	✓	✓	✓	✓	✓
Kobayashi 2007	✓	✓	✓	✓	✓	✓
NCT00595374	✓	✓	✓	✓	✓	✓

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Russell-Jones 2004	✓	✓	✓	✓	✓	✓
Standl 2004	✓	✓	✓	✓	✓	✓
Vague 2003	✓	✓	✓	✓	✓	✓
Subgroup 1.8.2 Children						
NCT00605137	✓	✓	✓	✓	✓	✓
Robertson 2007	✓	✓	✓	✓	✓	✓
Thalange 2013	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.10 Diabetic ketoacidosis

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.10.1 Adults						
Bartley 2008	✓	✓	✓	✓	✓	✓
Kobayashi 2007	✓	✓	✓	✓	✓	✓
Vague 2003	✓	✓	✓	✓	✓	✓
Subgroup 1.10.2 Children						
NCT00605137	✓	✓	✓	✓	✓	✓
Robertson 2007	✓	✓	✓	✓	✓	✓
Thalange 2013	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.12 Non-serious adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.12.1 Adults						
Bartley 2008	✓	✓	✓	~	✓	~
Kobayashi 2007	✓	✓	✓	~	✓	~
NCT00595374	✓	✓	✓	~	✓	~
Russell-Jones 2004	✓	✓	✓	~	✓	~
Standl 2004	✓	✓	✓	~	✓	~
Vague 2003	✓	✓	✓	~	✓	~
Subgroup 1.12.2 Children						
NCT00605137	✓	✓	✓	~	✓	~
Robertson 2007	✓	✓	✓	~	✓	~
Thalange 2013	✓	✓	✓	~	✓	~

Risk of bias for analysis 1.18 Severe nocturnal hypoglycaemia

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.18.1 Adults						
Bartley 2008	✓	✓	✓	✓	✓	✓
Russell-Jones 2004	✓	✓	✓	✓	✓	✓
Standl 2004	✓	✓	✓	✓	✓	✓

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Vague 2003	✓	✓	✓	✓	✓	✓
Subgroup 1.18.2 Children						
NCT00605137	✓	✓	✓	✓	✓	✓
Robertson 2007	✓	✓	✓	✓	✓	✓
Thalange 2013	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.22 Severe nocturnal hypoglycaemia (published vs. unpublished data)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.22.1 Published						
Bartley 2008	✓	✓	✓	✓	✓	✓
Robertson 2007	✓	✓	✓	✓	✓	✓
Russell-Jones 2004	✓	✓	✓	✓	✓	✓
Thalange 2013	✓	✓	✓	✓	✓	✓
Vague 2003	✓	✓	✓	✓	✓	✓
Subgroup 1.22.2 Unpublished						
NCT00605137	✓	✓	✓	✓	✓	✓
Standl 2004	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.24 Mild/moderate hypoglycaemia

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.24.1 Adults						
Bartley 2008	✓	✓	✓	~	✓	~
Kobayashi 2007	✓	✓	✓	~	✓	~
Russell-Jones 2004	✓	✓	✓	~	✓	~
Standl 2004	✓	✓	✓	~	✓	~
Vague 2003	✓	✓	✓	~	✓	~
Subgroup 1.24.2 Children						
NCT00605137	✓	✓	✓	~	✓	~
Robertson 2007	✓	✓	✓	~	✓	~
Thalange 2013	✓	✓	✓	~	✓	~

Risk of bias for analysis 1.26 HbA1c

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.26.1 Adults						
Bartley 2008	✓	✓	✓	✓	✓	✓
Kobayashi 2007	✓	✓	✓	✓	✓	✓
Russell-Jones 2004	✓	✓	✓	✓	✓	✓
Standl 2004	✓	✓	✓	✓	✓	✓

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Vague 2003	✓	✓	✓	✓	✓	✓
Subgroup 1.26.2 Children						
NCT00605137	✓	✓	✓	✓	✓	✓
Robertson 2007	✓	✓	✓	✓	✓	✓
Thalange 2013	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.1 All-cause mortality

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.1.1 Adults						
Fulcher 2005	✓	✓	✓	✓	✓	✓
Home 2005	✓	✓	✓	✓	✓	✓
Porcellati 2004	✓	✓	✓	✓	~	~
Ratner 2000	✓	✓	✓	✓	✓	✓
Subgroup 2.1.2 Children						
Chase 2008	✓	✓	✓	✓	✓	✓
Liu 2016	✓	✓	✓	✓	✓	✓
PRESCHOOL	✓	✓	✓	✓	✓	✓
Schober 2002	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.2 Health-realted quality of life

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Home 2005	✓	✓	✓	~	✓	~
Ratner 2000	✓	✓	✓	~	✓	~

Risk of bias for analysis 2.3 Severe hypoglycaemia

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.3.1 Adults						
Bolli 2009	~	✓	✓	✓	✓	~
Fulcher 2005	✓	✓	✓	✓	✓	✓
Home 2005	✓	✓	✓	✓	✓	✓
Porcellati 2004	✓	✓	✓	✓	~	~
Ratner 2000	✓	✓	✓	✓	✓	✓
Subgroup 2.3.2 Children						
Chase 2008	✓	✓	✓	✓	✓	✓
Liu 2016	✓	✓	✓	✓	✓	✓
PRESCHOOL	✓	✓	✓	✓	✓	✓
Schober 2002	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.6 Cardiovascular mortality

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.6.1 Adults						
Fulcher 2005	✓	✓	✓	✓	✓	✓
Home 2005	✓	✓	✓	✓	✓	✓
Porcellati 2004	✓	✓	✓	✓	~	~
Ratner 2000	✓	✓	✓	✓	✓	✓
Subgroup 2.6.2 Children						
Chase 2008	✓	✓	✓	✓	✓	✓
Liu 2016	✓	✓	✓	✓	✓	✓
PRESCHOOL	✓	✓	✓	✓	✓	✓
Schober 2002	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.7 Non-fatal myocardial infarction

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Home 2005	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.8 Non-fatal stroke

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Home 2005	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.9 Serious adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.9.1 Adults						
Bolli 2009	~	✓	✓	✓	✓	~
Fulcher 2005	✓	✓	✓	✓	✓	✓
Home 2005	✓	✓	✓	✓	✓	✓
Ratner 2000	✓	✓	✓	✓	✓	✓
Subgroup 2.9.2 Children						
Chase 2008	✓	✓	✓	✓	✓	✓
Liu 2016	✓	✓	✓	✓	✓	✓
PRESCHOOL	✓	✓	✓	✓	✓	✓
Schober 2002	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.11 Diabetic ketoacidosis

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.11.1 Adults						
Fulcher 2005	✓	✓	✓	✓	✓	✓
Home 2005	✓	✓	✓	✓	✓	✓
Ratner 2000	✓	✓	✓	✓	✓	✓
Subgroup 2.11.2 Children						
Chase 2008	✓	✓	✓	✓	✓	✓
Liu 2016	✓	✓	✓	✓	✓	✓
PRESCHOOL	✓	✓	✓	✓	✓	✓
Schober 2002	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.13 Non-serious adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.13.1 Adults						
Bolli 2009	~	✓	✓	~	✓	~
Fulcher 2005	✓	✓	✓	~	✓	~
Home 2005	✓	✓	✓	~	✓	~
Ratner 2000	✓	✓	✓	~	✓	~
Subgroup 2.13.2 Children						

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Chase 2008	✓	✓	✓	~	✓	~
Liu 2016	✓	✓	✓	~	✓	~
PRESCHOOL	✓	✓	✓	~	✓	~
Schober 2002	✓	✓	✓	~	✓	~

Risk of bias for analysis 2.19 Severe nocturnal hypoglycaemia

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.19.1 Adults						
Fulcher 2005	✓	✓	✓	✓	✓	✓
Home 2005	✓	✓	✓	✓	✓	✓
Ratner 2000	✓	✓	✓	✓	✓	✓
Subgroup 2.19.2 Children						
Chase 2008	✓	✓	✓	✓	✓	✓
PRESCHOOL	✓	✓	✓	✓	✓	✓
Schober 2002	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.22 Mild/moderate hypoglycaemia

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.22.1 Adults						
Fulcher 2005	✓	✓	✓	~	✓	~
Home 2005	✓	✓	✓	~	✓	~
Ratner 2000	✓	✓	✓	~	✓	~
Subgroup 2.22.2 Children						
Chase 2008	✓	✓	✓	~	✓	~
Liu 2016	✓	✓	✓	~	✓	~
PRESCHOOL	✓	✓	✓	~	✓	~
Schober 2002	✓	✓	✓	~	✓	~

Risk of bias for analysis 2.24 HbA1c

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.24.1 Adults						
Bolli 2009	~	✓	✓	✓	✓	~
Fulcher 2005	✓	✓	✓	✓	✓	✓
Home 2005	✓	✓	✓	✓	✓	✓
Porcellati 2004	✓	✓	✓	✓	~	~
Ratner 2000	✓	✓	✓	✓	✓	✓

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.24.2 Children						
Chase 2008	✓	✓	✓	✓	✓	✓
Liu 2016	✓	✓	✓	✓	✓	✓
PRESCHOOL	✓	✓	✓	✓	✓	✓
Schober 2002	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 3.1 All-cause mortality

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Heller 2009	✓	✓	✓	✓	✓	✓
Pieber 2007	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 3.2 Severe hypoglycaemia

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Heller 2009	✓	✓	✓	✓	✓	✓
Pieber 2007	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 3.5 Cardiovascular mortality

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Heller 2009	✓	✓	✓	✓	✓	✓
Pieber 2007	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 3.6 Non-fatal myocardial infarction

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Heller 2009	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 3.7 Non-fatal stroke

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Heller 2009	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 3.8 Serious adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Heller 2009	✓	✓	✓	✓	✓	✓
Pieber 2007	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 3.9 Diabetic ketoacidosis

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Heller 2009	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 3.10 Non-serious adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Heller 2009	✓	✓	✓	~	✓	~
Pieber 2007	✓	✓	✓	~	✓	~

Risk of bias for analysis 3.16 Severe nocturnal hypoglycaemia

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.16.1 Published						
Pieber 2007	✓	✓	✓	✓	✓	✓
Subgroup 3.16.2 Unpublished						
Heller 2009	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 3.17 Mild/moderate hypoglycaemia

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.17.1 Published						
Pieber 2007	✓	✓	✓	~	✓	~
Subgroup 3.17.2 Unpublished						
Heller 2009	✓	✓	✓	~	✓	~

Risk of bias for analysis 3.18 HbA1c

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Heller 2009	✓	✓	✓	✓	✓	✓
Pieber 2007	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 4.1 All-cause mortality

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 4.1.1 Adults						
Davies 2014	✓	✓	✓	✓	✓	✓
Subgroup 4.1.2 Children						
BEGIN Young	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 4.2 Health-related quality of life

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 4.2.1 Physical health score						
Davies 2014	✓	✓	✓	~	✓	~
Subgroup 4.2.2 Mental health score						
Davies 2014	✓	✓	✓	~	✓	~

Risk of bias for analysis 4.3 Severe hypoglycaemia

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 4.3.1 Adults						
Davies 2014	✓	✓	✓	✓	✓	✓
Subgroup 4.3.2 Children						
BEGIN Young	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 4.5 Cardiovascular mortality

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 4.5.1 Adults						
Davies 2014	✓	✓	✓	✓	✓	✓
Subgroup 4.5.2 Children						
BEGIN Young	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 4.6 Non-fatal myocardial infarction

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Davies 2014	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 4.7 Non-fatal stroke

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Davies 2014	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 4.8 End stage renal disease

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Davies 2014	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 4.9 Blindness

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Davies 2014	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 4.10 Serious adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 4.10.1 Adults						
Davies 2014	✓	✓	✓	✓	✓	✓
Subgroup 4.10.2 Children						
BEGIN Young	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 4.11 Diabetic ketoacidosis

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 4.11.1 Adults						
Davies 2014	✓	✓	✓	✓	✓	✓
Subgroup 4.11.2 Children						
BEGIN Young	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 4.12 Non-serious adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 4.12.1 Adults						
Davies 2014	✓	✓	✓	~	✓	~
Subgroup 4.12.2 Children						
BEGIN Young	✓	✓	✓	~	✓	~

Risk of bias for analysis 4.18 Severe nocturnal hypoglycaemia

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 4.18.1 Adults						
Davies 2014	✓	✓	✓	✓	✓	✓
Subgroup 4.18.2 Children						
BEGIN Young	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 4.19 Mild/moderate hypoglycaemia

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 4.19.1 Adults						
Davies 2014	✓	✓	✓	~	✓	~
Subgroup 4.19.2 Children						
BEGIN Young	✓	✓	✓	~	✓	~

Risk of bias for analysis 4.20 HbA1c

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 4.20.1 Adults						
Davies 2014	✓	✓	✓	✓	✓	✓
Subgroup 4.20.2 Children						

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
BEGIN Young	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 5.1 All-cause mortality

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
BEGIN Basal-Bolus Type 1	✓	✓	✓	✓	✓	✓
BEGIN Flex T1	✓	✓	✓	✓	✓	✓
Urakami 2017	~	~	✓	✓	~	~

Risk of bias for analysis 5.3 Health-related quality of life (physical health)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 5.3.1 Published						
BEGIN Basal-Bolus Type 1	✓	✓	✓	~	✓	~
Subgroup 5.3.2 Unpublished						
SWITCH 1	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 5.4 Health-related quality of life (mental health)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 5.4.1 Published						
BEGIN Basal-Bolus Type 1	✓	✓	✓	~	✓	~
Subgroup 5.4.2 Unpublished						
SWITCH 1	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 5.5 Severe hypoglycaemia

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 5.5.1 Adults						
BEGIN Basal-Bolus Type 1	✓	✓	✓	✓	✓	✓
BEGIN Flex T1	✓	✓	✓	✓	✓	✓
Subgroup 5.5.2 Children						
Urakami 2017	~	~	✓	✓	~	~

Risk of bias for analysis 5.7 Cardiovascular mortality

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 5.7.1 Adults						
BEGIN Basal-Bolus Type 1	✓	✓	✓	✓	✓	✓
BEGIN Flex T1	✓	✓	✓	✓	✓	✓

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 5.7.2 Children						
Urakami 2017	~	~	✓	✓	~	~

Risk of bias for analysis 5.8 Non-fatal myocardial infarction

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 5.8.1 Adults						
BEGIN Basal-Bolus Type 1	✓	✓	✓	✓	✓	✓
BEGIN Flex T1	✓	✓	✓	✓	✓	✓
Subgroup 5.8.2 Children						
Urakami 2017	~	~	✓	✓	~	~

Risk of bias for analysis 5.9 Non-fatal stroke

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
BEGIN Basal-Bolus Type 1	✓	✓	✓	✓	✓	✓
BEGIN Flex T1	✓	✓	✓	✓	✓	✓
Urakami 2017	~	~	✓	✓	~	~

Risk of bias for analysis 5.10 Serious adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 5.10.1 Adults						
BEGIN Basal-Bolus Type 1	✓	✓	✓	✓	✓	✓
BEGIN Flex T1	✓	✓	✓	✓	✓	✓
Subgroup 5.10.2 Children						
Urakami 2017	~	~	✓	✓	~	~

Risk of bias for analysis 5.11 Diabetic ketoacidosis

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 5.11.1 Adults						
BEGIN Basal-Bolus Type 1	✓	✓	✓	✓	✓	✓
BEGIN Flex T1	✓	✓	✓	✓	✓	✓
Subgroup 5.11.2 Children						
Urakami 2017	~	~	✓	✓	~	~

Risk of bias for analysis 5.13 Non-serious adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 5.13.1 Adults						
BEGIN Basal-Bolus Type 1	✓	✓	✓	~	✓	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
BEGIN Flex T1	✓	✓	✓	~	✓	~
Subgroup 5.13.2 Children						
Urakami 2017	~	~	✓	~	~	~

Risk of bias for analysis 5.19 Severe nocturnal hypoglycaemia

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
BEGIN Basal-Bolus Type 1	✓	✓	✓	✓	✓	✓
BEGIN Flex T1	✓	✓	✓	✓	✓	✓
Urakami 2017	~	~	✓	✓	~	~

Risk of bias for analysis 5.20 Mild/moderate hypoglycaemia

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 5.20.1 Adults						
BEGIN Basal-Bolus Type 1	✓	✓	✓	~	✓	~
BEGIN Flex T1	✓	✓	✓	~	✓	~
Subgroup 5.20.2 Children						
Urakami 2017	~	~	✓	~	~	~

Risk of bias for analysis 5.21 HbA1c

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 5.21.1 Adults						
BEGIN Basal-Bolus Type 1	✓	✓	✓	✓	✓	✓
BEGIN Flex T1	✓	✓	✓	✓	✓	✓
SWITCH 1	✓	✓	✓	✓	✓	✓
Subgroup 5.21.2 Children						
Urakami 2017	~	~	✓	✓	~	~

DATA AND ANALYSES

Comparison 1. Insulin detemir versus NPH insulin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 All-cause mortality	9	3334	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.97 [0.79, 31.38]
1.1.1 Adults	6	2558	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.97 [0.79, 31.38]
1.1.2 Children	3	776	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.2 All-cause mortality (published vs. unpublished data)	9	3334	Risk Ratio (M-H, Random, 95% CI)	3.64 [0.42, 31.40]
1.2.1 Published	2	842	Risk Ratio (M-H, Random, 95% CI)	4.47 [0.24, 82.58]
1.2.2 Unpublished	7	2492	Risk Ratio (M-H, Random, 95% CI)	2.85 [0.12, 69.55]
1.3 Severe hypoglycaemia	8	3219	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.52, 0.92]
1.3.1 Adults	5	2443	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.49, 1.03]
1.3.2 Children	3	776	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.30, 1.23]

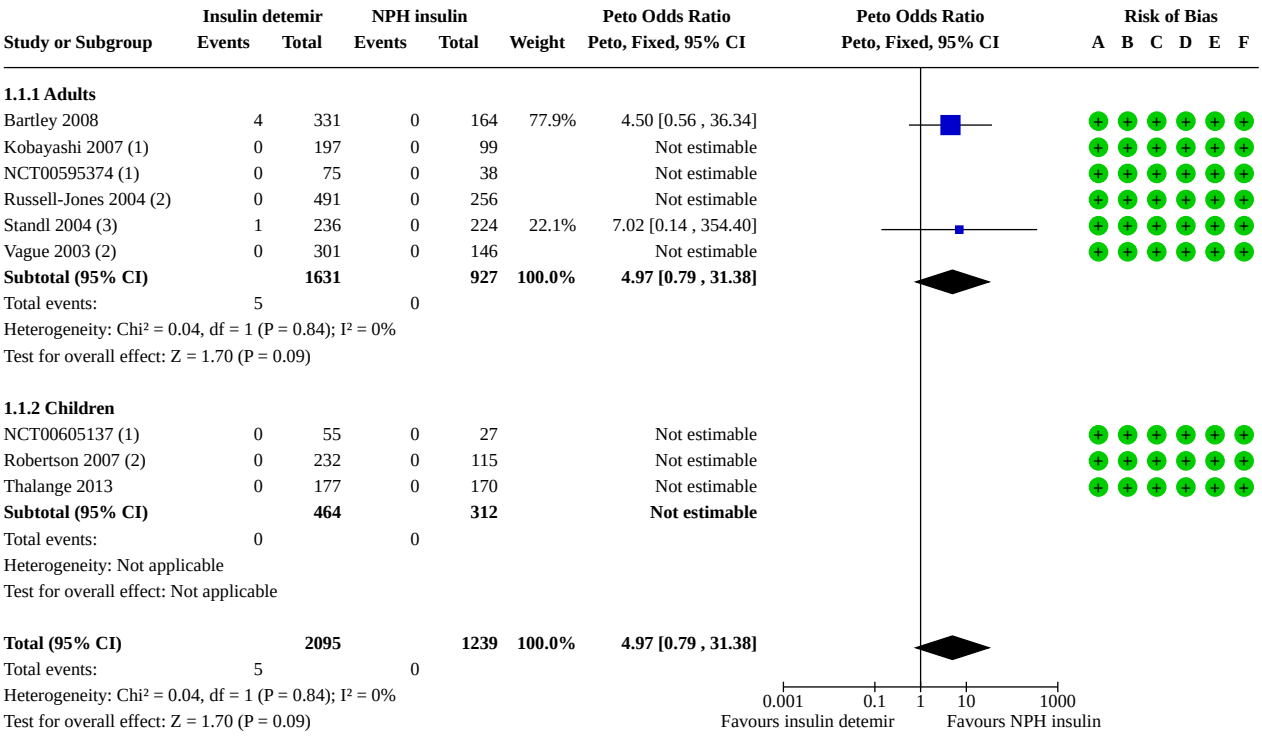
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4 Severe hypoglycaemia (published vs. unpublished data)	8	3175	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.51, 0.93]
1.4.1 Published	6	2677	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.50, 0.78]
1.4.2 Unpublished	2	498	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.77, 2.62]
1.5 Hypoglycaemia reported as a serious adverse event	8	3219	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.51, 1.71]
1.5.1 Adults	5	2443	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.48, 1.86]
1.5.2 Children	3	776	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.16, 5.57]
1.6 Cardiovascular mortality	9		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.6.1 Adults	6		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.6.2 Children	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.7 Non-fatal myocardial infarction	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.8 Serious adverse events	9	3332	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.75, 1.21]
1.8.1 Adults	6	2556	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.73, 1.28]
1.8.2 Children	3	776	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.56, 1.43]
1.9 Serious adverse events (published vs. unpublished data)	9	3332	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.75, 1.21]
1.9.1 Published	2	641	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.40, 1.09]
1.9.2 Unpublished	7	2691	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.80, 1.39]
1.10 Diabetic ketoacidosis	6	2012	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.36, 1.76]
1.10.1 Adults	3	1236	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.24, 2.92]
1.10.2 Children	3	776	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.27, 2.15]
1.11 Diabetic ketoacidosis (published vs. unpublished data)	6	2012	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.36, 1.76]
1.11.1 Published data	2	694	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.27, 2.52]
1.11.2 Unpublished data	4	1318	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.25, 2.38]
1.12 Non-serious adverse events	9	3332	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.95, 1.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.12.1 Adults	6	2556	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.95, 1.03]
1.12.2 Children	3	776	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.90, 1.02]
1.13 Non-serious adverse events (published vs unpublished data)	9	3332	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.94, 1.01]
1.13.1 Published data	3	1141	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.90, 1.01]
1.13.2 Unpublished data	6	2191	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.95, 1.04]
1.14 Withdrawals due to adverse events	8	3222	Risk Ratio (M-H, Random, 95% CI)	2.23 [0.98, 5.05]
1.14.1 Adults	5	2445	Risk Ratio (M-H, Random, 95% CI)	2.25 [0.94, 5.41]
1.14.2 Children	3	777	Risk Ratio (M-H, Random, 95% CI)	2.08 [0.22, 19.90]
1.15 Any nocturnal hypoglycaemia	8	3219	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.87, 0.95]
1.15.1 Adults	5	2443	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.88, 0.98]
1.15.2 Children	3	776	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.81, 0.94]
1.16 Mild nocturnal hypoglycaemia	7	3073	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.85, 0.96]
1.16.1 Adults	4	2149	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.83, 1.00]
1.16.2 Children	3	924	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.78, 1.00]
1.17 Nocturnal hypoglycaemia (symptoms)	6	2578	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.79, 0.98]
1.17.1 Adults	4	2149	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.82, 1.01]
1.17.2 Children	2	429	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.19, 1.61]
1.18 Severe nocturnal hypoglycaemia	7	2925	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.39, 1.17]
1.18.1 Adults	4	2149	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.35, 0.93]
1.18.2 Children	3	776	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.13, 3.17]
1.19 Any nocturnal hypoglycaemia (published vs. unpublished data)	8	3219	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.87, 0.95]
1.19.1 Published	6	2677	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.86, 0.95]
1.19.2 Unpublished	2	542	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.80, 1.04]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.20 Mild nocturnal hypoglycaemia (published vs. unpublished data)	7	3073	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.85, 0.96]
1.20.1 Published	4	2084	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.85, 0.98]
1.20.2 Unpublished	3	989	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.75, 1.07]
1.21 Nocturnal hypoglycaemia, symptoms only (published vs. unpublished data)	6	2578	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.79, 0.98]
1.21.1 Published	3	1589	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.81, 0.99]
1.21.2 Unpublished	3	989	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.57, 1.08]
1.22 Severe nocturnal hypoglycaemia (published vs. unpublished data)	7	2925	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.39, 1.17]
1.22.1 Published	5	2383	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.32, 1.25]
1.22.2 Unpublished	2	542	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.33, 2.45]
1.23 Nocturnal hypoglycaemia, asymptomatic (children vs. adults)	2	429	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.78, 1.18]
1.24 Mild/moderate hypoglycaemia	8	3219	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.94, 0.99]
1.24.1 Adults	5	2443	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.93, 1.02]
1.24.2 Children	3	776	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.93, 1.01]
1.25 Mild/moderate hypoglycaemia (published vs. unpublished data)	8	3219	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.94, 0.99]
1.25.1 Published	6	2677	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.93, 1.00]
1.25.2 Unpublished	2	542	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.92, 1.05]
1.26 HbA1c	8	3122	Mean Difference (IV, Random, 95% CI)	0.01 [-0.08, 0.10]
1.26.1 Adults	5	2354	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.14, 0.07]
1.26.2 Children	3	768	Mean Difference (IV, Random, 95% CI)	0.13 [-0.04, 0.31]
1.27 HbA1c (published vs. unpublished data)	8	3122	Mean Difference (IV, Random, 95% CI)	0.00 [-0.09, 0.09]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.27.1 Published	6	2624	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.13, 0.09]
1.27.2 Unpublished	2	498	Mean Difference (IV, Random, 95% CI)	0.10 [-0.08, 0.28]

Analysis 1.1. Comparison 1: Insulin detemir versus NPH insulin, Outcome 1: All-cause mortality



Footnotes

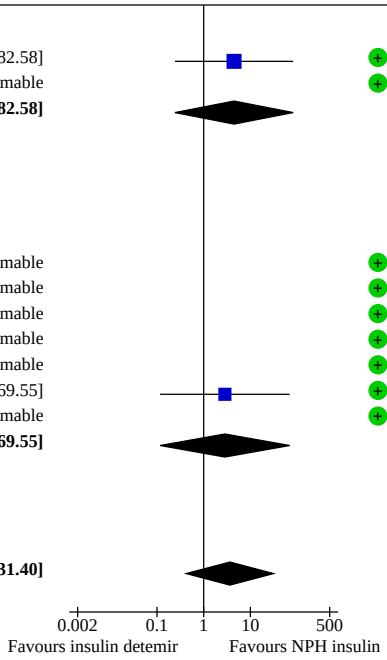
(1) Data from study synopsis
(2) Data from FDA medical review and CSR
(3) Data after 6 months intervention from FDA medical review and CSR

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: All-cause mortality
(C) Bias due to missing outcome data: All-cause mortality
(D) Bias in measurement of the outcome: All-cause mortality
(E) Bias in selection of the reported result: All-cause mortality
(F) Overall bias: All-cause mortality

Analysis 1.2. Comparison 1: Insulin detemir versus NPH insulin, Outcome 2: All-cause mortality (published vs. unpublished data)

Study or Subgroup	Insulin detemir Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Published						
Bartley 2008	4	331	0	164	54.6%	4.47 [0.24 , 82.58]
Thalange 2013	0	177	0	170		Not estimable
Subtotal (95% CI)		**508**		**334**	**54.6%**	**4.47 [0.24 , 82.58]**
Total events:	4		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.01 (P = 0.31)						
1.2.2 Unpublished						
Kobayashi 2007	0	197	0	99		Not estimable
NCT00595374	0	75	0	38		Not estimable
NCT00605137	0	55	0	27		Not estimable
Robertson 2007	0	232	0	115		Not estimable
Russell-Jones 2004	0	491	0	256		Not estimable
Standl 2004	1	236	0	224	45.4%	2.85 [0.12 , 69.55]
Vague 2003	0	301	0	146		Not estimable
Subtotal (95% CI)		**1587**		**905**	**45.4%**	**2.85 [0.12 , 69.55]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						
Total (95% CI)		**2095**		**1239**	**100.0%**	**3.64 [0.42 , 31.40]**
Total events:	5		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%						
Test for overall effect: Z = 1.18 (P = 0.24)						
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.84), I² = 0%						



Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions: All-cause mortality (published vs. unpublished data)

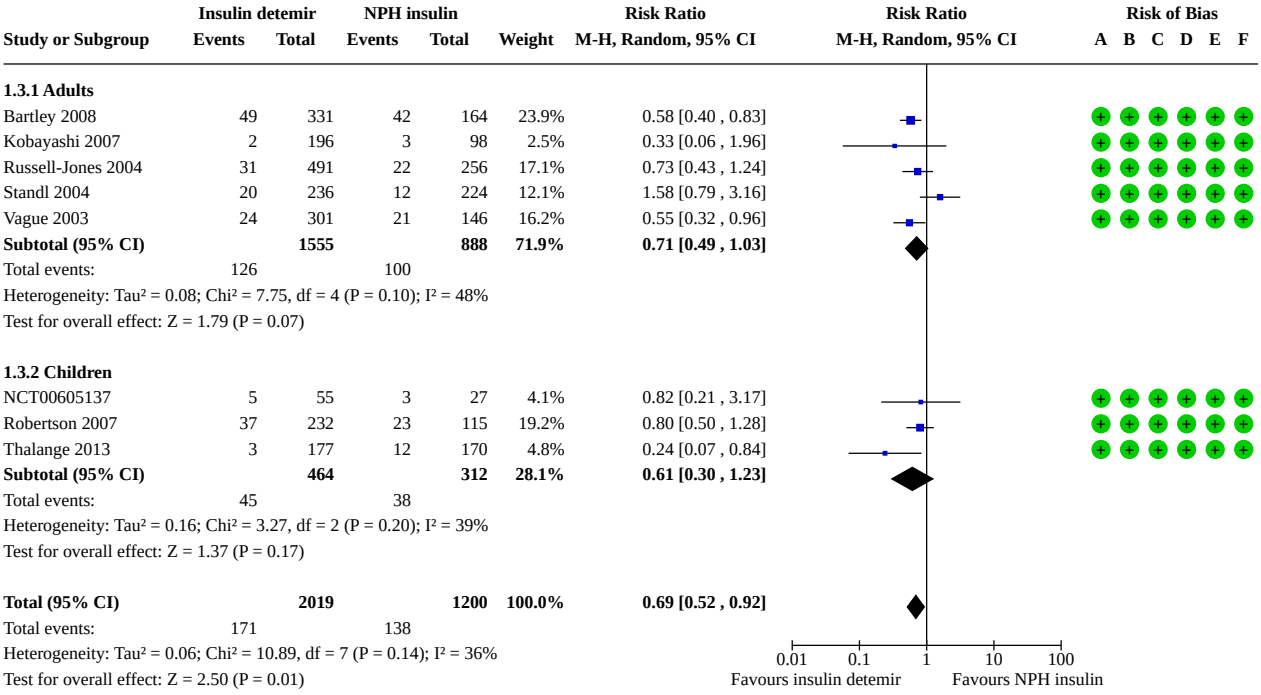
(C) Bias due to missing outcome data: All-cause mortality (published vs. unpublished data)

(D) Bias in measurement of the outcome: All-cause mortality (published vs. unpublished data)

(E) Bias in selection of the reported result: All-cause mortality (published vs. unpublished data)

(F) Overall bias: All-cause mortality (published vs. unpublished data)

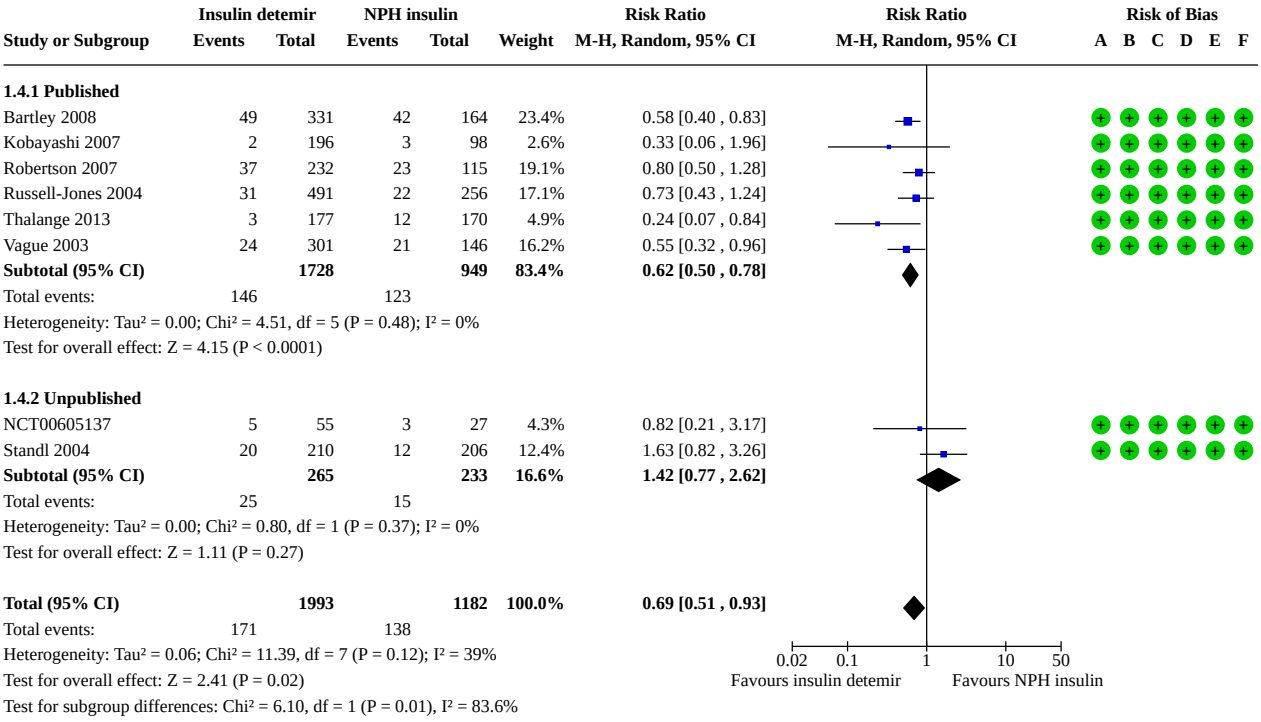
Analysis 1.3. Comparison 1: Insulin detemir versus NPH insulin, Outcome 3: Severe hypoglycaemia



Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Severe hypoglycaemia
(C) Bias due to missing outcome data: Severe hypoglycaemia
(D) Bias in measurement of the outcome: Severe hypoglycaemia
(E) Bias in selection of the reported result: Severe hypoglycaemia
(F) Overall bias: Severe hypoglycaemia

Analysis 1.4. Comparison 1: Insulin detemir versus NPH insulin, Outcome 4: Severe hypoglycaemia (published vs. unpublished data)



Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions: Severe hypoglycaemia (published vs. unpublished data)

(C) Bias due to missing outcome data: Severe hypoglycaemia (published vs. unpublished data)

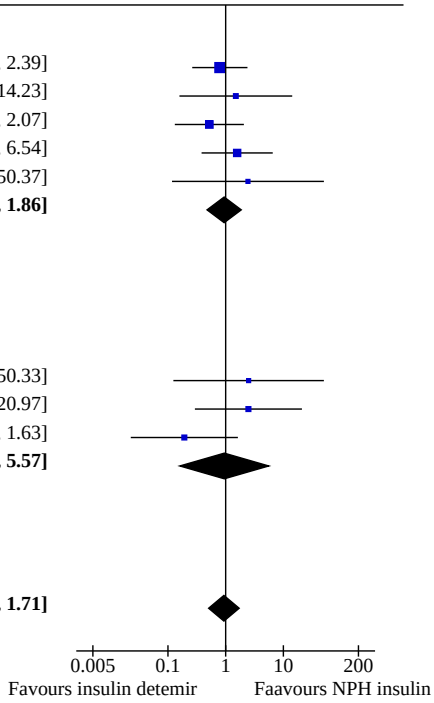
(D) Bias in measurement of the outcome: Severe hypoglycaemia (published vs. unpublished data)

(E) Bias in selection of the reported result: Severe hypoglycaemia (published vs. unpublished data)

(F) Overall bias: Severe hypoglycaemia (published vs. unpublished data)

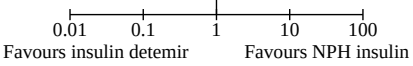
Analysis 1.5. Comparison 1: Insulin detemir versus NPH insulin, Outcome 5: Hypoglycaemia reported as a serious adverse event

Study or Subgroup	Insulin detemir Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Adults						
Bartley 2008	8	331	5	164	30.5%	0.79 [0.26 , 2.39]
Kobayashi 2007	3	196	1	98	7.3%	1.50 [0.16 , 14.23]
Russell-Jones 2004	4	491	4	256	19.5%	0.52 [0.13 , 2.07]
Standl 2004	5	236	3	224	18.4%	1.58 [0.38 , 6.54]
Vague 2003	2	301	0	146	4.0%	2.43 [0.12 , 50.37]
Subtotal (95% CI)		**1555**		**888**	**79.7%**	**0.94 [0.48 , 1.86]**
Total events:	22		13			
Heterogeneity: Tau² = 0.00; Chi² = 1.86, df = 4 (P = 0.76); I² = 0%						
Test for overall effect: Z = 0.17 (P = 0.86)						
1.5.2 Children						
NCT00605137	2	55	0	27	4.1%	2.50 [0.12 , 50.33]
Robertson 2007	5	232	1	115	8.1%	2.48 [0.29 , 20.97]
Thalange 2013	1	177	5	170	8.1%	0.19 [0.02 , 1.63]
Subtotal (95% CI)		**464**		**312**	**20.3%**	**0.95 [0.16 , 5.57]**
Total events:	8		6			
Heterogeneity: Tau² = 0.98; Chi² = 3.33, df = 2 (P = 0.19); I² = 40%						
Test for overall effect: Z = 0.06 (P = 0.95)						
Total (95% CI)		**2019**		**1200**	**100.0%**	**0.93 [0.51 , 1.71]**
Total events:	30		19			
Heterogeneity: Tau² = 0.00; Chi² = 5.18, df = 7 (P = 0.64); I² = 0%						
Test for overall effect: Z = 0.23 (P = 0.82)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 1.00), I² = 0%						



Analysis 1.6. Comparison 1: Insulin detemir versus NPH insulin, Outcome 6: Cardiovascular mortality

Study or Subgroup	Insulin detemir Events	Total	NPH insulin Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
1.6.1 Adults							
Bartley 2008	1	331	0	164	1.49 [0.06 , 36.40]		+ + + + + +
Kobayashi 2007	0	197	0	99	Not estimable		+ + + + + +
NCT00595374	0	75	0	38	Not estimable		+ + + + + +
Russell-Jones 2004	0	491	0	256	Not estimable		+ + + + + +
Standl 2004 (1)	0	210	0	206	Not estimable		+ + + + + +
Vague 2003	0	301	0	146	Not estimable		+ + + + + +
1.6.2 Children							
NCT00605137	0	55	0	27	Not estimable		+ + + + + +
Robertson 2007	0	232	0	115	Not estimable		+ + + + + +
Thalange 2013	0	177	0	170	Not estimable		+ + + + + +



Footnotes

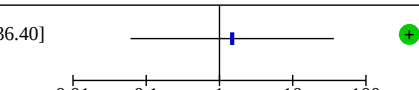
(1) Data after 6 months intervention

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Cardiovascular mortality
(C) Bias due to missing outcome data: Cardiovascular mortality
(D) Bias in measurement of the outcome: Cardiovascular mortality
(E) Bias in selection of the reported result: Cardiovascular mortality
(F) Overall bias: Cardiovascular mortality

Analysis 1.7. Comparison 1: Insulin detemir versus NPH insulin, Outcome 7: Non-fatal myocardial infarction

Study or Subgroup	Insulin detemir Events	Total	NPH insulin Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Bartley 2008	1	331	0	164	1.49 [0.06 , 36.40]		+ + + + + +
Test for subgroup differences: Not applicable							

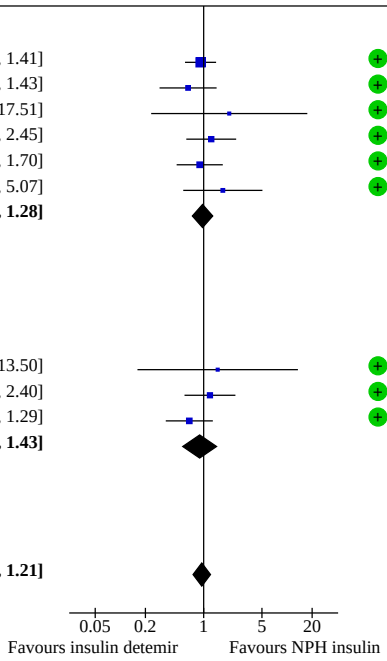


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Non-fatal myocardial infarction
(C) Bias due to missing outcome data: Non-fatal myocardial infarction
(D) Bias in measurement of the outcome: Non-fatal myocardial infarction
(E) Bias in selection of the reported result: Non-fatal myocardial infarction
(F) Overall bias: Non-fatal myocardial infarction

Analysis 1.8. Comparison 1: Insulin detemir versus NPH insulin, Outcome 8: Serious adverse events

Study or Subgroup	Insulin detemir Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 Adults						
Bartley 2008	50	331	27	164	31.5%	0.92 [0.60 , 1.41]
Kobayashi 2007	13	196	10	98	9.3%	0.65 [0.30 , 1.43]
NCT00595374	4	75	1	38	1.2%	2.03 [0.23 , 17.51]
Russell-Jones 2004	26	491	11	256	12.2%	1.23 [0.62 , 2.45]
Standl 2004	17	236	18	224	14.3%	0.90 [0.47 , 1.70]
Vague 2003	14	301	4	146	4.8%	1.70 [0.57 , 5.07]
Subtotal (95% CI)		**1630**		**926**	**73.4%**	**0.97 [0.73 , 1.28]**
Total events:	124		71			
Heterogeneity: Tau² = 0.00; Chi² = 3.05, df = 5 (P = 0.69); I² = 0%						
Test for overall effect: Z = 0.22 (P = 0.83)						
1.8.2 Children						
NCT00605137	3	55	1	27	1.2%	1.47 [0.16 , 13.50]
Robertson 2007	24	232	10	115	11.7%	1.19 [0.59 , 2.40]
Thalange 2013	14	177	20	170	13.7%	0.67 [0.35 , 1.29]
Subtotal (95% CI)		**464**		**312**	**26.6%**	**0.89 [0.56 , 1.43]**
Total events:	41		31			
Heterogeneity: Tau² = 0.00; Chi² = 1.57, df = 2 (P = 0.46); I² = 0%						
Test for overall effect: Z = 0.47 (P = 0.64)						
Total (95% CI)		**2094**		**1238**	**100.0%**	**0.95 [0.75 , 1.21]**
Total events:	165		102			
Heterogeneity: Tau² = 0.00; Chi² = 4.70, df = 8 (P = 0.79); I² = 0%						
Test for overall effect: Z = 0.43 (P = 0.67)						
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.77), I² = 0%						

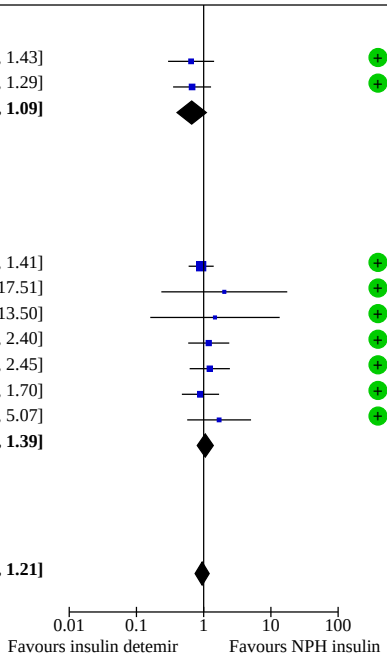


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Serious adverse events
(C) Bias due to missing outcome data: Serious adverse events
(D) Bias in measurement of the outcome: Serious adverse events
(E) Bias in selection of the reported result: Serious adverse events
(F) Overall bias: Serious adverse events

Analysis 1.9. Comparison 1: Insulin detemir versus NPH insulin, Outcome 9: Serious adverse events (published vs. unpublished data)

Study or Subgroup	Insulin detemir Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
1.9.1 Published								
Kobayashi 2007	13	196	10	98	9.3%	0.65 [0.30 , 1.43]		+ + + + + +
Thalange 2013	14	177	20	170	13.7%	0.67 [0.35 , 1.29]		+ + + + + +
Subtotal (95% CI)		**373**		**268**	**23.1%**	**0.66 [0.40 , 1.09]**		
Total events:	27		30					
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%								
Test for overall effect: Z = 1.61 (P = 0.11)								
1.9.2 Unpublished								
Bartley 2008	50	331	27	164	31.5%	0.92 [0.60 , 1.41]		+ + + + + +
NCT00595374	4	75	1	38	1.2%	2.03 [0.23 , 17.51]		+ + + + + +
NCT00605137	3	55	1	27	1.2%	1.47 [0.16 , 13.50]		+ + + + + +
Robertson 2007	24	232	10	115	11.7%	1.19 [0.59 , 2.40]		+ + + + + +
Russell-Jones 2004	26	491	11	256	12.2%	1.23 [0.62 , 2.45]		+ + + + + +
Standl 2004	17	236	18	224	14.3%	0.90 [0.47 , 1.70]		+ + + + + +
Vague 2003	14	301	4	146	4.8%	1.70 [0.57 , 5.07]		+ + + + + +
Subtotal (95% CI)		**1721**		**970**	**76.9%**	**1.06 [0.80 , 1.39]**		
Total events:	138		72					
Heterogeneity: Tau² = 0.00; Chi² = 2.15, df = 6 (P = 0.91); I² = 0%								
Test for overall effect: Z = 0.39 (P = 0.70)								
Total (95% CI)		**2094**		**1238**	**100.0%**	**0.95 [0.75 , 1.21]**		
Total events:	165		102					
Heterogeneity: Tau² = 0.00; Chi² = 4.70, df = 8 (P = 0.79); I² = 0%								
Test for overall effect: Z = 0.43 (P = 0.67)								
Test for subgroup differences: Chi² = 2.55, df = 1 (P = 0.11), I² = 60.8%								



Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions: Serious adverse events (published vs. unpublished data)

(C) Bias due to missing outcome data: Serious adverse events (published vs. unpublished data)

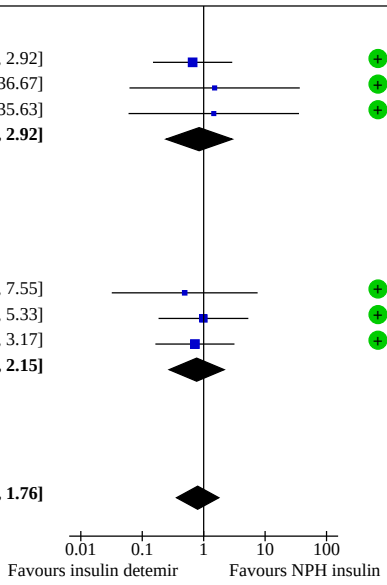
(D) Bias in measurement of the outcome: Serious adverse events (published vs. unpublished data)

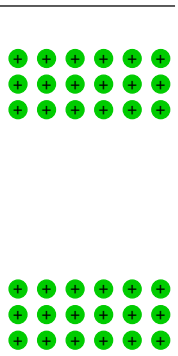
(E) Bias in selection of the reported result: Serious adverse events (published vs. unpublished data)

(F) Overall bias: Serious adverse events (published vs. unpublished data)

Analysis 1.10. Comparison 1: Insulin detemir versus NPH insulin, Outcome 10: Diabetic ketoacidosis

Study or Subgroup	Insulin detemir Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.10.1 Adults						
Bartley 2008	4	331	3	164	28.5%	0.66 [0.15 , 2.92]
Kobayashi 2007	1	196	0	98	6.2%	1.51 [0.06 , 36.67]
Vague 2003	1	301	0	146	6.2%	1.46 [0.06 , 35.63]
Subtotal (95% CI)		**828**		**408**	**40.8%**	**0.84 [0.24 , 2.92]**
Total events:	6		3			
Heterogeneity: Tau² = 0.00; Chi² = 0.35, df = 2 (P = 0.84); I² = 0%						
Test for overall effect: Z = 0.27 (P = 0.79)						
1.10.2 Children						
NCT00605137	1	55	1	27	8.4%	0.49 [0.03 , 7.55]
Robertson 2007	4	232	2	115	22.2%	0.99 [0.18 , 5.33]
Thalange 2013	3	177	4	170	28.6%	0.72 [0.16 , 3.17]
Subtotal (95% CI)		**464**		**312**	**59.2%**	**0.77 [0.27 , 2.15]**
Total events:	8		7			
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 2 (P = 0.91); I² = 0%						
Test for overall effect: Z = 0.50 (P = 0.62)						
Total (95% CI)		**1292**		**720**	**100.0%**	**0.80 [0.36 , 1.76]**
Total events:	14		10			
Heterogeneity: Tau² = 0.00; Chi² = 0.56, df = 5 (P = 0.99); I² = 0%						
Test for overall effect: Z = 0.56 (P = 0.58)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.91), I² = 0%						



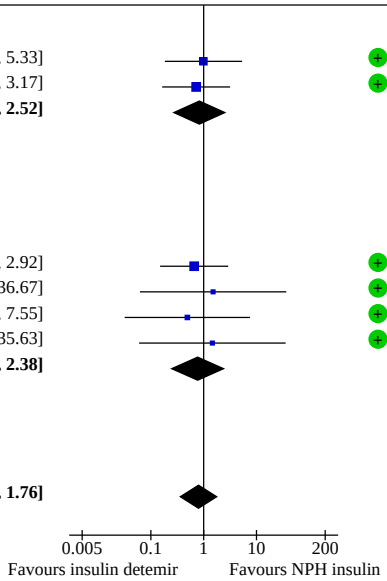


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Diabetic ketoacidosis
(C) Bias due to missing outcome data: Diabetic ketoacidosis
(D) Bias in measurement of the outcome: Diabetic ketoacidosis
(E) Bias in selection of the reported result: Diabetic ketoacidosis
(F) Overall bias: Diabetic ketoacidosis

Analysis 1.11. Comparison 1: Insulin detemir versus NPH insulin, Outcome 11: Diabetic ketoacidosis (published vs. unpublished data)

Study or Subgroup	Insulin detemir Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.11.1 Published data						
Robertson 2007	4	232	2	115	22.2%	0.99 [0.18 , 5.33]
Thalange 2013	3	177	4	170	28.6%	0.72 [0.16 , 3.17]
Subtotal (95% CI)		**409**		**285**	**50.8%**	**0.83 [0.27 , 2.52]**
Total events:	7		6			
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%						
Test for overall effect: Z = 0.33 (P = 0.74)						
1.11.2 Unpublished data						
Bartley 2008 (1)	4	331	3	164	28.5%	0.66 [0.15 , 2.92]
Kobayashi 2007 (1)	1	196	0	98	6.2%	1.51 [0.06 , 36.67]
NCT00605137 (2)	1	55	1	27	8.4%	0.49 [0.03 , 7.55]
Vague 2003 (1)	1	301	0	146	6.2%	1.46 [0.06 , 35.63]
Subtotal (95% CI)		**883**		**435**	**49.2%**	**0.77 [0.25 , 2.38]**
Total events:	7		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.47, df = 3 (P = 0.93); I² = 0%						
Test for overall effect: Z = 0.46 (P = 0.65)						
Total (95% CI)		**1292**		**720**	**100.0%**	**0.80 [0.36 , 1.76]**
Total events:	14		10			
Heterogeneity: Tau² = 0.00; Chi² = 0.56, df = 5 (P = 0.99); I² = 0%						
Test for overall effect: Z = 0.56 (P = 0.58)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.93), I² = 0%						



Risk of Bias: A B C D E F

Footnotes

(1) Data from CSR

(2) Data from study synopsis

Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions: Diabetic ketoacidosis (published vs. unpublished data)

(C) Bias due to missing outcome data: Diabetic ketoacidosis (published vs. unpublished data)

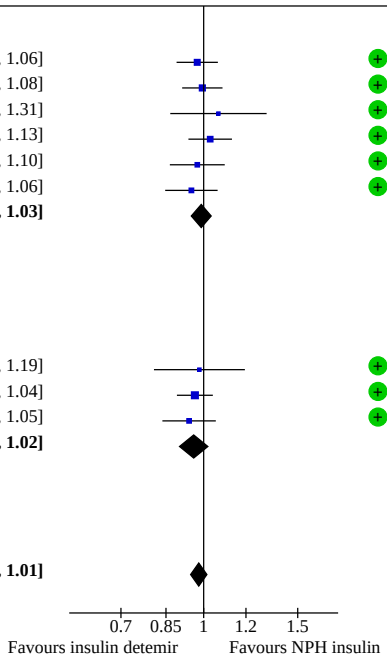
(D) Bias in measurement of the outcome: Diabetic ketoacidosis (published vs. unpublished data)

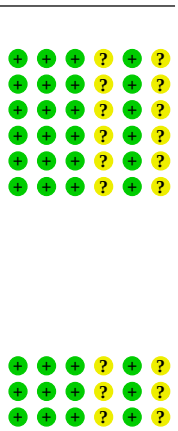
(E) Bias in selection of the reported result: Diabetic ketoacidosis (published vs. unpublished data)

(F) Overall bias: Diabetic ketoacidosis (published vs. unpublished data)

Analysis 1.12. Comparison 1: Insulin detemir versus NPH insulin, Outcome 12: Non-serious adverse events

Study or Subgroup	Insulin detemir Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.12.1 Adults						
Bartley 2008	265	331	135	164	15.5%	0.97 [0.89 , 1.06]
Kobayashi 2007	173	196	87	98	16.3%	0.99 [0.91 , 1.08]
NCT00595374	61	75	29	38	2.9%	1.07 [0.87 , 1.31]
Russell-Jones 2004	361	491	183	256	14.0%	1.03 [0.94 , 1.13]
Standl 2004	164	236	160	224	8.8%	0.97 [0.86 , 1.10]
Vague 2003	219	301	112	146	9.6%	0.95 [0.85 , 1.06]
Subtotal (95% CI)		**1630**		**926**	**67.0%**	**0.99 [0.95 , 1.03]**
Total events:	1243		706			
Heterogeneity: Tau² = 0.00; Chi² = 1.92, df = 5 (P = 0.86); I² = 0%						
Test for overall effect: Z = 0.48 (P = 0.63)						
1.12.2 Children						
NCT00605137	46	55	23	27	3.2%	0.98 [0.81 , 1.19]
Robertson 2007	202	232	104	115	20.5%	0.96 [0.89 , 1.04]
Thalange 2013	132	177	135	170	9.3%	0.94 [0.84 , 1.05]
Subtotal (95% CI)		**464**		**312**	**33.0%**	**0.96 [0.90 , 1.02]**
Total events:	380		262			
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 2 (P = 0.90); I² = 0%						
Test for overall effect: Z = 1.38 (P = 0.17)						
Total (95% CI)		**2094**		**1238**	**100.0%**	**0.98 [0.95 , 1.01]**
Total events:	1623		968			
Heterogeneity: Tau² = 0.00; Chi² = 2.86, df = 8 (P = 0.94); I² = 0%						
Test for overall effect: Z = 1.19 (P = 0.24)						
Test for subgroup differences: Chi² = 0.73, df = 1 (P = 0.39), I² = 0%						



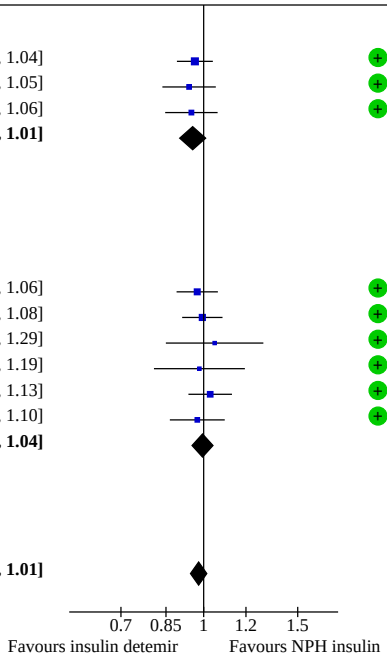


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Non-serious adverse events
(C) Bias due to missing outcome data: Non-serious adverse events
(D) Bias in measurement of the outcome: Non-serious adverse events
(E) Bias in selection of the reported result: Non-serious adverse events
(F) Overall bias: Non-serious adverse events

Analysis 1.13. Comparison 1: Insulin detemir versus NPH insulin, Outcome 13: Non-serious adverse events (published vs unpublished data)

Study or Subgroup	Insulin detemir Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.13.1 Published data						
Robertson 2007	202	232	104	115	20.5%	0.96 [0.89 , 1.04]
Thalange 2013	132	177	135	170	9.3%	0.94 [0.84 , 1.05]
Vague 2003 (1)	219	301	112	146	9.6%	0.95 [0.85 , 1.06]
Subtotal (95% CI)		**710**		**431**	**39.5%**	**0.95 [0.90 , 1.01]**
Total events:	553		351			
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 2 (P = 0.93); I² = 0%						
Test for overall effect: Z = 1.67 (P = 0.10)						
1.13.2 Unpublished data						
Bartley 2008	265	331	135	164	15.5%	0.97 [0.89 , 1.06]
Kobayashi 2007	173	196	87	98	16.3%	0.99 [0.91 , 1.08]
NCT00595374	60	75	29	38	2.8%	1.05 [0.85 , 1.29]
NCT00605137	46	55	23	27	3.2%	0.98 [0.81 , 1.19]
Russell-Jones 2004	361	491	183	256	14.0%	1.03 [0.94 , 1.13]
Standl 2004	164	236	160	224	8.8%	0.97 [0.86 , 1.10]
Subtotal (95% CI)		**1384**		**807**	**60.5%**	**1.00 [0.95 , 1.04]**
Total events:	1069		617			
Heterogeneity: Tau² = 0.00; Chi² = 1.14, df = 5 (P = 0.95); I² = 0%						
Test for overall effect: Z = 0.22 (P = 0.83)						
Total (95% CI)		**2094**		**1238**	**100.0%**	**0.98 [0.94 , 1.01]**
Total events:	1622		968			
Heterogeneity: Tau² = 0.00; Chi² = 2.62, df = 8 (P = 0.96); I² = 0%						
Test for overall effect: Z = 1.21 (P = 0.22)						
Test for subgroup differences: Chi² = 1.35, df = 1 (P = 0.25), I² = 25.7%						



Footnotes

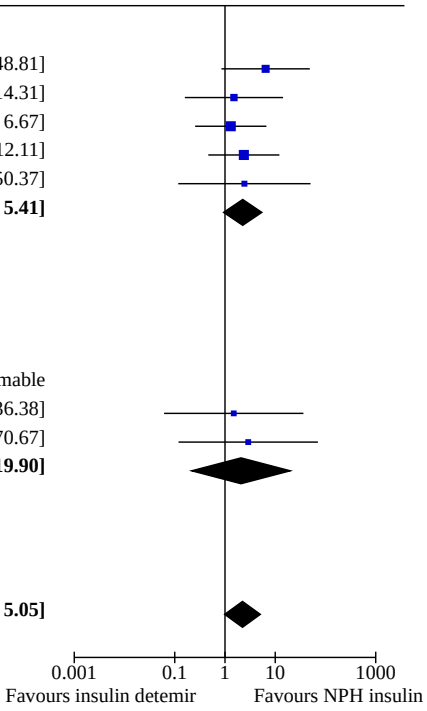
(1) Proportion of participants with adverse events after 6 months reported in extension period of the trial

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Non-serious adverse events (published vs unpublished data)
(C) Bias due to missing outcome data: Non-serious adverse events (published vs unpublished data)
(D) Bias in measurement of the outcome: Non-serious adverse events (published vs unpublished data)
(E) Bias in selection of the reported result: Non-serious adverse events (published vs unpublished data)
(F) Overall bias: Non-serious adverse events (published vs unpublished data)

Analysis 1.14. Comparison 1: Insulin detemir versus NPH insulin, Outcome 14: Withdrawals due to adverse events

Study or Subgroup	Insulin detemir Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.14.1 Adults						
Bartley 2008	13	331	1	164	16.3%	6.44 [0.85 , 48.81]
Kobayashi 2007	3	197	1	99	13.2%	1.51 [0.16 , 14.31]
Russell-Jones 2004	5	491	2	256	25.0%	1.30 [0.25 , 6.67]
Standl 2004	5	236	2	224	25.1%	2.37 [0.47 , 12.11]
Vague 2003 (1)	2	301	0	146	7.3%	2.43 [0.12 , 50.37]
Subtotal (95% CI)		**1556**		**889**	**86.9%**	**2.25 [0.94 , 5.41]**
Total events:	28		6			
Heterogeneity: Tau² = 0.00; Chi² = 1.68, df = 4 (P = 0.79); I² = 0%						
Test for overall effect: Z = 1.82 (P = 0.07)						
1.14.2 Children						
NCT00605137	0	55	0	27		Not estimable
Robertson 2007	1	232	0	115	6.5%	1.49 [0.06 , 36.38]
Thalange 2013	1	177	0	171	6.5%	2.90 [0.12 , 70.67]
Subtotal (95% CI)		**464**		**313**	**13.1%**	**2.08 [0.22 , 19.90]**
Total events:	2		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.77); I² = 0%						
Test for overall effect: Z = 0.64 (P = 0.52)						
Total (95% CI)		**2020**		**1202**	**100.0%**	**2.23 [0.98 , 5.05]**
Total events:	30		6			
Heterogeneity: Tau² = 0.00; Chi² = 1.76, df = 6 (P = 0.94); I² = 0%						
Test for overall effect: Z = 1.92 (P = 0.05)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.95), I² = 0%						

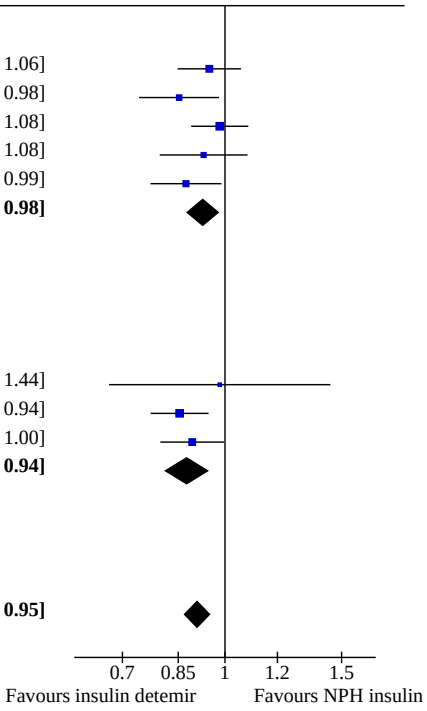


Footnotes

(1) Proportion of participants with adverse events after 6 months reported in extension period of the trial

Analysis 1.15. Comparison 1: Insulin detemir versus NPH insulin, Outcome 15: Any nocturnal hypoglycaemia

Study or Subgroup	Insulin detemir Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.15.1 Adults						
Bartley 2008	237	331	124	164	15.5%	0.95 [0.85 , 1.06]
Kobayashi 2007	133	196	78	98	9.7%	0.85 [0.74 , 0.98]
Russell-Jones 2004	339	491	180	256	19.1%	0.98 [0.89 , 1.08]
Standl 2004 (1)	134	236	137	224	8.1%	0.93 [0.80 , 1.08]
Vague 2003	198	301	110	146	12.4%	0.87 [0.77 , 0.99]
Subtotal (95% CI)		**1555**		**888**	**64.8%**	**0.93 [0.88 , 0.98]**
Total events:	1041		629			
Heterogeneity: Tau² = 0.00; Chi² = 3.74, df = 4 (P = 0.44); I² = 0%						
Test for overall effect: Z = 2.82 (P = 0.005)						
1.15.2 Children						
NCT00605137	32	55	16	27	1.3%	0.98 [0.67 , 1.44]
Robertson 2007	174	232	101	115	18.6%	0.85 [0.77 , 0.94]
Thalange 2013	131	177	141	170	15.4%	0.89 [0.80 , 1.00]
Subtotal (95% CI)		**464**		**312**	**35.2%**	**0.87 [0.81 , 0.94]**
Total events:	337		258			
Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 2 (P = 0.69); I² = 0%						
Test for overall effect: Z = 3.58 (P = 0.0003)						
Total (95% CI)		**2019**		**1200**	**100.0%**	**0.91 [0.87 , 0.95]**
Total events:	1378		887			
Heterogeneity: Tau² = 0.00; Chi² = 6.04, df = 7 (P = 0.54); I² = 0%						
Test for overall effect: Z = 4.39 (P < 0.0001)						
Test for subgroup differences: Chi² = 1.46, df = 1 (P = 0.23), I² = 31.7%						

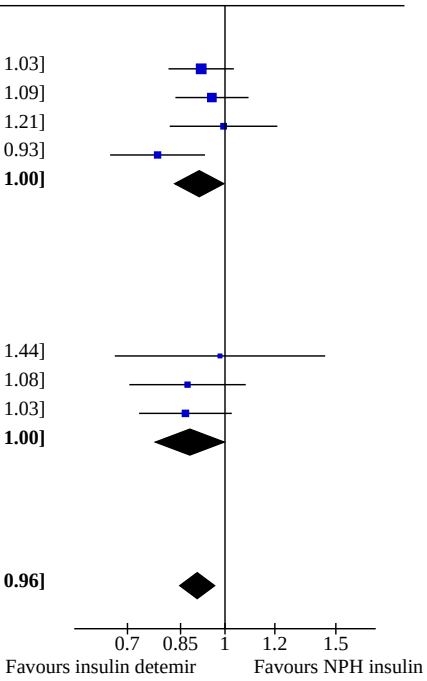


Footnotes

(1) Data from CSR after 6 months

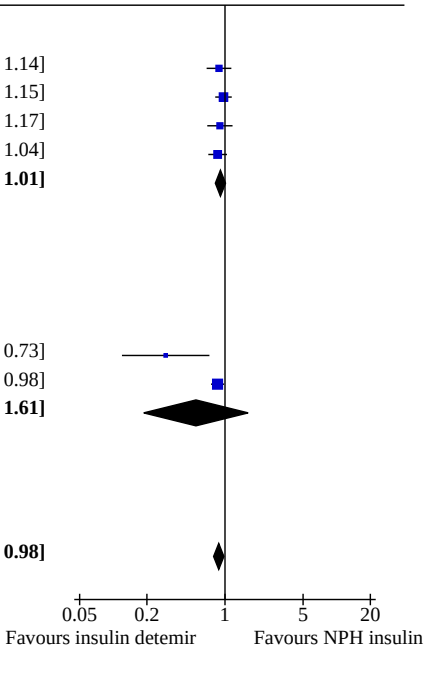
Analysis 1.16. Comparison 1: Insulin detemir versus NPH insulin, Outcome 16: Mild nocturnal hypoglycaemia

Study or Subgroup	Insulin detemir Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.16.1 Adults						
Bartley 2008	222	331	120	164	28.2%	0.92 [0.81 , 1.03]
Russell-Jones 2004	267	491	146	256	22.5%	0.95 [0.83 , 1.09]
Standl 2004	109	236	104	224	10.4%	0.99 [0.82 , 1.21]
Vague 2003	145	301	90	146	13.4%	0.78 [0.66 , 0.93]
Subtotal (95% CI)		**1359**		**790**	**74.4%**	**0.91 [0.83 , 1.00]**
Total events:	743		460			
Heterogeneity: Tau² = 0.00; Chi² = 4.23, df = 3 (P = 0.24); I² = 29%						
Test for overall effect: Z = 2.07 (P = 0.04)						
1.16.2 Children						
NCT00605137	32	55	16	27	2.7%	0.98 [0.67 , 1.44]
Robertson 2007	132	331	75	164	8.9%	0.87 [0.70 , 1.08]
Thalange 2013	100	177	111	170	14.0%	0.87 [0.73 , 1.03]
Subtotal (95% CI)		**563**		**361**	**25.6%**	**0.88 [0.78 , 1.00]**
Total events:	264		202			
Heterogeneity: Tau² = 0.00; Chi² = 0.36, df = 2 (P = 0.84); I² = 0%						
Test for overall effect: Z = 2.01 (P = 0.04)						
Total (95% CI)		**1922**		**1151**	**100.0%**	**0.90 [0.85 , 0.96]**
Total events:	1007		662			
Heterogeneity: Tau² = 0.00; Chi² = 4.82, df = 6 (P = 0.57); I² = 0%						
Test for overall effect: Z = 3.14 (P = 0.002)						
Test for subgroup differences: Chi² = 0.19, df = 1 (P = 0.66), I² = 0%						

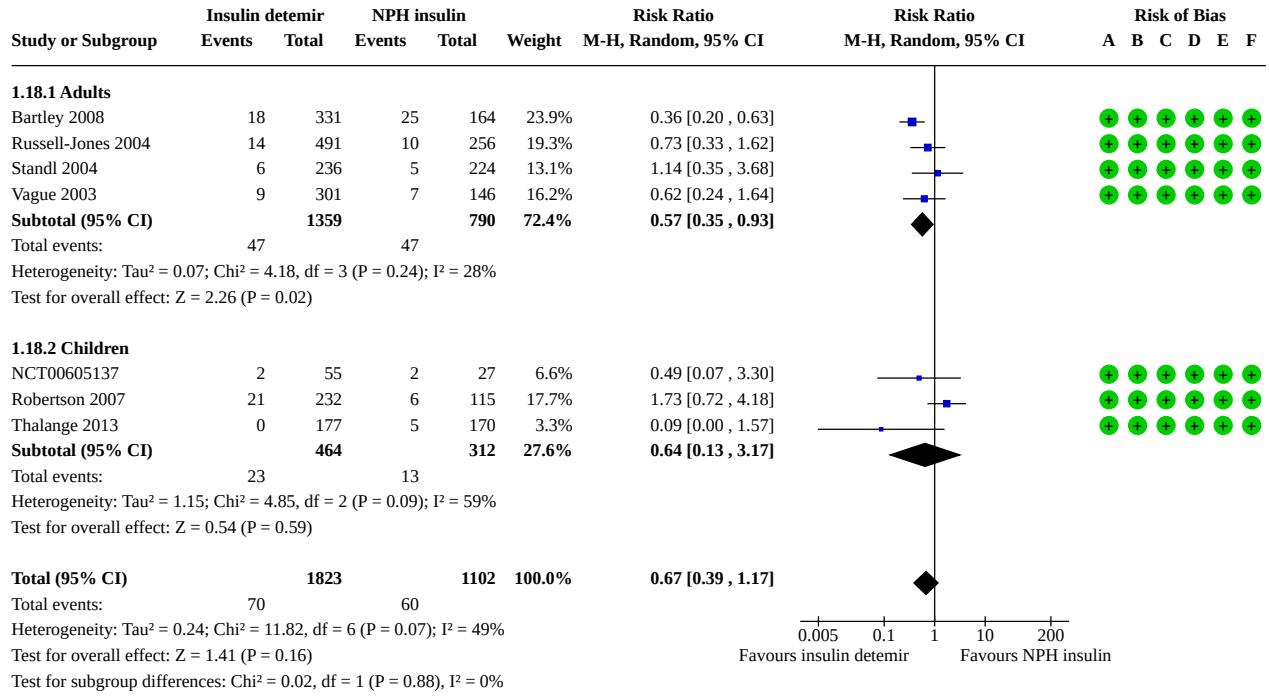


Analysis 1.17. Comparison 1: Insulin detemir versus NPH insulin, Outcome 17: Nocturnal hypoglycaemia (symptoms)

Study or Subgroup	Insulin detemir Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.17.1 Adults						
Bartley 2008	107	331	60	164	13.2%	0.88 [0.68 , 1.14]
Russell-Jones 2004	212	491	114	256	23.1%	0.97 [0.82 , 1.15]
Standl 2004	74	236	78	224	12.8%	0.90 [0.69 , 1.17]
Vague 2003	140	301	79	146	19.8%	0.86 [0.71 , 1.04]
Subtotal (95% CI)		**1359**		**790**	**68.9%**	**0.91 [0.82 , 1.01]**
Total events:	533		331			
Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 3 (P = 0.82); I² = 0%						
Test for overall effect: Z = 1.76 (P = 0.08)						
1.17.2 Children						
NCT00605137	6	55	10	27	1.3%	0.29 [0.12 , 0.73]
Robertson 2007	154	232	89	115	29.8%	0.86 [0.75 , 0.98]
Subtotal (95% CI)		**287**		**142**	**31.1%**	**0.55 [0.19 , 1.61]**
Total events:	160		99			
Heterogeneity: Tau² = 0.51; Chi² = 5.73, df = 1 (P = 0.02); I² = 83%						
Test for overall effect: Z = 1.09 (P = 0.28)						
Total (95% CI)		**1646**		**932**	**100.0%**	**0.88 [0.79 , 0.98]**
Total events:	693		430			
Heterogeneity: Tau² = 0.00; Chi² = 7.14, df = 5 (P = 0.21); I² = 30%						
Test for overall effect: Z = 2.40 (P = 0.02)						
Test for subgroup differences: Chi² = 0.84, df = 1 (P = 0.36), I² = 0%						



Analysis 1.18. Comparison 1: Insulin detemir versus NPH insulin, Outcome 18: Severe nocturnal hypoglycaemia



Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions: Severe nocturnal hypoglycaemia

(C) Bias due to missing outcome data: Severe nocturnal hypoglycaemia

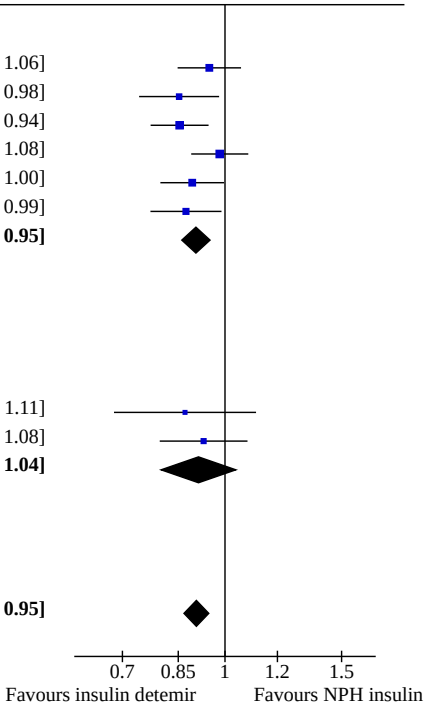
(D) Bias in measurement of the outcome: Severe nocturnal hypoglycaemia

(E) Bias in selection of the reported result: Severe nocturnal hypoglycaemia

(F) Overall bias: Severe nocturnal hypoglycaemia

Analysis 1.19. Comparison 1: Insulin detemir versus NPH insulin, Outcome 19: Any nocturnal hypoglycaemia (published vs. unpublished data)

Study or Subgroup	Insulin detemir Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.19.1 Published						
Bartley 2008	237	331	124	164	15.2%	0.95 [0.85 , 1.06]
Kobayashi 2007	133	196	78	98	9.6%	0.85 [0.74 , 0.98]
Robertson 2007	174	232	101	115	18.2%	0.85 [0.77 , 0.94]
Russell-Jones 2004	339	491	180	256	18.8%	0.98 [0.89 , 1.08]
Thalange 2013	131	177	141	170	15.1%	0.89 [0.80 , 1.00]
Vague 2003	198	301	110	146	12.1%	0.87 [0.77 , 0.99]
Subtotal (95% CI)		**1728**		**949**	**89.0%**	**0.90 [0.86 , 0.95]**
Total events:	1212		734			
Heterogeneity: Tau² = 0.00; Chi² = 5.74, df = 5 (P = 0.33); I² = 13%						
Test for overall effect: Z = 4.05 (P < 0.0001)						
1.19.2 Unpublished						
NCT00605137	39	55	22	27	3.0%	0.87 [0.68 , 1.11]
Standl 2004 (1)	134	236	137	224	7.9%	0.93 [0.80 , 1.08]
Subtotal (95% CI)		**291**		**251**	**11.0%**	**0.91 [0.80 , 1.04]**
Total events:	173		159			
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.65); I² = 0%						
Test for overall effect: Z = 1.39 (P = 0.16)						
Total (95% CI)		**2019**		**1200**	**100.0%**	**0.91 [0.87 , 0.95]**
Total events:	1385		893			
Heterogeneity: Tau² = 0.00; Chi² = 5.96, df = 7 (P = 0.54); I² = 0%						
Test for overall effect: Z = 4.53 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.90), I² = 0%						

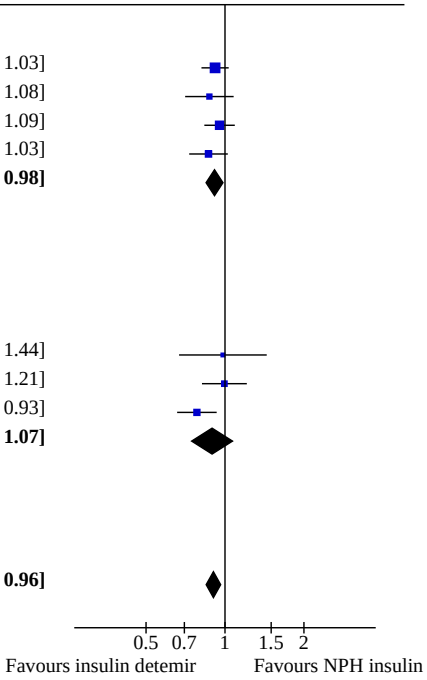


Footnotes

(1) Data from CSR after 6 months

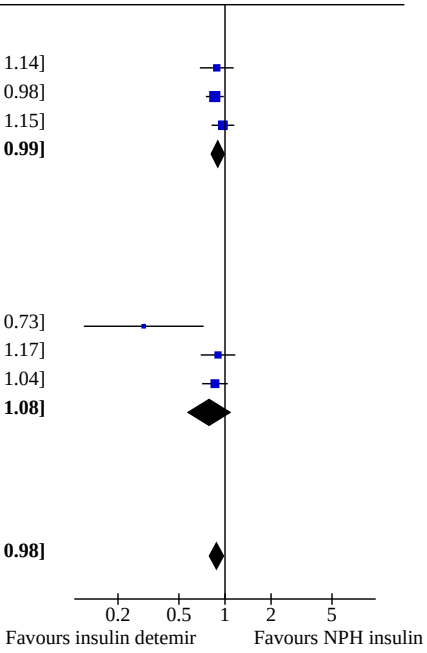
Analysis 1.20. Comparison 1: Insulin detemir versus NPH insulin, Outcome 20: Mild nocturnal hypoglycaemia (published vs. unpublished data)

Study or Subgroup	Insulin detemir Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.20.1 Published						
Bartley 2008	222	331	120	164	28.2%	0.92 [0.81 , 1.03]
Robertson 2007	132	331	75	164	8.9%	0.87 [0.70 , 1.08]
Russell-Jones 2004	267	491	146	256	22.5%	0.95 [0.83 , 1.09]
Thalange 2013	100	177	111	170	14.0%	0.87 [0.73 , 1.03]
Subtotal (95% CI)		**1330**		**754**	**73.5%**	**0.91 [0.85 , 0.98]**
Total events:	721		452			
Heterogeneity: Tau² = 0.00; Chi² = 0.97, df = 3 (P = 0.81); I² = 0%						
Test for overall effect: Z = 2.44 (P = 0.01)						
1.20.2 Unpublished						
NCT00605137	32	55	16	27	2.7%	0.98 [0.67 , 1.44]
Standl 2004	109	236	104	224	10.4%	0.99 [0.82 , 1.21]
Vague 2003	145	301	90	146	13.4%	0.78 [0.66 , 0.93]
Subtotal (95% CI)		**592**		**397**	**26.5%**	**0.89 [0.75 , 1.07]**
Total events:	286		210			
Heterogeneity: Tau² = 0.01; Chi² = 3.64, df = 2 (P = 0.16); I² = 45%						
Test for overall effect: Z = 1.24 (P = 0.21)						
Total (95% CI)		**1922**		**1151**	**100.0%**	**0.90 [0.85 , 0.96]**
Total events:	1007		662			
Heterogeneity: Tau² = 0.00; Chi² = 4.82, df = 6 (P = 0.57); I² = 0%						
Test for overall effect: Z = 3.14 (P = 0.002)						
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.83), I² = 0%						



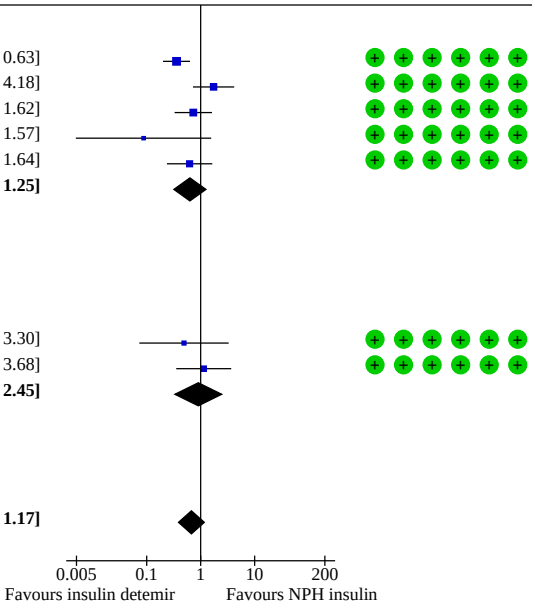
Analysis 1.21. Comparison 1: Insulin detemir versus NPH insulin, Outcome 21: Nocturnal hypoglycaemia, symptoms only (published vs. unpublished data)

Study or Subgroup	Insulin detemir Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.21.1 Published						
Bartley 2008	107	331	60	164	13.2%	0.88 [0.68 , 1.14]
Robertson 2007	154	232	89	115	29.8%	0.86 [0.75 , 0.98]
Russell-Jones 2004	212	491	114	256	23.1%	0.97 [0.82 , 1.15]
Subtotal (95% CI)		**1054**		**535**	**66.1%**	**0.90 [0.81 , 0.99]**
Total events:	473		263			
Heterogeneity: Tau² = 0.00; Chi² = 1.35, df = 2 (P = 0.51); I² = 0%						
Test for overall effect: Z = 2.19 (P = 0.03)						
1.21.2 Unpublished						
NCT00605137	6	55	10	27	1.3%	0.29 [0.12 , 0.73]
Standl 2004	74	236	78	224	12.8%	0.90 [0.69 , 1.17]
Vague 2003	140	301	79	146	19.8%	0.86 [0.71 , 1.04]
Subtotal (95% CI)		**592**		**397**	**33.9%**	**0.79 [0.57 , 1.08]**
Total events:	220		167			
Heterogeneity: Tau² = 0.04; Chi² = 5.53, df = 2 (P = 0.06); I² = 64%						
Test for overall effect: Z = 1.49 (P = 0.13)						
Total (95% CI)		**1646**		**932**	**100.0%**	**0.88 [0.79 , 0.98]**
Total events:	693		430			
Heterogeneity: Tau² = 0.00; Chi² = 7.14, df = 5 (P = 0.21); I² = 30%						
Test for overall effect: Z = 2.40 (P = 0.02)						
Test for subgroup differences: Chi² = 0.61, df = 1 (P = 0.44), I² = 0%						



Analysis 1.22. Comparison 1: Insulin detemir versus NPH insulin, Outcome 22: Severe nocturnal hypoglycaemia (published vs. unpublished data)

Study or Subgroup	Insulin detemir Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.22.1 Published						
Bartley 2008	18	331	25	164	23.9%	0.36 [0.20 , 0.63]
Robertson 2007	21	232	6	115	17.7%	1.73 [0.72 , 4.18]
Russell-Jones 2004	14	491	10	256	19.3%	0.73 [0.33 , 1.62]
Thalange 2013	0	177	5	170	3.3%	0.09 [0.00 , 1.57]
Vague 2003	9	301	7	146	16.2%	0.62 [0.24 , 1.64]
Subtotal (95% CI)		**1532**		**851**	**80.3%**	**0.63 [0.32 , 1.25]**
Total events:	62		53			
Heterogeneity: Tau² = 0.35; Chi² = 10.68, df = 4 (P = 0.03); I² = 63%						
Test for overall effect: Z = 1.32 (P = 0.19)						
1.22.2 Unpublished						
NCT00605137	2	55	2	27	6.6%	0.49 [0.07 , 3.30]
Standl 2004	6	236	5	224	13.1%	1.14 [0.35 , 3.68]
Subtotal (95% CI)		**291**		**251**	**19.7%**	**0.90 [0.33 , 2.45]**
Total events:	8		7			
Heterogeneity: Tau² = 0.00; Chi² = 0.54, df = 1 (P = 0.46); I² = 0%						
Test for overall effect: Z = 0.20 (P = 0.84)						
Total (95% CI)		**1823**		**1102**	**100.0%**	**0.67 [0.39 , 1.17]**
Total events:	70		60			
Heterogeneity: Tau² = 0.24; Chi² = 11.82, df = 6 (P = 0.07); I² = 49%						
Test for overall effect: Z = 1.41 (P = 0.16)						
Test for subgroup differences: Chi² = 0.34, df = 1 (P = 0.56), I² = 0%						

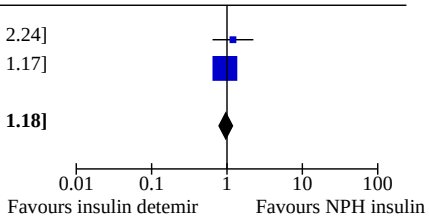


Risk of bias legend

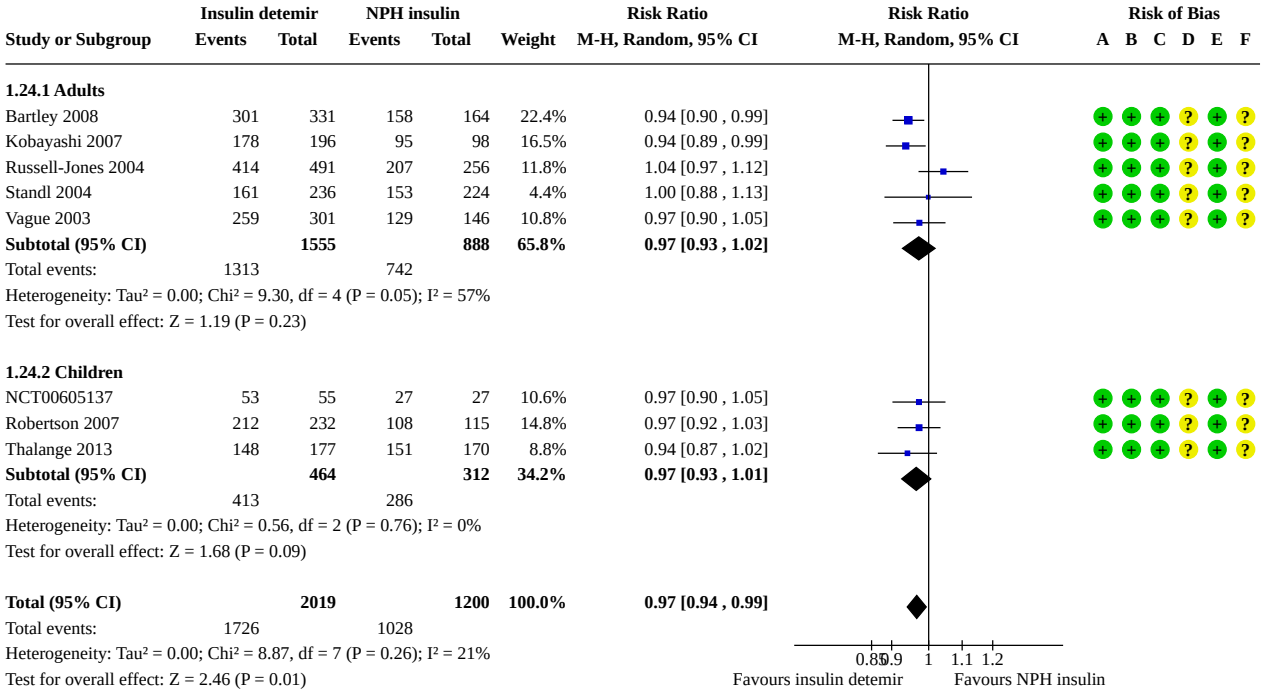
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Severe nocturnal hypoglycaemia (published vs. unpublished data)
(C) Bias due to missing outcome data: Severe nocturnal hypoglycaemia (published vs. unpublished data)
(D) Bias in measurement of the outcome: Severe nocturnal hypoglycaemia (published vs. unpublished data)
(E) Bias in selection of the reported result: Severe nocturnal hypoglycaemia (published vs. unpublished data)
(F) Overall bias: Severe nocturnal hypoglycaemia (published vs. unpublished data)

Analysis 1.23. Comparison 1: Insulin detemir versus NPH insulin, Outcome 23: Nocturnal hypoglycaemia, asymptomatic (children vs. adults)

Study or Subgroup	Insulin detemir Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
NCT00605137	22	55	9	27	10.8%	1.20 [0.64 , 2.24]
Thalange 2013	83	177	85	170	89.2%	0.94 [0.75 , 1.17]
Total (95% CI)		**232**		**197**	**100.0%**	**0.96 [0.78 , 1.18]**
Total events:	105		94			
Heterogeneity: Tau² = 0.00; Chi² = 0.54, df = 1 (P = 0.46); I² = 0%						
Test for overall effect: Z = 0.36 (P = 0.72)						
Test for subgroup differences: Not applicable						



Analysis 1.24. Comparison 1: Insulin detemir versus NPH insulin, Outcome 24: Mild/moderate hypoglycaemia



Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions: Mild/moderate hypoglycaemia

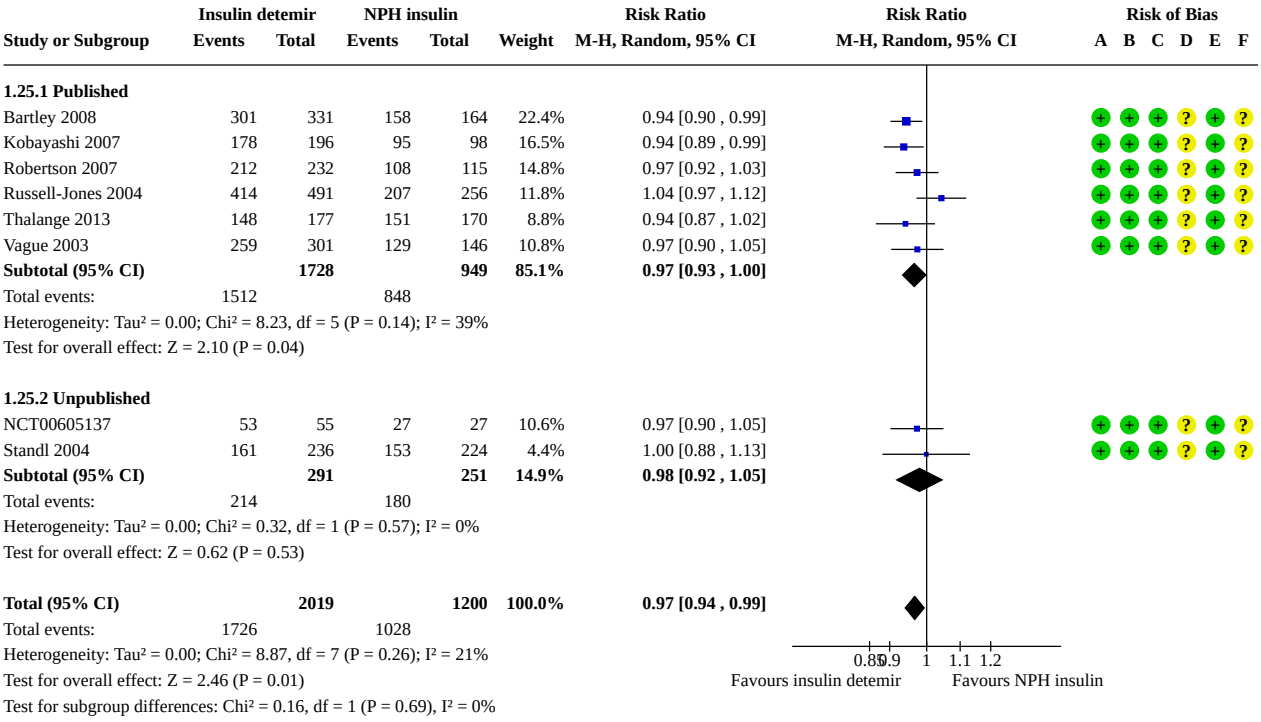
(C) Bias due to missing outcome data: Mild/moderate hypoglycaemia

(D) Bias in measurement of the outcome: Mild/moderate hypoglycaemia

(E) Bias in selection of the reported result: Mild/moderate hypoglycaemia

(F) Overall bias: Mild/moderate hypoglycaemia

Analysis 1.25. Comparison 1: Insulin detemir versus NPH insulin, Outcome 25: Mild/moderate hypoglycaemia (published vs. unpublished data)



Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions: Mild/moderate hypoglycaemia (published vs. unpublished data)

(C) Bias due to missing outcome data: Mild/moderate hypoglycaemia (published vs. unpublished data)

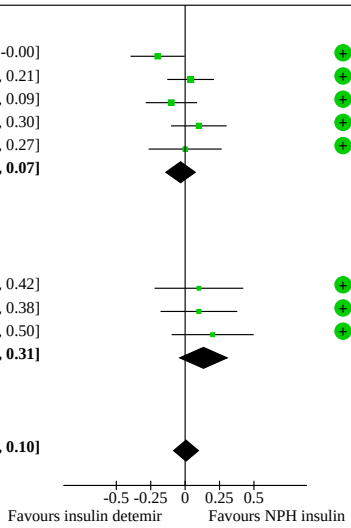
(D) Bias in measurement of the outcome: Mild/moderate hypoglycaemia (published vs. unpublished data)

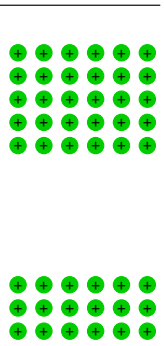
(E) Bias in selection of the reported result: Mild/moderate hypoglycaemia (published vs. unpublished data)

(F) Overall bias: Mild/moderate hypoglycaemia (published vs. unpublished data)

Analysis 1.26. Comparison 1: Insulin detemir versus NPH insulin, Outcome 26: HbA1c

Study or Subgroup	Insulin detemir Mean	SD	Total	NPH insulin Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.26.1 Adults								
Bartley 2008 (1)	7.4	1.1	320	7.6	1	159	15.6%	-0.20 [-0.40 , -0.00]
Kobayashi 2007 (1)	7.33	0.7	195	7.29	0.7	98	19.2%	0.04 [-0.13 , 0.21]
Russell-Jones 2004	8.3	1.1	491	8.4	1.3	256	16.8%	-0.10 [-0.29 , 0.09]
Standl 2004 (2)	7.7	1.1	210	7.6	1	206	15.0%	0.10 [-0.10 , 0.30]
Vague 2003 (1)	7.6	1.5	280	7.6	1.2	139	9.6%	0.00 [-0.27 , 0.27]
Subtotal (95% CI)			**1496**			**858**	**76.3%**	**-0.03 [-0.14 , 0.07]**
Heterogeneity: Tau² = 0.00; Chi² = 5.70, df = 4 (P = 0.22); I² = 30%								
Test for overall effect: Z = 0.61 (P = 0.54)								
1.26.2 Children								
NCT00605137 (3)	7.6	0.7	55	7.5	0.7	27	6.9%	0.10 [-0.22 , 0.42]
Robertson 2007	8	1.5	232	7.9	1.1	115	8.9%	0.10 [-0.18 , 0.38]
Thalange 2013 (4)	8.8	1.4	171	8.6	1.4	168	7.9%	0.20 [-0.10 , 0.50]
Subtotal (95% CI)			**458**			**310**	**23.7%**	**0.13 [-0.04 , 0.31]**
Heterogeneity: Tau² = 0.00; Chi² = 0.29, df = 2 (P = 0.87); I² = 0%								
Test for overall effect: Z = 1.52 (P = 0.13)								
Total (95% CI)			**1954**			**1168**	**100.0%**	**0.01 [-0.08 , 0.10]**
Heterogeneity: Tau² = 0.00; Chi² = 8.82, df = 7 (P = 0.27); I² = 21%								
Test for overall effect: Z = 0.14 (P = 0.89)								
Test for subgroup differences: Chi² = 2.60, df = 1 (P = 0.11), I² = 61.5%								





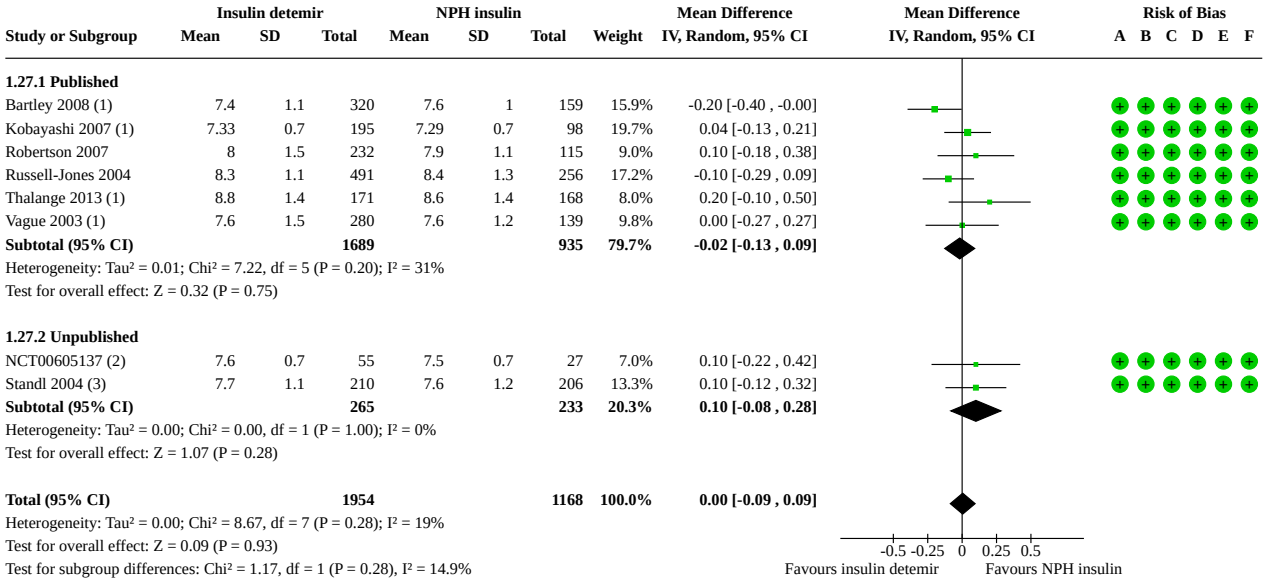
Footnotes

(1) SD calculated from SE
(2) Data after 26 weeks of intervention from FDA medical review and CSR
(3) Data from study synopsis. LS mean adjusted for baseline value. SD calculated from SE.
(4) SD from SE (reported from ClinicalTrials.gov)

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: HbA1c
(C) Bias due to missing outcome data: HbA1c
(D) Bias in measurement of the outcome: HbA1c
(E) Bias in selection of the reported result: HbA1c
(F) Overall bias: HbA1c

Analysis 1.27. Comparison 1: Insulin detemir versus NPH insulin, Outcome 27: HbA1c (published vs. unpublished data)



Footnotes

(1) SD calculated from SE
(2) Data from study synopsis. LS mean adjusted for baseline value. SD calculated from SE.
(3) Data after 26 weeks of intervention from FDA medical review and CSR

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: HbA1c (published vs. unpublished data)
(C) Bias due to missing outcome data: HbA1c (published vs. unpublished data)
(D) Bias in measurement of the outcome: HbA1c (published vs. unpublished data)
(E) Bias in selection of the reported result: HbA1c (published vs. unpublished data)
(F) Overall bias: HbA1c (published vs. unpublished data)

Comparison 2. Insulin glargine versus NPH insulin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 All-cause mortality	8	2175	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.00, 6.98]
2.1.1 Adults	4	1365	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.00, 6.98]
2.1.2 Children	4	810	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.2 Health-realted quality of life	2	880	Mean Difference (IV, Random, 95% CI)	0.62 [-0.71, 1.96]
2.3 Severe hypoglycaemia	9	2350	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.67, 1.04]
2.3.1 Adults	5	1540	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.58, 1.05]
2.3.2 Children	4	810	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.59, 2.21]

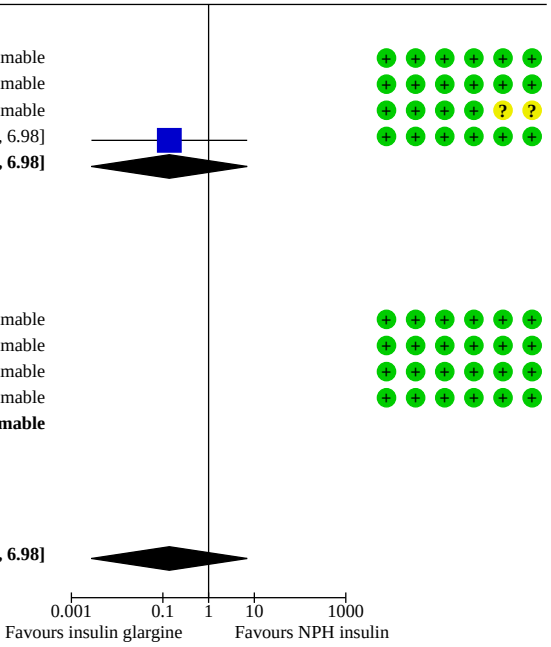
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.4 Severe hypoglycaemia (published vs. unpublished data)	9	2350	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.67, 1.04]
2.4.1 Published	7	1691	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.63, 1.22]
2.4.2 Unpublished	2	659	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.56, 1.25]
2.5 Hypoglycaemia reported as a serious adverse event	8	2229	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.64, 1.39]
2.5.1 Adults	4	1419	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.57, 1.37]
2.5.2 Children	4	810	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.32, 2.87]
2.6 Cardiovascular mortality	8		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.6.1 Adults	4		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.6.2 Children	4		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.7 Non-fatal myocardial infarction	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.8 Non-fatal stroke	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.9 Serious adverse events	8	2229	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.63, 1.84]
2.9.1 Adults	4	1419	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.72, 1.35]
2.9.2 Children	4	810	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.28, 3.64]
2.10 Serious adverse events (published vs. unpublished data)	8	2229	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.63, 1.84]
2.10.1 Published	4	1284	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.45, 2.70]
2.10.2 Unpublished	4	945	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.46, 2.60]
2.11 Diabetic ketoacidosis	7	2054	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.19, 1.44]
2.11.1 Adults	3	1244	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.11, 9.58]
2.11.2 Children	4	810	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.15, 1.39]
2.12 Diabetic ketoacidosis (published vs. unpublished data)	7	2054	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.19, 1.44]
2.12.1 Published	3	685	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.11, 1.31]
2.12.2 Unpublished	4	1369	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.18, 5.77]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.13 Non-serious adverse events	8	2229	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.96, 1.06]
2.13.1 Adults	4	1419	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.95, 1.07]
2.13.2 Children	4	810	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.93, 1.12]
2.14 Non-serious adverse events (published vs. unpublished data)	8	2229	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.96, 1.06]
2.14.1 Published	5	1308	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.94, 1.05]
2.14.2 Unpublished	3	921	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.94, 1.14]
2.15 Withdrawals due to adverse events	8	2230	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.24, 2.81]
2.15.1 Adults	4	1419	Risk Ratio (M-H, Random, 95% CI)	1.74 [0.29, 10.39]
2.15.2 Children	4	811	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.06, 1.53]
2.16 Nocturnal hypoglycaemia	7	2054	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.96, 1.05]
2.16.1 Adults	3	1244	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.92, 1.06]
2.16.2 Children	4	810	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.95, 1.08]
2.17 Mild nocturnal hypoglycaemia	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.18 Nocturnal hypoglycaemia (symptoms)	4	996	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.82, 1.05]
2.18.1 Adults	2	710	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.88, 1.08]
2.18.2 Children	2	286	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.55, 1.00]
2.19 Severe nocturnal hypoglycaemia	6	1893	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.62, 1.12]
2.19.1 Adults	3	1244	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.60, 1.27]
2.19.2 Children	3	649	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.47, 1.25]
2.20 Nocturnal hypoglycaemia (published vs. unpublished data)	7	2054	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.96, 1.05]
2.20.1 Published	5	1345	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.95, 1.06]
2.20.2 Unpublished	2	709	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.91, 1.08]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.21 Symptomatic nocturnal hypoglycaemia (published vs. unpublished data)	4	996	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.82, 1.05]
2.21.1 Published	3	871	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.67, 1.12]
2.21.2 Unpublished	1	125	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.80, 1.10]
2.22 Mild/moderate hypoglycaemia	7	2054	Risk Ratio (M-H, Random, 95% CI)	1.02 [1.00, 1.04]
2.22.1 Adults	3	1244	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.99, 1.06]
2.22.2 Children	4	810	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.99, 1.04]
2.23 Mild/moderate hypoglycaemia (published vs. unpublished data)	7	2054	Risk Ratio (M-H, Random, 95% CI)	1.02 [1.00, 1.04]
2.23.1 Published	5	1395	Risk Ratio (M-H, Random, 95% CI)	1.02 [1.00, 1.05]
2.23.2 Unpublished	2	659	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.98, 1.05]
2.24 HbA1c	9	2285	Mean Difference (IV, Random, 95% CI)	0.02 [-0.06, 0.11]
2.24.1 Adults	5	1523	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.16, 0.13]
2.24.2 Children	4	762	Mean Difference (IV, Random, 95% CI)	0.03 [-0.13, 0.20]
2.25 HbA1c (published vs unpublished data)	9	2285	Mean Difference (IV, Random, 95% CI)	0.02 [-0.06, 0.11]
2.25.1 Published	6	1868	Mean Difference (IV, Random, 95% CI)	0.02 [-0.09, 0.14]
2.25.2 Unpublished	3	417	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.26, 0.18]
2.26 HbA1c (NPH < 2x/day vs ≥ 2x/day)	9	2285	Mean Difference (IV, Random, 95% CI)	0.02 [-0.06, 0.11]
2.26.1 NPH up to twice a day	8	2164	Mean Difference (IV, Random, 95% CI)	0.05 [-0.03, 0.13]
2.26.2 NPH more than twice a day	1	121	Mean Difference (IV, Random, 95% CI)	-0.50 [-0.93, -0.07]

Analysis 2.1. Comparison 2: Insulin glargine versus NPH insulin, Outcome 1: All-cause mortality

Study or Subgroup	Insulin glargine Events	Total	NPH insulin Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Risk of Bias A B C D E F
2.1.1 Adults							
Fulcher 2005	0	62	0	63		Not estimable	+ + + + + +
Home 2005 (1)	0	292	0	293		Not estimable	+ + + + + +
Porcellati 2004	0	61	0	60		Not estimable	+ + + + ? ?
Ratner 2000	0	264	1	270	100.0%	0.14 [0.00 , 6.98]	+ + + + + +
Subtotal (95% CI)		**679**		**686**	**100.0%**	**0.14 [0.00 , 6.98]**	
Total events:	0		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.99 (P = 0.32)							
2.1.2 Children							
Chase 2008	0	85	0	90		Not estimable	+ + + + + +
Liu 2016	0	107	0	54		Not estimable	+ + + + + +
PRESCHOOL	0	62	0	63		Not estimable	+ + + + + +
Schober 2002	0	174	0	175		Not estimable	+ + + + + +
Subtotal (95% CI)		**428**		**382**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total (95% CI)		**1107**		**1068**	**100.0%**	**0.14 [0.00 , 6.98]**	
Total events:	0		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.99 (P = 0.32)							
Test for subgroup differences: Not applicable							



Footnotes

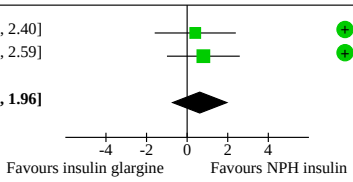
(1) Data from investigators/CSR

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: All-cause mortality
(C) Bias due to missing outcome data: All-cause mortality
(D) Bias in measurement of the outcome: All-cause mortality
(E) Bias in selection of the reported result: All-cause mortality
(F) Overall bias: All-cause mortality

Analysis 2.2. Comparison 2: Insulin glargine versus NPH insulin, Outcome 2: Health-realted quality of life

Study or Subgroup	Insulin glargine Mean	SD	Total	NPH insulin Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F
Home 2005	51.4	10.1	158	51	9.9	249	44.6%	0.40 [-1.60 , 2.40]	+ + + ? + ?
Ratner 2000	51.6	9.7	233	50.8	10.2	240	55.4%	0.80 [-0.99 , 2.59]	+ + + ? + ?
Total (95% CI)			**391**			**489**	**100.0%**	**0.62 [-0.71 , 1.96]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.77); I² = 0%									
Test for overall effect: Z = 0.91 (P = 0.36)									
Test for subgroup differences: Not applicable									

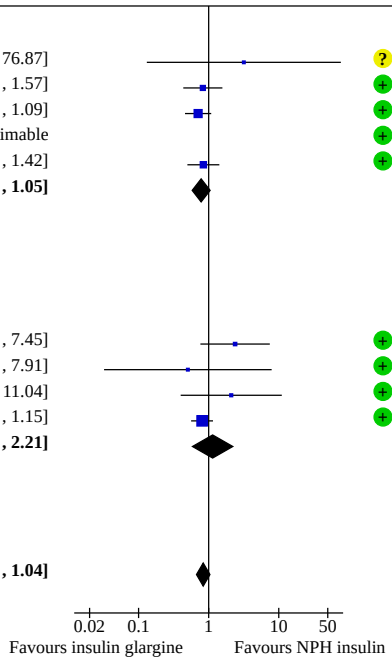


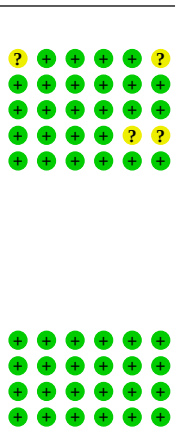
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Health-realted quality of life
(C) Bias due to missing outcome data: Health-realted quality of life
(D) Bias in measurement of the outcome: Health-realted quality of life
(E) Bias in selection of the reported result: Health-realted quality of life
(F) Overall bias: Health-realted quality of life

Analysis 2.3. Comparison 2: Insulin glargine versus NPH insulin, Outcome 3: Severe hypoglycaemia

Study or Subgroup	Insulin glargine Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 Adults						
Bolli 2009	1	85	0	90	0.5%	3.17 [0.13 , 76.87]
Fulcher 2005	13	62	16	63	11.8%	0.83 [0.43 , 1.57]
Home 2005	31	292	44	293	26.3%	0.71 [0.46 , 1.09]
Porcellati 2004	0	61	0	60		Not estimable
Ratner 2000	23	264	28	270	17.6%	0.84 [0.50 , 1.42]
Subtotal (95% CI)		**764**		**776**	**56.2%**	**0.78 [0.58 , 1.05]**
Total events:	68		88			
Heterogeneity: Tau² = 0.00; Chi² = 1.05, df = 3 (P = 0.79); I² = 0%						
Test for overall effect: Z = 1.65 (P = 0.10)						
2.3.2 Children						
Chase 2008	9	85	4	90	3.7%	2.38 [0.76 , 7.45]
Liu 2016	1	107	1	54	0.6%	0.50 [0.03 , 7.91]
PRESCHOOL	4	61	2	64	1.8%	2.10 [0.40 , 11.04]
Schober 2002	40	174	50	175	37.7%	0.80 [0.56 , 1.15]
Subtotal (95% CI)		**427**		**383**	**43.8%**	**1.14 [0.59 , 2.21]**
Total events:	54		57			
Heterogeneity: Tau² = 0.16; Chi² = 4.40, df = 3 (P = 0.22); I² = 32%						
Test for overall effect: Z = 0.39 (P = 0.70)						
Total (95% CI)		**1191**		**1159**	**100.0%**	**0.84 [0.67 , 1.04]**
Total events:	122		145			
Heterogeneity: Tau² = 0.00; Chi² = 5.87, df = 7 (P = 0.55); I² = 0%						
Test for overall effect: Z = 1.60 (P = 0.11)						
Test for subgroup differences: Chi² = 1.04, df = 1 (P = 0.31), I² = 4.2%						

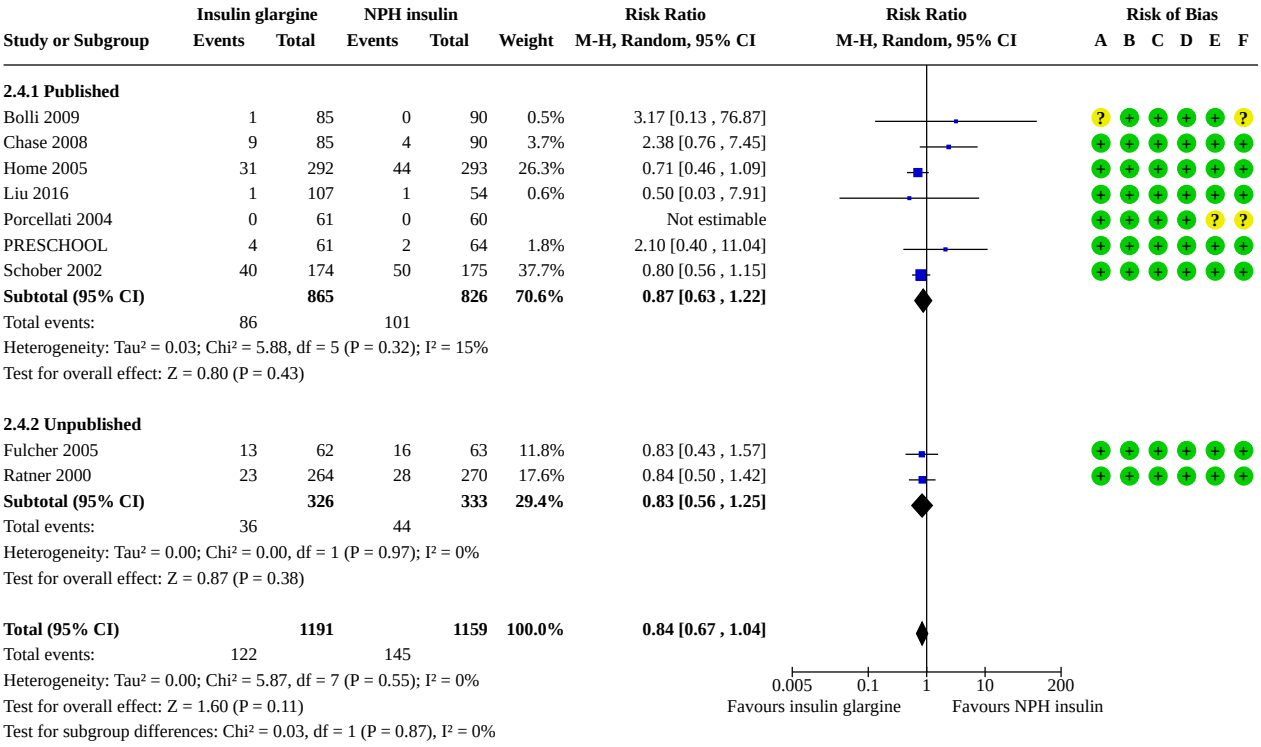




Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Severe hypoglycaemia
(C) Bias due to missing outcome data: Severe hypoglycaemia
(D) Bias in measurement of the outcome: Severe hypoglycaemia
(E) Bias in selection of the reported result: Severe hypoglycaemia
(F) Overall bias: Severe hypoglycaemia

Analysis 2.4. Comparison 2: Insulin glargine versus NPH insulin, Outcome 4: Severe hypoglycaemia (published vs. unpublished data)



Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions: Severe hypoglycaemia (published vs. unpublished data)

(C) Bias due to missing outcome data: Severe hypoglycaemia (published vs. unpublished data)

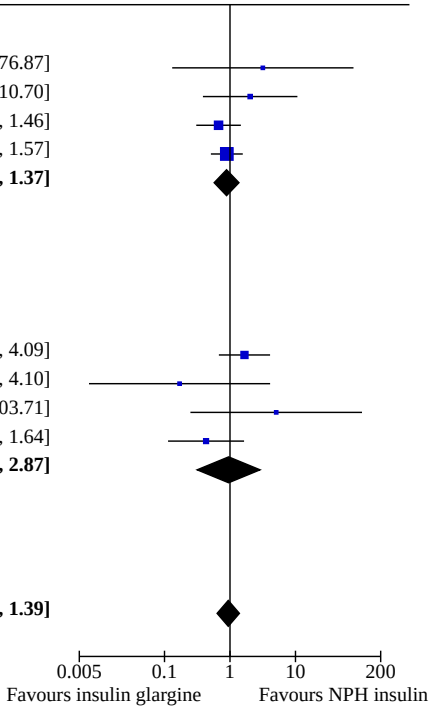
(D) Bias in measurement of the outcome: Severe hypoglycaemia (published vs. unpublished data)

(E) Bias in selection of the reported result: Severe hypoglycaemia (published vs. unpublished data)

(F) Overall bias: Severe hypoglycaemia (published vs. unpublished data)

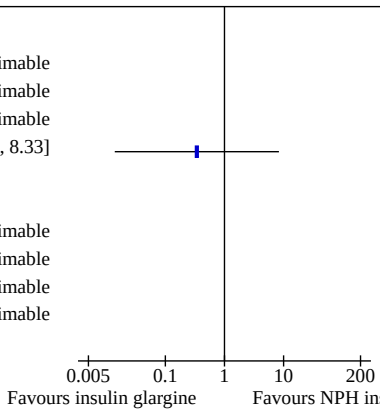
Analysis 2.5. Comparison 2: Insulin glargine versus NPH insulin, Outcome 5: Hypoglycaemia reported as a serious adverse event

Study or Subgroup	Insulin glargine Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.5.1 Adults						
Bolli 2009	1	85	0	90	1.5%	3.17 [0.13 , 76.87]
Fulcher 2005	4	62	2	63	5.4%	2.03 [0.39 , 10.70]
Home 2005	10	292	15	293	22.8%	0.67 [0.31 , 1.46]
Ratner 2000	21	264	24	270	41.1%	0.89 [0.51 , 1.57]
Subtotal (95% CI)		**703**		**716**	**70.9%**	**0.89 [0.57 , 1.37]**
Total events:	36		41			
Heterogeneity: Tau² = 0.00; Chi² = 2.07, df = 3 (P = 0.56); I² = 0%						
Test for overall effect: Z = 0.54 (P = 0.59)						
2.5.2 Children						
Chase 2008	11	85	7	90	17.6%	1.66 [0.68 , 4.09]
Liu 2016	0	107	1	54	1.5%	0.17 [0.01 , 4.10]
PRESCHOOL	2	62	0	63	1.7%	5.08 [0.25 , 103.71]
Schober 2002	3	174	7	175	8.3%	0.43 [0.11 , 1.64]
Subtotal (95% CI)		**428**		**382**	**29.1%**	**0.95 [0.32 , 2.87]**
Total events:	16		15			
Heterogeneity: Tau² = 0.49; Chi² = 5.02, df = 3 (P = 0.17); I² = 40%						
Test for overall effect: Z = 0.09 (P = 0.93)						
Total (95% CI)		**1131**		**1098**	**100.0%**	**0.94 [0.64 , 1.39]**
Total events:	52		56			
Heterogeneity: Tau² = 0.02; Chi² = 7.31, df = 7 (P = 0.40); I² = 4%						
Test for overall effect: Z = 0.31 (P = 0.76)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.90), I² = 0%						



Analysis 2.6. Comparison 2: Insulin glargine versus NPH insulin, Outcome 6: Cardiovascular mortality

Study or Subgroup	Insulin glargine Events	Total	NPH insulin Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
2.6.1 Adults						
Fulcher 2005	0	62	0	63	Not estimable	+ + + + + +
Home 2005 (1)	0	292	0	293	Not estimable	+ + + + + +
Porcellati 2004	0	61	0	60	Not estimable	+ + + + ? ?
Ratner 2000	0	264	1	270	0.34 [0.01 , 8.33]	+ + + + + +
2.6.2 Children						
Chase 2008	0	85	0	90	Not estimable	+ + + + + +
Liu 2016	0	107	0	54	Not estimable	+ + + + + +
PRESCHOOL	0	62	0	63	Not estimable	+ + + + + +
Schober 2002	0	174	0	175	Not estimable	+ + + + + +



Footnotes

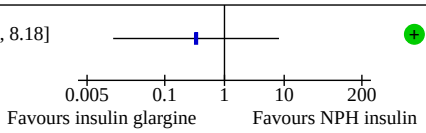
(1) Data from investigators/CSR

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Cardiovascular mortality
(C) Bias due to missing outcome data: Cardiovascular mortality
(D) Bias in measurement of the outcome: Cardiovascular mortality
(E) Bias in selection of the reported result: Cardiovascular mortality
(F) Overall bias: Cardiovascular mortality

Analysis 2.7. Comparison 2: Insulin glargine versus NPH insulin, Outcome 7: Non-fatal myocardial infarction

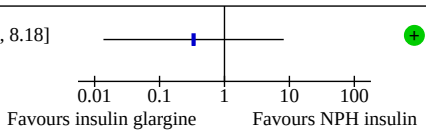
Study or Subgroup	Insulin glargine Events	Total	NPH insulin Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
Home 2005	0	292	1	293	0.33 [0.01 , 8.18]		+	+	+	+	+	+
Test for subgroup differences: Not applicable												



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Non-fatal myocardial infarction
(C) Bias due to missing outcome data: Non-fatal myocardial infarction
(D) Bias in measurement of the outcome: Non-fatal myocardial infarction
(E) Bias in selection of the reported result: Non-fatal myocardial infarction
(F) Overall bias: Non-fatal myocardial infarction

Analysis 2.8. Comparison 2: Insulin glargine versus NPH insulin, Outcome 8: Non-fatal stroke

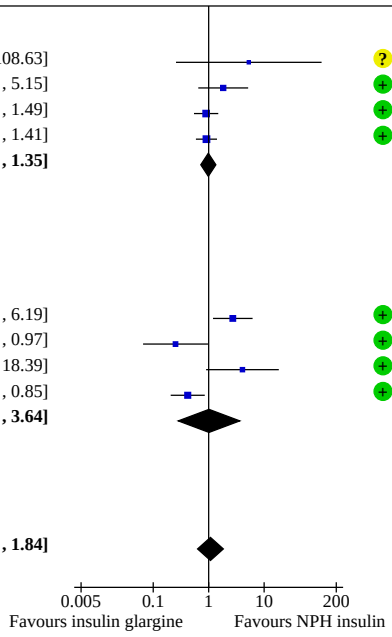
Study or Subgroup	Insulin glargine Events	Total	NPH insulin Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
Home 2005	0	292	1	293	0.33 [0.01 , 8.18]		+	+	+	+	+	+
Test for subgroup differences: Not applicable												



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Non-fatal stroke
(C) Bias due to missing outcome data: Non-fatal stroke
(D) Bias in measurement of the outcome: Non-fatal stroke
(E) Bias in selection of the reported result: Non-fatal stroke
(F) Overall bias: Non-fatal stroke

Analysis 2.9. Comparison 2: Insulin glargine versus NPH insulin, Outcome 9: Serious adverse events

Study or Subgroup	Insulin glargine Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
2.9.1 Adults							
Bolli 2009	2	85	0	90	2.7%	5.29 [0.26 , 108.63]	? + + + + ?
Fulcher 2005	9	62	5	63	12.1%	1.83 [0.65 , 5.15]	+ + + + + +
Home 2005	26	292	29	293	18.4%	0.90 [0.54 , 1.49]	+ + + + + +
Ratner 2000	33	264	37	270	19.2%	0.91 [0.59 , 1.41]	+ + + + + +
Subtotal (95% CI)		**703**		**716**	**52.4%**	**0.99 [0.72 , 1.35]**	
Total events:	70		71				
Heterogeneity: Tau² = 0.00; Chi² = 2.81, df = 3 (P = 0.42); I² = 0%							
Test for overall effect: Z = 0.09 (P = 0.93)							
2.9.2 Children							
Chase 2008	18	85	7	90	14.5%	2.72 [1.20 , 6.19]	+ + + + + +
Liu 2016	3	107	6	54	9.2%	0.25 [0.07 , 0.97]	+ + + + + +
PRESCHOOL	8	62	2	63	8.0%	4.06 [0.90 , 18.39]	+ + + + + +
Schober 2002	10	174	24	175	15.9%	0.42 [0.21 , 0.85]	+ + + + + +
Subtotal (95% CI)		**428**		**382**	**47.6%**	**1.02 [0.28 , 3.64]**	
Total events:	39		39				
Heterogeneity: Tau² = 1.38; Chi² = 18.74, df = 3 (P = 0.0003); I² = 84%							
Test for overall effect: Z = 0.02 (P = 0.98)							
Total (95% CI)		**1131**		**1098**	**100.0%**	**1.08 [0.63 , 1.84]**	
Total events:	109		110				
Heterogeneity: Tau² = 0.34; Chi² = 21.61, df = 7 (P = 0.003); I² = 68%							
Test for overall effect: Z = 0.27 (P = 0.79)							
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.96), I² = 0%							

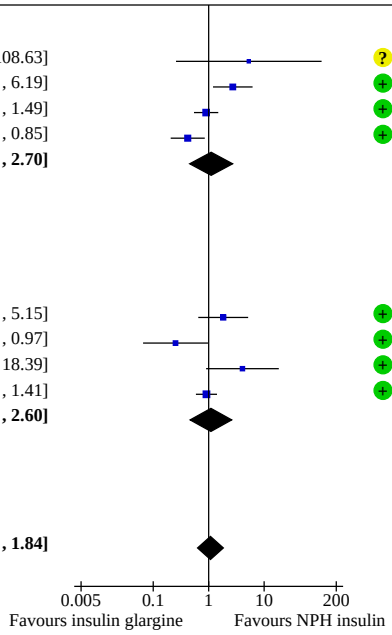


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Serious adverse events
(C) Bias due to missing outcome data: Serious adverse events
(D) Bias in measurement of the outcome: Serious adverse events
(E) Bias in selection of the reported result: Serious adverse events
(F) Overall bias: Serious adverse events

Analysis 2.10. Comparison 2: Insulin glargine versus NPH insulin, Outcome 10: Serious adverse events (published vs. unpublished data)

Study or Subgroup	Insulin glargine Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
2.10.1 Published							
Bolli 2009	2	85	0	90	2.7%	5.29 [0.26 , 108.63]	? + + + + ?
Chase 2008	18	85	7	90	14.5%	2.72 [1.20 , 6.19]	+ + + + + +
Home 2005	26	292	29	293	18.4%	0.90 [0.54 , 1.49]	+ + + + + +
Schober 2002	10	174	24	175	15.9%	0.42 [0.21 , 0.85]	+ + + + + +
Subtotal (95% CI)		**636**		**648**	**51.6%**	**1.11 [0.45 , 2.70]**	
Total events:	56		60				
Heterogeneity: Tau² = 0.55; Chi² = 12.75, df = 3 (P = 0.005); I² = 76%							
Test for overall effect: Z = 0.23 (P = 0.82)							
2.10.2 Unpublished							
Fulcher 2005	9	62	5	63	12.1%	1.83 [0.65 , 5.15]	+ + + + + +
Liu 2016	3	107	6	54	9.2%	0.25 [0.07 , 0.97]	+ + + + + +
PRESCHOOL	8	62	2	63	8.0%	4.06 [0.90 , 18.39]	+ + + + + +
Ratner 2000	33	264	37	270	19.2%	0.91 [0.59 , 1.41]	+ + + + + +
Subtotal (95% CI)		**495**		**450**	**48.4%**	**1.10 [0.46 , 2.60]**	
Total events:	53		50				
Heterogeneity: Tau² = 0.48; Chi² = 8.83, df = 3 (P = 0.03); I² = 66%							
Test for overall effect: Z = 0.21 (P = 0.83)							
Total (95% CI)		**1131**		**1098**	**100.0%**	**1.08 [0.63 , 1.84]**	
Total events:	109		110				
Heterogeneity: Tau² = 0.34; Chi² = 21.61, df = 7 (P = 0.003); I² = 68%							
Test for overall effect: Z = 0.27 (P = 0.79)							
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² = 0%							



Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions: Serious adverse events (published vs. unpublished data)

(C) Bias due to missing outcome data: Serious adverse events (published vs. unpublished data)

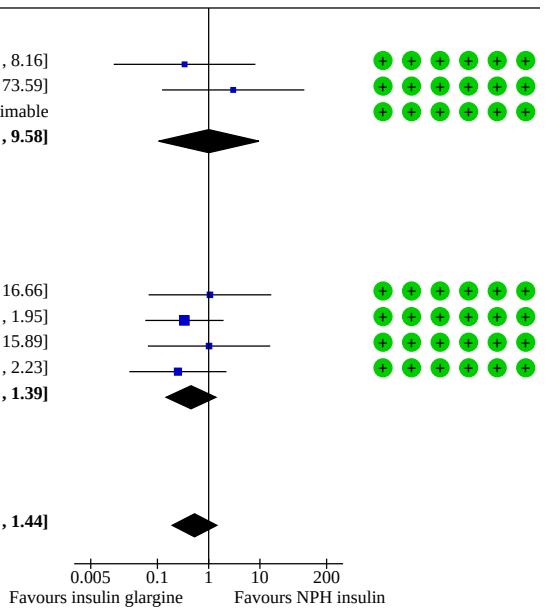
(D) Bias in measurement of the outcome: Serious adverse events (published vs. unpublished data)

(E) Bias in selection of the reported result: Serious adverse events (published vs. unpublished data)

(F) Overall bias: Serious adverse events (published vs. unpublished data)

Analysis 2.11. Comparison 2: Insulin glargine versus NPH insulin, Outcome 11: Diabetic ketoacidosis

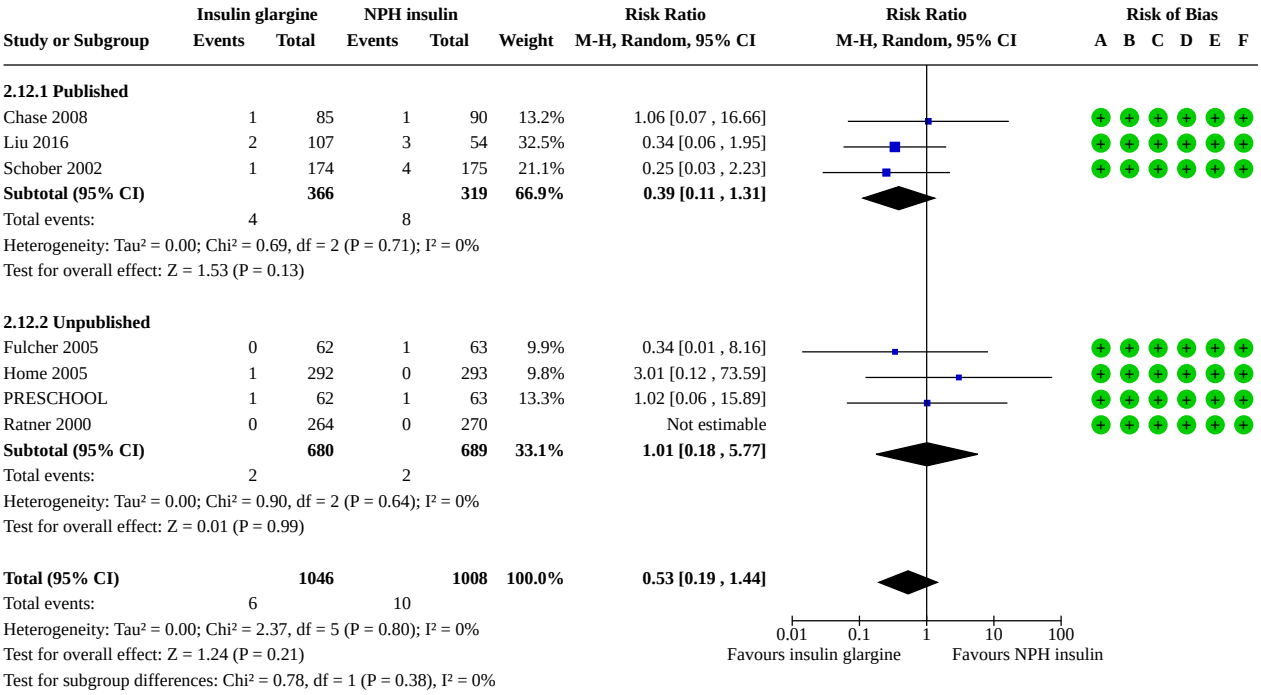
Study or Subgroup	Insulin glargine Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.11.1 Adults						
Fulcher 2005	0	62	1	63	9.9%	0.34 [0.01 , 8.16]
Home 2005	1	292	0	293	9.8%	3.01 [0.12 , 73.59]
Ratner 2000	0	264	0	270		Not estimable
Subtotal (95% CI)		**618**		**626**	**19.8%**	**1.00 [0.11 , 9.58]**
Total events:	1		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.90, df = 1 (P = 0.34); I² = 0%						
Test for overall effect: Z = 0.00 (P = 1.00)						
2.11.2 Children						
Chase 2008	1	85	1	90	13.2%	1.06 [0.07 , 16.66]
Liu 2016	2	107	3	54	32.5%	0.34 [0.06 , 1.95]
PRESCHOOL	1	62	1	63	13.3%	1.02 [0.06 , 15.89]
Schober 2002	1	174	4	175	21.1%	0.25 [0.03 , 2.23]
Subtotal (95% CI)		**428**		**382**	**80.2%**	**0.45 [0.15 , 1.39]**
Total events:	5		9			
Heterogeneity: Tau² = 0.00; Chi² = 1.09, df = 3 (P = 0.78); I² = 0%						
Test for overall effect: Z = 1.39 (P = 0.16)						
Total (95% CI)		**1046**		**1008**	**100.0%**	**0.53 [0.19 , 1.44]**
Total events:	6		10			
Heterogeneity: Tau² = 0.00; Chi² = 2.37, df = 5 (P = 0.80); I² = 0%						
Test for overall effect: Z = 1.24 (P = 0.21)						
Test for subgroup differences: Chi² = 0.39, df = 1 (P = 0.53), I² = 0%						



Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Diabetic ketoacidosis
(C) Bias due to missing outcome data: Diabetic ketoacidosis
(D) Bias in measurement of the outcome: Diabetic ketoacidosis
(E) Bias in selection of the reported result: Diabetic ketoacidosis
(F) Overall bias: Diabetic ketoacidosis

Analysis 2.12. Comparison 2: Insulin glargine versus NPH insulin, Outcome 12: Diabetic ketoacidosis (published vs. unpublished data)



Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions: Diabetic ketoacidosis (published vs. unpublished data)

(C) Bias due to missing outcome data: Diabetic ketoacidosis (published vs. unpublished data)

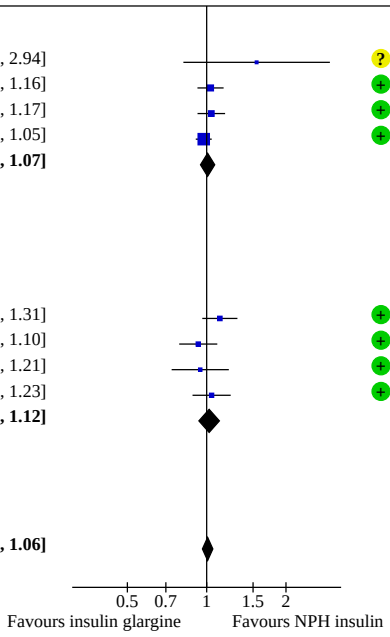
(D) Bias in measurement of the outcome: Diabetic ketoacidosis (published vs. unpublished data)

(E) Bias in selection of the reported result: Diabetic ketoacidosis (published vs. unpublished data)

(F) Overall bias: Diabetic ketoacidosis (published vs. unpublished data)

Analysis 2.13. Comparison 2: Insulin glargine versus NPH insulin, Outcome 13: Non-serious adverse events

Study or Subgroup	Insulin glargine Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.13.1 Adults						
Bolli 2009	19	85	13	90	0.5%	1.55 [0.82 , 2.94]
Fulcher 2005	57	62	56	63	15.8%	1.03 [0.92 , 1.16]
Home 2005	192	292	185	293	14.2%	1.04 [0.92 , 1.17]
Ratner 2000	223	264	234	270	42.5%	0.97 [0.91 , 1.05]
Subtotal (95% CI)		**703**		**716**	**73.0%**	**1.01 [0.95 , 1.07]**
Total events:	491		488			
Heterogeneity: Tau² = 0.00; Chi² = 3.52, df = 3 (P = 0.32); I² = 15%						
Test for overall effect: Z = 0.26 (P = 0.80)						
2.13.2 Children						
Chase 2008	71	85	67	90	8.8%	1.12 [0.96 , 1.31]
Liu 2016 (1)	81	107	44	54	7.5%	0.93 [0.79 , 1.10]
PRESCHOOL	40	62	43	63	3.3%	0.95 [0.74 , 1.21]
Schober 2002	109	174	105	175	7.4%	1.04 [0.88 , 1.23]
Subtotal (95% CI)		**428**		**382**	**27.0%**	**1.02 [0.93 , 1.12]**
Total events:	301		259			
Heterogeneity: Tau² = 0.00; Chi² = 3.12, df = 3 (P = 0.37); I² = 4%						
Test for overall effect: Z = 0.47 (P = 0.64)						
Total (95% CI)		**1131**		**1098**	**100.0%**	**1.01 [0.96 , 1.06]**
Total events:	792		747			
Heterogeneity: Tau² = 0.00; Chi² = 6.65, df = 7 (P = 0.47); I² = 0%						
Test for overall effect: Z = 0.36 (P = 0.72)						
Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.81), I² = 0%						



Footnotes

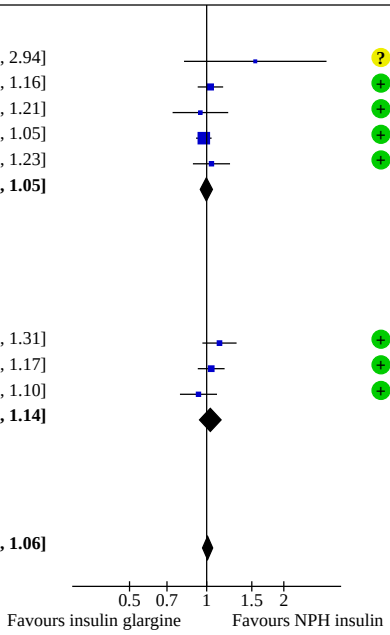
(1) Data from EudraCT. In the CSR the number is 88/107 (insulin glargine) vs 46/54 (NPH insulin)

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Non-serious adverse events
(C) Bias due to missing outcome data: Non-serious adverse events
(D) Bias in measurement of the outcome: Non-serious adverse events
(E) Bias in selection of the reported result: Non-serious adverse events
(F) Overall bias: Non-serious adverse events

Analysis 2.14. Comparison 2: Insulin glargine versus NPH insulin, Outcome 14: Non-serious adverse events (published vs. unpublished data)

Study or Subgroup	Insulin glargine Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
2.14.1 Published							
Bolli 2009	19	85	13	90	0.5%	1.55 [0.82 , 2.94]	? + + ? + ?
Fulcher 2005	57	62	56	63	15.8%	1.03 [0.92 , 1.16]	+ + + ? + ?
PRESCHOOL	40	62	43	63	3.3%	0.95 [0.74 , 1.21]	+ + + ? + ?
Ratner 2000	223	264	234	270	42.5%	0.97 [0.91 , 1.05]	+ + + ? + ?
Schober 2002	109	174	105	175	7.4%	1.04 [0.88 , 1.23]	+ + + ? + ?
Subtotal (95% CI)		**647**		**661**	**69.5%**	**1.00 [0.94 , 1.05]**	
Total events:	448		451				
Heterogeneity: Tau² = 0.00; Chi² = 3.36, df = 4 (P = 0.50); I² = 0%							
Test for overall effect: Z = 0.11 (P = 0.92)							
2.14.2 Unpublished							
Chase 2008	71	85	67	90	8.8%	1.12 [0.96 , 1.31]	+ + + ? + ?
Home 2005	192	292	185	293	14.2%	1.04 [0.92 , 1.17]	+ + + ? + ?
Liu 2016	81	107	44	54	7.5%	0.93 [0.79 , 1.10]	+ + + ? + ?
Subtotal (95% CI)		**484**		**437**	**30.5%**	**1.03 [0.94 , 1.14]**	
Total events:	344		296				
Heterogeneity: Tau² = 0.00; Chi² = 2.69, df = 2 (P = 0.26); I² = 26%							
Test for overall effect: Z = 0.66 (P = 0.51)							
Total (95% CI)		**1131**		**1098**	**100.0%**	**1.01 [0.96 , 1.06]**	
Total events:	792		747				
Heterogeneity: Tau² = 0.00; Chi² = 6.65, df = 7 (P = 0.47); I² = 0%							
Test for overall effect: Z = 0.36 (P = 0.72)							
Test for subgroup differences: Chi² = 0.39, df = 1 (P = 0.53), I² = 0%							



Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions: Non-serious adverse events (published vs. unpublished data)

(C) Bias due to missing outcome data: Non-serious adverse events (published vs. unpublished data)

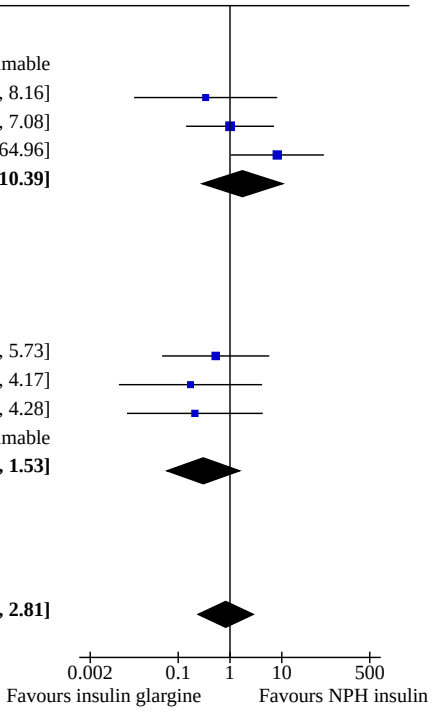
(D) Bias in measurement of the outcome: Non-serious adverse events (published vs. unpublished data)

(E) Bias in selection of the reported result: Non-serious adverse events (published vs. unpublished data)

(F) Overall bias: Non-serious adverse events (published vs. unpublished data)

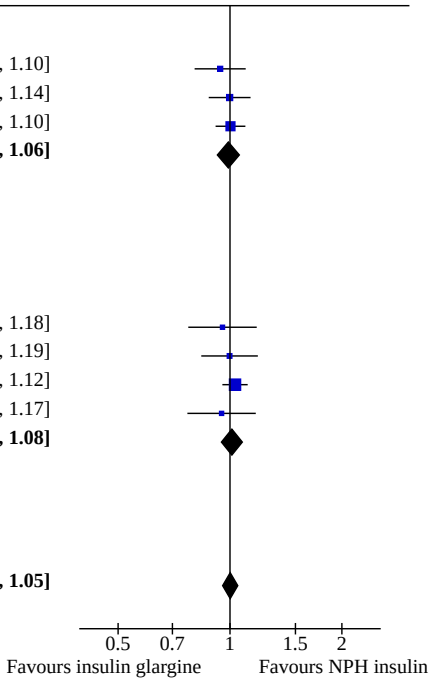
Analysis 2.15. Comparison 2: Insulin glargine versus NPH insulin, Outcome 15: Withdrawals due to adverse events

Study or Subgroup	Insulin glargine Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.15.1 Adults						
Bolli 2009	0	85	0	90		Not estimable
Fulcher 2005	0	62	1	63	11.8%	0.34 [0.01 , 8.16]
Home 2005	2	292	2	293	23.5%	1.00 [0.14 , 7.08]
Ratner 2000	8	264	1	270	21.9%	8.18 [1.03 , 64.96]
Subtotal (95% CI)		**703**		**716**	**57.2%**	**1.74 [0.29 , 10.39]**
Total events:	10		4			
Heterogeneity: Tau² = 1.09; Chi² = 3.55, df = 2 (P = 0.17); I² = 44%						
Test for overall effect: Z = 0.60 (P = 0.55)						
2.15.2 Children						
Chase 2008	1	85	2	90	18.2%	0.53 [0.05 , 5.73]
Liu 2016	0	107	1	55	11.8%	0.17 [0.01 , 4.17]
PRESCHOOL	0	61	2	64	12.9%	0.21 [0.01 , 4.28]
Schober 2002	0	174	0	175		Not estimable
Subtotal (95% CI)		**427**		**384**	**42.8%**	**0.30 [0.06 , 1.53]**
Total events:	1		5			
Heterogeneity: Tau² = 0.00; Chi² = 0.39, df = 2 (P = 0.82); I² = 0%						
Test for overall effect: Z = 1.44 (P = 0.15)						
Total (95% CI)		**1130**		**1100**	**100.0%**	**0.83 [0.24 , 2.81]**
Total events:	11		9			
Heterogeneity: Tau² = 0.67; Chi² = 7.03, df = 5 (P = 0.22); I² = 29%						
Test for overall effect: Z = 0.31 (P = 0.76)						
Test for subgroup differences: Chi² = 2.00, df = 1 (P = 0.16), I² = 50.1%						



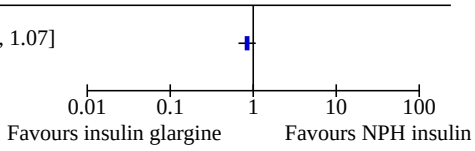
Analysis 2.16. Comparison 2: Insulin glargine versus NPH insulin, Outcome 16: Nocturnal hypoglycaemia

Study or Subgroup	Insulin glargine Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.16.1 Adults						
Fulcher 2005	50	62	54	63	8.7%	0.94 [0.80 , 1.10]
Home 2005	178	292	179	293	13.0%	1.00 [0.88 , 1.14]
Ratner 2000	204	264	208	270	25.7%	1.00 [0.91 , 1.10]
Subtotal (95% CI)		**618**		**626**	**47.5%**	**0.99 [0.92 , 1.06]**
Total events:	432		441			
Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 2 (P = 0.78); I² = 0%						
Test for overall effect: Z = 0.29 (P = 0.77)						
2.16.2 Children						
Chase 2008	55	85	61	90	4.9%	0.95 [0.77 , 1.18]
Liu 2016	83	107	42	54	7.1%	1.00 [0.84 , 1.19]
PRESCHOOL	59	61	60	64	35.7%	1.03 [0.95 , 1.12]
Schober 2002	84	174	89	175	4.9%	0.95 [0.77 , 1.17]
Subtotal (95% CI)		**427**		**383**	**52.5%**	**1.01 [0.95 , 1.08]**
Total events:	281		252			
Heterogeneity: Tau² = 0.00; Chi² = 1.89, df = 3 (P = 0.59); I² = 0%						
Test for overall effect: Z = 0.35 (P = 0.72)						
Total (95% CI)		**1045**		**1009**	**100.0%**	**1.00 [0.96 , 1.05]**
Total events:	713		693			
Heterogeneity: Tau² = 0.00; Chi² = 1.91, df = 6 (P = 0.93); I² = 0%						
Test for overall effect: Z = 0.05 (P = 0.96)						
Test for subgroup differences: Chi² = 0.21, df = 1 (P = 0.65), I² = 0%						



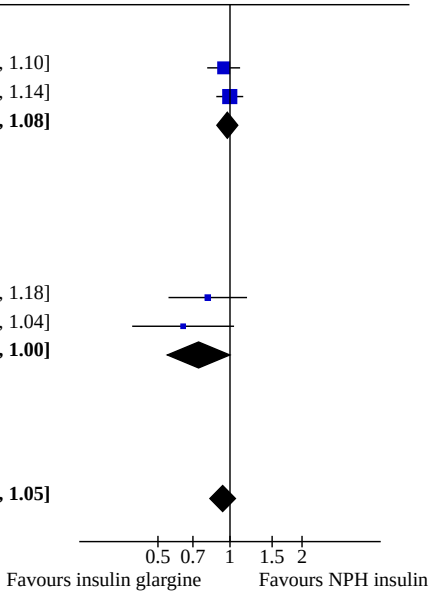
Analysis 2.17. Comparison 2: Insulin glargine versus NPH insulin, Outcome 17: Mild nocturnal hypoglycaemia

Study or Subgroup	Insulin glargine Events	Total	NPH insulin Events	Total	Risk Ratio M-H, Fixed, 95% CI
Fulcher 2005	39	62	47	63	0.84 [0.66 , 1.07]
Test for subgroup differences: Not applicable					

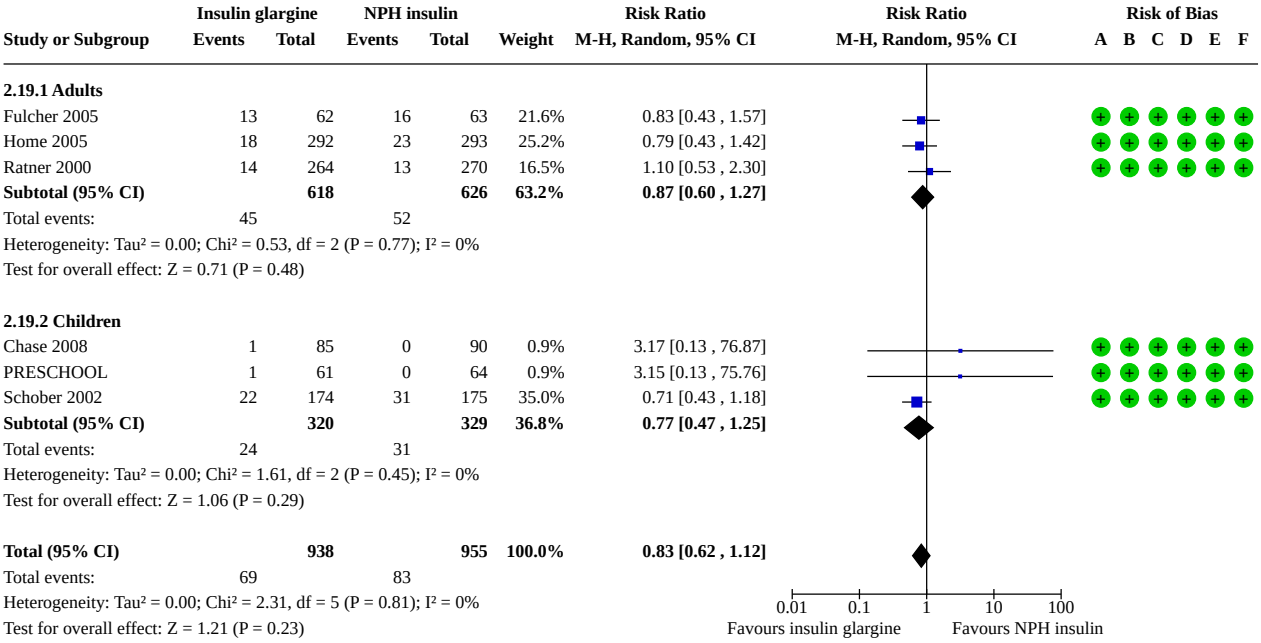


Analysis 2.18. Comparison 2: Insulin glargine versus NPH insulin, Outcome 18: Nocturnal hypoglycaemia (symptoms)

Study or Subgroup	Insulin glargine Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.18.1 Adults						
Fulcher 2005	50	62	54	63	37.4%	0.94 [0.80 , 1.10]
Home 2005	178	292	179	293	47.2%	1.00 [0.88 , 1.14]
Subtotal (95% CI)		**354**		**356**	**84.6%**	**0.97 [0.88 , 1.08]**
Total events:	228		233			
Heterogeneity: Tau² = 0.00; Chi² = 0.36, df = 1 (P = 0.55); I² = 0%						
Test for overall effect: Z = 0.50 (P = 0.61)						
2.18.2 Children						
Liu 2016	40	107	25	54	9.5%	0.81 [0.55 , 1.18]
PRESCHOOL	17	61	28	64	5.9%	0.64 [0.39 , 1.04]
Subtotal (95% CI)		**168**		**118**	**15.4%**	**0.74 [0.55 , 1.00]**
Total events:	57		53			
Heterogeneity: Tau² = 0.00; Chi² = 0.57, df = 1 (P = 0.45); I² = 0%						
Test for overall effect: Z = 1.98 (P = 0.05)						
Total (95% CI)		**522**		**474**	**100.0%**	**0.93 [0.82 , 1.05]**
Total events:	285		286			
Heterogeneity: Tau² = 0.00; Chi² = 3.95, df = 3 (P = 0.27); I² = 24%						
Test for overall effect: Z = 1.13 (P = 0.26)						
Test for subgroup differences: Chi² = 2.95, df = 1 (P = 0.09), I² = 66.1%						



Analysis 2.19. Comparison 2: Insulin glargine versus NPH insulin, Outcome 19: Severe nocturnal hypoglycaemia



Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions: Severe nocturnal hypoglycaemia

(C) Bias due to missing outcome data: Severe nocturnal hypoglycaemia

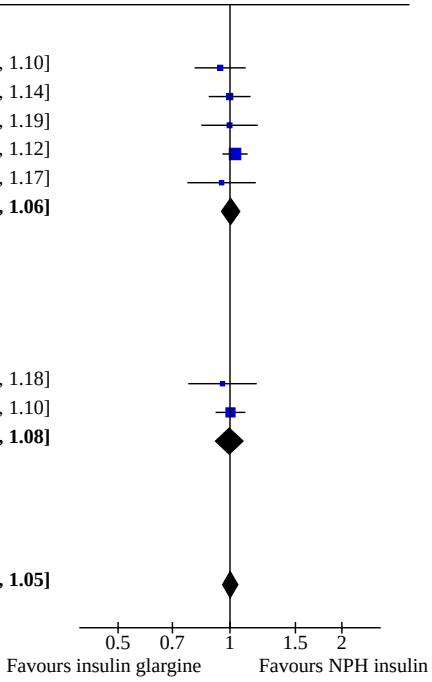
(D) Bias in measurement of the outcome: Severe nocturnal hypoglycaemia

(E) Bias in selection of the reported result: Severe nocturnal hypoglycaemia

(F) Overall bias: Severe nocturnal hypoglycaemia

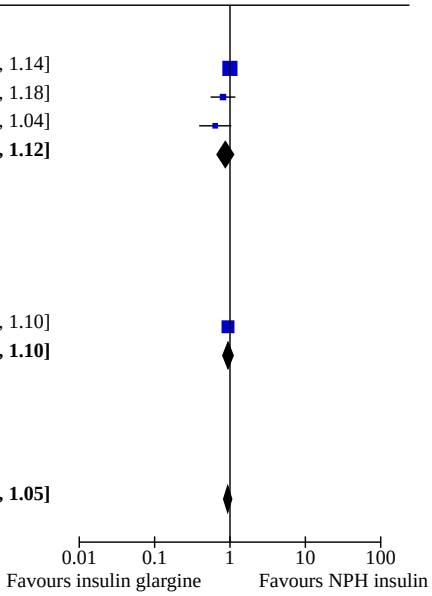
Analysis 2.20. Comparison 2: Insulin glargine versus NPH insulin, Outcome 20: Nocturnal hypoglycaemia (published vs. unpublished data)

Study or Subgroup	Insulin glargine Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.20.1 Published						
Fulcher 2005	50	62	54	63	8.7%	0.94 [0.80 , 1.10]
Home 2005	178	292	179	293	13.0%	1.00 [0.88 , 1.14]
Liu 2016	83	107	42	54	7.1%	1.00 [0.84 , 1.19]
PRESCHOOL	59	61	60	64	35.7%	1.03 [0.95 , 1.12]
Schober 2002	84	174	89	175	4.9%	0.95 [0.77 , 1.17]
Subtotal (95% CI)		**696**		**649**	**69.4%**	**1.00 [0.95 , 1.06]**
Total events:	454		424			
Heterogeneity: Tau² = 0.00; Chi² = 1.82, df = 4 (P = 0.77); I² = 0%						
Test for overall effect: Z = 0.14 (P = 0.89)						
2.20.2 Unpublished						
Chase 2008	55	85	61	90	4.9%	0.95 [0.77 , 1.18]
Ratner 2000	204	264	208	270	25.7%	1.00 [0.91 , 1.10]
Subtotal (95% CI)		**349**		**360**	**30.6%**	**1.00 [0.91 , 1.08]**
Total events:	259		269			
Heterogeneity: Tau² = 0.00; Chi² = 0.18, df = 1 (P = 0.67); I² = 0%						
Test for overall effect: Z = 0.11 (P = 0.91)						
Total (95% CI)		**1045**		**1009**	**100.0%**	**1.00 [0.96 , 1.05]**
Total events:	713		693			
Heterogeneity: Tau² = 0.00; Chi² = 1.91, df = 6 (P = 0.93); I² = 0%						
Test for overall effect: Z = 0.05 (P = 0.96)						
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.86), I² = 0%						



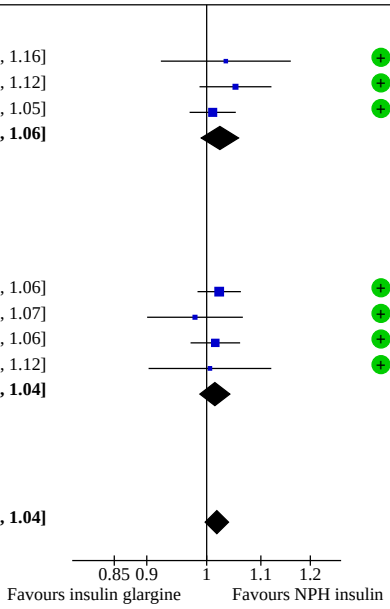
Analysis 2.21. Comparison 2: Insulin glargine versus NPH insulin, Outcome 21: Symptomatic nocturnal hypoglycaemia (published vs. unpublished data)

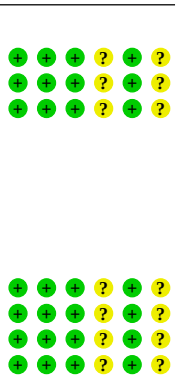
Study or Subgroup	Insulin glargine Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.21.1 Published						
Home 2005	178	292	179	293	47.2%	1.00 [0.88 , 1.14]
Liu 2016	40	107	25	54	9.5%	0.81 [0.55 , 1.18]
PRESCHOOL	17	61	28	64	5.9%	0.64 [0.39 , 1.04]
Subtotal (95% CI)		**460**		**411**	**62.6%**	**0.87 [0.67 , 1.12]**
Total events:	235		232			
Heterogeneity: Tau² = 0.03; Chi² = 3.96, df = 2 (P = 0.14); I² = 49%						
Test for overall effect: Z = 1.10 (P = 0.27)						
2.21.2 Unpublished						
Fulcher 2005	50	62	54	63	37.4%	0.94 [0.80 , 1.10]
Subtotal (95% CI)		**62**		**63**	**37.4%**	**0.94 [0.80 , 1.10]**
Total events:	50		54			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.76 (P = 0.45)						
Total (95% CI)		**522**		**474**	**100.0%**	**0.93 [0.82 , 1.05]**
Total events:	285		286			
Heterogeneity: Tau² = 0.00; Chi² = 3.95, df = 3 (P = 0.27); I² = 24%						
Test for overall effect: Z = 1.13 (P = 0.26)						
Test for subgroup differences: Chi² = 0.29, df = 1 (P = 0.59), I² = 0%						



Analysis 2.22. Comparison 2: Insulin glargine versus NPH insulin, Outcome 22: Mild/moderate hypoglycaemia

Study or Subgroup	Insulin glargine Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.22.1 Adults						
Fulcher 2005	57	62	56	63	3.2%	1.03 [0.92 , 1.16]
Home 2005	260	292	248	293	10.5%	1.05 [0.99 , 1.12]
Ratner 2000	251	264	254	270	25.5%	1.01 [0.97 , 1.05]
Subtotal (95% CI)		**618**		**626**	**39.3%**	**1.02 [0.99 , 1.06]**
Total events:	568		558			
Heterogeneity: Tau² = 0.00; Chi² = 1.34, df = 2 (P = 0.51); I² = 0%						
Test for overall effect: Z = 1.39 (P = 0.16)						
2.22.2 Children						
Chase 2008	85	85	88	90	29.0%	1.02 [0.98 , 1.06]
Liu 2016	99	107	51	54	5.9%	0.98 [0.90 , 1.07]
PRESCHOOL	61	61	63	64	22.2%	1.02 [0.97 , 1.06]
Schober 2002	138	174	138	175	3.6%	1.01 [0.90 , 1.12]
Subtotal (95% CI)		**427**		**383**	**60.7%**	**1.01 [0.99 , 1.04]**
Total events:	383		340			
Heterogeneity: Tau² = 0.00; Chi² = 1.19, df = 3 (P = 0.75); I² = 0%						
Test for overall effect: Z = 1.07 (P = 0.28)						
Total (95% CI)		**1045**		**1009**	**100.0%**	**1.02 [1.00 , 1.04]**
Total events:	951		898			
Heterogeneity: Tau² = 0.00; Chi² = 2.26, df = 6 (P = 0.89); I² = 0%						
Test for overall effect: Z = 1.71 (P = 0.09)						
Test for subgroup differences: Chi² = 0.17, df = 1 (P = 0.68), I² = 0%						



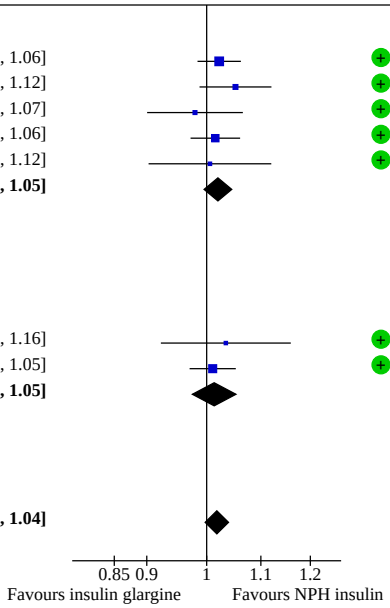


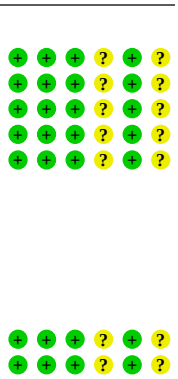
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Mild/moderate hypoglycaemia
(C) Bias due to missing outcome data: Mild/moderate hypoglycaemia
(D) Bias in measurement of the outcome: Mild/moderate hypoglycaemia
(E) Bias in selection of the reported result: Mild/moderate hypoglycaemia
(F) Overall bias: Mild/moderate hypoglycaemia

Analysis 2.23. Comparison 2: Insulin glargine versus NPH insulin, Outcome 23: Mild/moderate hypoglycaemia (published vs. unpublished data)

Study or Subgroup	Insulin glargine Events	Total	NPH insulin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.23.1 Published						
Chase 2008	85	85	88	90	29.0%	1.02 [0.98 , 1.06]
Home 2005	260	292	248	293	10.5%	1.05 [0.99 , 1.12]
Liu 2016	99	107	51	54	5.9%	0.98 [0.90 , 1.07]
PRESCHOOL	61	61	63	64	22.2%	1.02 [0.97 , 1.06]
Schober 2002	138	174	138	175	3.6%	1.01 [0.90 , 1.12]
Subtotal (95% CI)		**719**		**676**	**71.2%**	**1.02 [1.00 , 1.05]**
Total events:	643		588			
Heterogeneity: Tau² = 0.00; Chi² = 2.09, df = 4 (P = 0.72); I² = 0%						
Test for overall effect: Z = 1.59 (P = 0.11)						
2.23.2 Unpublished						
Fulcher 2005	57	62	56	63	3.2%	1.03 [0.92 , 1.16]
Ratner 2000	251	264	254	270	25.5%	1.01 [0.97 , 1.05]
Subtotal (95% CI)		**326**		**333**	**28.8%**	**1.01 [0.98 , 1.05]**
Total events:	308		310			
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%						
Test for overall effect: Z = 0.68 (P = 0.50)						
Total (95% CI)		**1045**		**1009**	**100.0%**	**1.02 [1.00 , 1.04]**
Total events:	951		898			
Heterogeneity: Tau² = 0.00; Chi² = 2.26, df = 6 (P = 0.89); I² = 0%						
Test for overall effect: Z = 1.71 (P = 0.09)						
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.78), I² = 0%						





Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions: Mild/moderate hypoglycaemia (published vs. unpublished data)

(C) Bias due to missing outcome data: Mild/moderate hypoglycaemia (published vs. unpublished data)

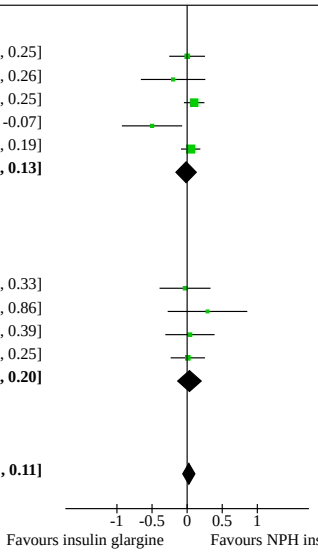
(D) Bias in measurement of the outcome: Mild/moderate hypoglycaemia (published vs. unpublished data)

(E) Bias in selection of the reported result: Mild/moderate hypoglycaemia (published vs. unpublished data)

(F) Overall bias: Mild/moderate hypoglycaemia (published vs. unpublished data)

Analysis 2.24. Comparison 2: Insulin glargine versus NPH insulin, Outcome 24: HbA1c

Study or Subgroup	Insulin glargine Mean	SD	Total	NPH insulin Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.24.1 Adults								
Bolli 2009	7.3	0.7	85	7.3	1	90	10.6%	0.00 [-0.25 , 0.25]
Fulcher 2005	-0.9	1.2	62	-0.7	1.4	62	3.5%	-0.20 [-0.66 , 0.26]
Home 2005 (1)	0.2	0.9	292	0.1	0.9	293	27.3%	0.10 [-0.05 , 0.25]
Porcellati 2004 (1)	6.6	0.8	61	7.1	1.5	60	3.9%	-0.50 [-0.93 , -0.07]
Ratner 2000 (1)	-0.16	0.8	256	-0.21	0.8	262	29.8%	0.05 [-0.09 , 0.19]
Subtotal (95% CI)			**756**			**767**	**75.1%**	**-0.01 [-0.16 , 0.13]**
Heterogeneity: Tau² = 0.01; Chi² = 7.84, df = 4 (P = 0.10); I² = 49%								
Test for overall effect: Z = 0.20 (P = 0.84)								
2.24.2 Children								
Chase 2008	-0.18	1.2	84	-0.15	1.2	84	5.4%	-0.03 [-0.39 , 0.33]
Liu 2016	-0.25	1.7	107	-0.54	1.7	51	2.3%	0.29 [-0.28 , 0.86]
PRESCHOOL	0.04	1	61	0	1	64	5.8%	0.04 [-0.31 , 0.39]
Schober 2002 (1)	0.28	1.1	155	0.27	1.1	156	11.4%	0.01 [-0.23 , 0.25]
Subtotal (95% CI)			**407**			**355**	**24.9%**	**0.03 [-0.13 , 0.20]**
Heterogeneity: Tau² = 0.00; Chi² = 0.94, df = 3 (P = 0.82); I² = 0%								
Test for overall effect: Z = 0.38 (P = 0.70)								
Total (95% CI)			**1163**			**1122**	**100.0%**	**0.02 [-0.06 , 0.11]**
Heterogeneity: Tau² = 0.00; Chi² = 8.78, df = 8 (P = 0.36); I² = 9%								
Test for overall effect: Z = 0.54 (P = 0.59)								
Test for subgroup differences: Chi² = 0.18, df = 1 (P = 0.67), I² = 0%								



Risk of Bias: A B C D E F

Footnotes

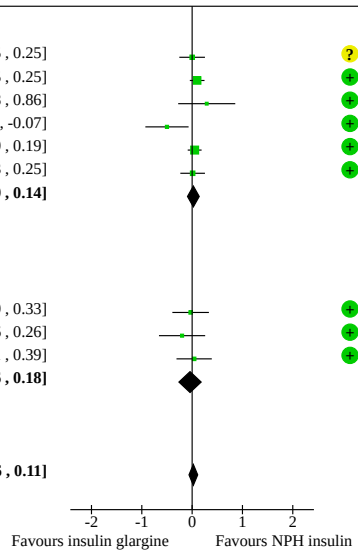
(1) SD calculated from SE

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: HbA1c
(C) Bias due to missing outcome data: HbA1c
(D) Bias in measurement of the outcome: HbA1c
(E) Bias in selection of the reported result: HbA1c
(F) Overall bias: HbA1c

Analysis 2.25. Comparison 2: Insulin glargine versus NPH insulin, Outcome 25: HbA1c (published vs unpublished data)

Study or Subgroup	Insulin glargine Mean	SD	Total	NPH insulin Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F
2.25.1 Published									
Bolli 2009	7.3	0.7	85	7.3	1	90	10.6%	0.00 [-0.25 , 0.25]	? + + + + ?
Home 2005 (1)	0.2	0.9	292	0.1	0.9	293	27.3%	0.10 [-0.05 , 0.25]	+ + + + + +
Liu 2016	-0.25	1.7	107	-0.54	1.7	51	2.3%	0.29 [-0.28 , 0.86]	+ + + + + +
Porcellati 2004 (1)	6.6	0.8	61	7.1	1.5	60	3.9%	-0.50 [-0.93 , -0.07]	+ + + + ? ?
Ratner 2000 (1)	-0.16	0.8	256	-0.21	0.8	262	29.8%	0.05 [-0.09 , 0.19]	+ + + + + +
Schober 2002 (1)	0.28	1.1	155	0.27	1.1	156	11.4%	0.01 [-0.23 , 0.25]	+ + + + + +
Subtotal (95% CI)			**956**			**912**	**85.3%**	**0.02 [-0.09 , 0.14]**	
Heterogeneity: Tau² = 0.01; Chi² = 7.65, df = 5 (P = 0.18); I² = 35%									
Test for overall effect: Z = 0.41 (P = 0.68)									
2.25.2 Unpublished									
Chase 2008	-0.18	1.2	84	-0.15	1.2	84	5.4%	-0.03 [-0.39 , 0.33]	+ + + + + +
Fulcher 2005	-0.9	1.2	62	-0.7	1.4	62	3.5%	-0.20 [-0.66 , 0.26]	+ + + + + +
PRESCHOOL	0.04	1	61	0	1	64	5.8%	0.04 [-0.31 , 0.39]	+ + + + + +
Subtotal (95% CI)			**207**			**210**	**14.7%**	**-0.04 [-0.26 , 0.18]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.67, df = 2 (P = 0.72); I² = 0%									
Test for overall effect: Z = 0.37 (P = 0.71)									
Total (95% CI)			**1163**			**1122**	**100.0%**	**0.02 [-0.06 , 0.11]**	
Heterogeneity: Tau² = 0.00; Chi² = 8.78, df = 8 (P = 0.36); I² = 9%									
Test for overall effect: Z = 0.54 (P = 0.59)									
Test for subgroup differences: Chi² = 0.27, df = 1 (P = 0.60), I² = 0%									



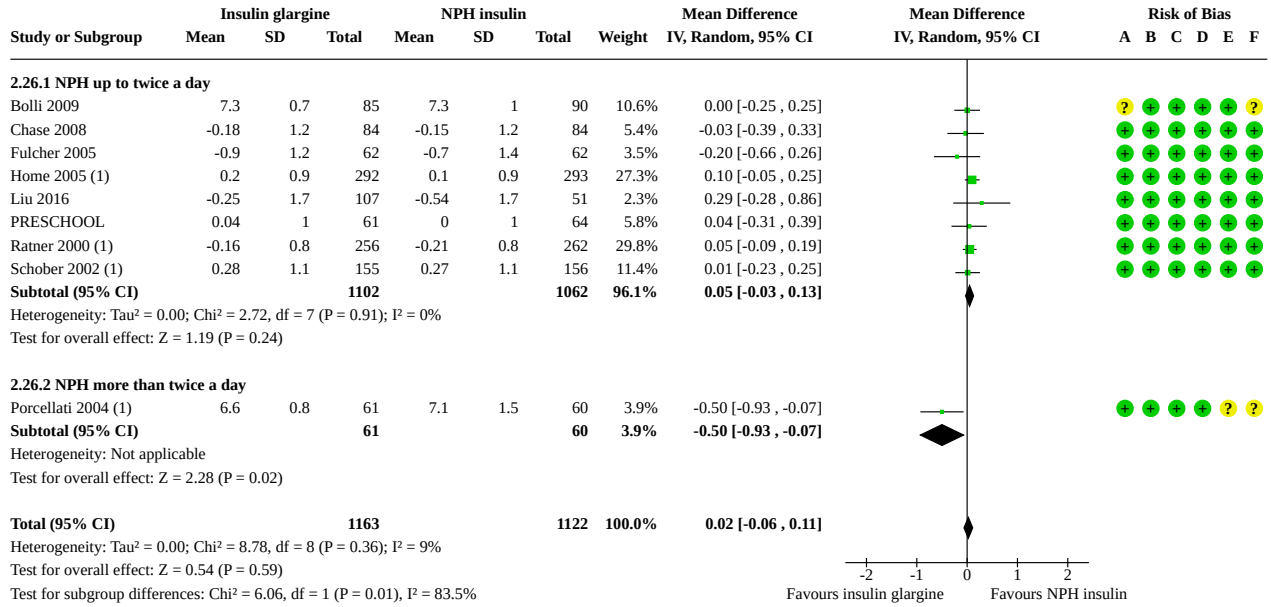
Footnotes

(1) SD calculated from SE

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: HbA1c (published vs unpublished data)
(C) Bias due to missing outcome data: HbA1c (published vs unpublished data)
(D) Bias in measurement of the outcome: HbA1c (published vs unpublished data)
(E) Bias in selection of the reported result: HbA1c (published vs unpublished data)
(F) Overall bias: HbA1c (published vs unpublished data)

Analysis 2.26. Comparison 2: Insulin glargine versus NPH insulin, Outcome 26: HbA1c (NPH < 2x/day vs ≥ 2x/day)



Study or Subgroup	Insulin glargine Mean	SD	Total	NPH insulin Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.26.1 NPH up to twice a day								
Bolli 2009	7.3	0.7	85	7.3	1	90	10.6%	0.00 [-0.25 , 0.25]
Chase 2008	-0.18	1.2	84	-0.15	1.2	84	5.4%	-0.03 [-0.39 , 0.33]
Fulcher 2005	-0.9	1.2	62	-0.7	1.4	62	3.5%	-0.20 [-0.66 , 0.26]
Home 2005 (1)	0.2	0.9	292	0.1	0.9	293	27.3%	0.10 [-0.05 , 0.25]
Liu 2016	-0.25	1.7	107	-0.54	1.7	51	2.3%	0.29 [-0.28 , 0.86]
PRESCHOOL	0.04	1	61	0	1	64	5.8%	0.04 [-0.31 , 0.39]
Ratner 2000 (1)	-0.16	0.8	256	-0.21	0.8	262	29.8%	0.05 [-0.09 , 0.19]
Schober 2002 (1)	0.28	1.1	155	0.27	1.1	156	11.4%	0.01 [-0.23 , 0.25]
Subtotal (95% CI)			**1102**			**1062**	**96.1%**	**0.05 [-0.03 , 0.13]**
Heterogeneity: Tau² = 0.00; Chi² = 2.72, df = 7 (P = 0.91); I² = 0%								
Test for overall effect: Z = 1.19 (P = 0.24)								
2.26.2 NPH more than twice a day								
Porcellati 2004 (1)	6.6	0.8	61	7.1	1.5	60	3.9%	-0.50 [-0.93 , -0.07]
Subtotal (95% CI)			**61**			**60**	**3.9%**	**-0.50 [-0.93 , -0.07]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.28 (P = 0.02)								
Total (95% CI)			**1163**			**1122**	**100.0%**	**0.02 [-0.06 , 0.11]**
Heterogeneity: Tau² = 0.00; Chi² = 8.78, df = 8 (P = 0.36); I² = 9%								
Test for overall effect: Z = 0.54 (P = 0.59)								
Test for subgroup differences: Chi² = 6.06, df = 1 (P = 0.01), I² = 83.5%								

Footnotes
(1) SD calculated from SE

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: HbA1c (NPH < 2x/day vs ≥ 2x/day)
(C) Bias due to missing outcome data: HbA1c (NPH < 2x/day vs ≥ 2x/day)
(D) Bias in measurement of the outcome: HbA1c (NPH < 2x/day vs ≥ 2x/day)
(E) Bias in selection of the reported result: HbA1c (NPH < 2x/day vs ≥ 2x/day)
(F) Overall bias: HbA1c (NPH < 2x/day vs ≥ 2x/day)

Comparison 3. Insulin detemir versus insulin glargine

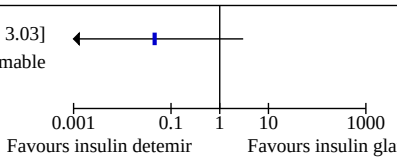
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 All-cause mortality	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
3.2 Severe hypoglycaemia	2	763	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.13, 2.63]
3.3 Severe hypoglycaemia (published vs. unpublished data)	2	763	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.13, 2.63]
3.3.1 Published	1	320	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.07, 0.86]
3.3.2 Unpublished	1	443	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.72, 1.77]
3.4 Hypoglycaemia reported as a serious adverse event	2	763	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.14, 9.48]
3.5 Cardiovascular mortality	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.6 Non-fatal myocardial infarction	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.7 Non-fatal stroke	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.8 Serious adverse events	2	763	Risk Ratio (M-H, Random, 95% CI)	1.72 [0.91, 3.28]
3.9 Diabetic ketoacidosis	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.10 Non-serious adverse events	2	763	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.93, 1.09]
3.11 Non-serious adverse events (published vs. unpublished data)	2	763	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.93, 1.09]
3.11.1 Published	1	443	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.97, 1.10]
3.11.2 Unpublished	1	320	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.84, 1.09]
3.12 Withdrawals due to adverse events	2	763	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.31, 3.67]
3.13 Any nocturnal hypoglycaemia	2	763	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.93, 1.09]
3.13.1 Published	1	320	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.75, 1.17]
3.13.2 Unpublished	1	443	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.94, 1.11]
3.14 Confirmed nocturnal hypoglycaemia (PG < 3.1 mmol/L and no assistance)	2	763	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.92, 1.10]
3.14.1 Published	1	320	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.71, 1.16]
3.14.2 Unpublished	1	443	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.93, 1.12]
3.15 Symptomatic nocturnal hypoglycaemia (PG ≥ 3.1 or no PG and no assistance required)	2	763	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.81, 1.29]
3.15.1 Published	1	320	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.78, 2.12]
3.15.2 Unpublished	1	443	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.77, 1.21]
3.16 Severe nocturnal hypoglycaemia	2	763	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.06, 5.12]
3.16.1 Published	1	320	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.01, 2.02]
3.16.2 Unpublished	1	443	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.60, 2.32]
3.17 Mild/moderate hypoglycaemia	2	763	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.94, 1.14]
3.17.1 Published	1	320	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.95, 1.26]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.17.2 Unpublished	1	443	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.96, 1.06]
3.18 HbA1c	2	717	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.13, 0.12]
3.19 Individuals with HbA1c < 7% without severe hypoglycaemia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3: Insulin detemir versus insulin glargine, Outcome 1: All-cause mortality

Study or Subgroup	Insulin detemir Events	Total	Insulin glargine Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI	Risk of Bias A B C D E F
Heller 2009	0	299	1	144	0.05 [0.00 , 3.03]	+ + + + + +
Pieber 2007	0	161	0	159	Not estimable	+ + + + + +

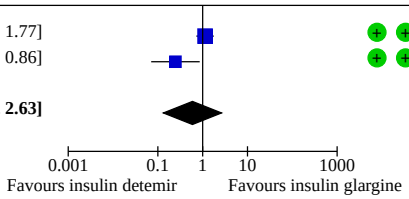


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: All-cause mortality
(C) Bias due to missing outcome data: All-cause mortality
(D) Bias in measurement of the outcome: All-cause mortality
(E) Bias in selection of the reported result: All-cause mortality
(F) Overall bias: All-cause mortality

Analysis 3.2. Comparison 3: Insulin detemir versus insulin glargine, Outcome 2: Severe hypoglycaemia

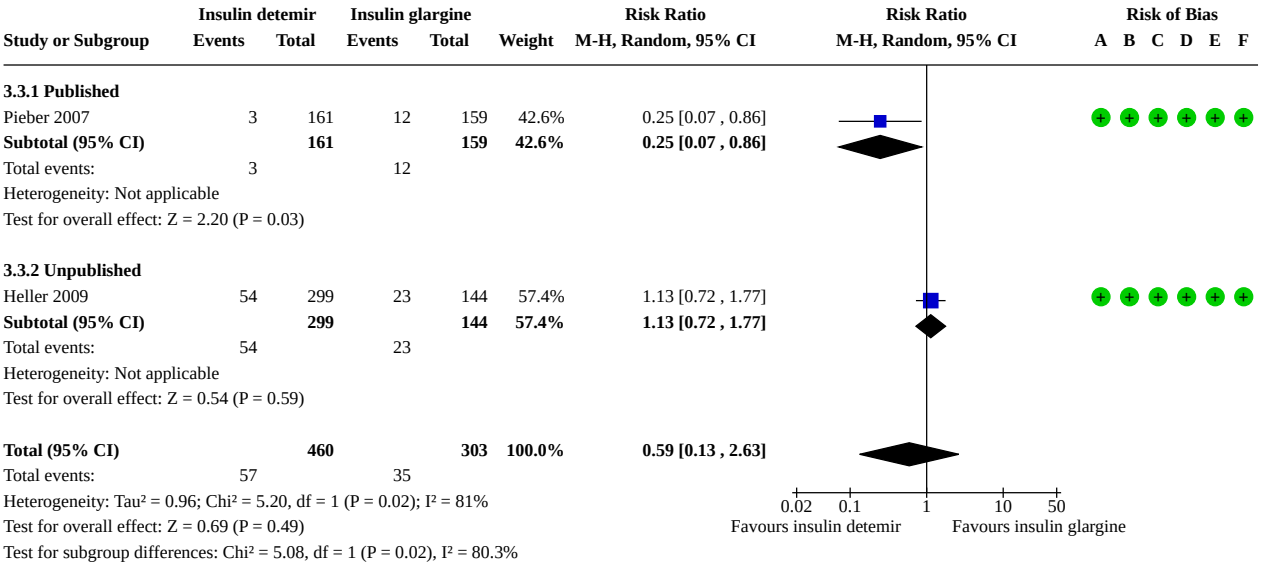
Study or Subgroup	Insulin detemir Events	Total	Insulin glargine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Heller 2009	54	299	23	144	57.4%	1.13 [0.72 , 1.77]	+ + + + + +
Pieber 2007	3	161	12	159	42.6%	0.25 [0.07 , 0.86]	+ + + + + +
Total (95% CI)		**460**		**303**	**100.0%**	**0.59 [0.13 , 2.63]**	
Total events:	57		35				

Heterogeneity: Tau² = 0.96; Chi² = 5.20, df = 1 (P = 0.02); I² = 81%
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Severe hypoglycaemia
(C) Bias due to missing outcome data: Severe hypoglycaemia
(D) Bias in measurement of the outcome: Severe hypoglycaemia
(E) Bias in selection of the reported result: Severe hypoglycaemia
(F) Overall bias: Severe hypoglycaemia

Analysis 3.3. Comparison 3: Insulin detemir versus insulin glargine, Outcome 3: Severe hypoglycaemia (published vs. unpublished data)



Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions: Severe hypoglycaemia (published vs. unpublished data)

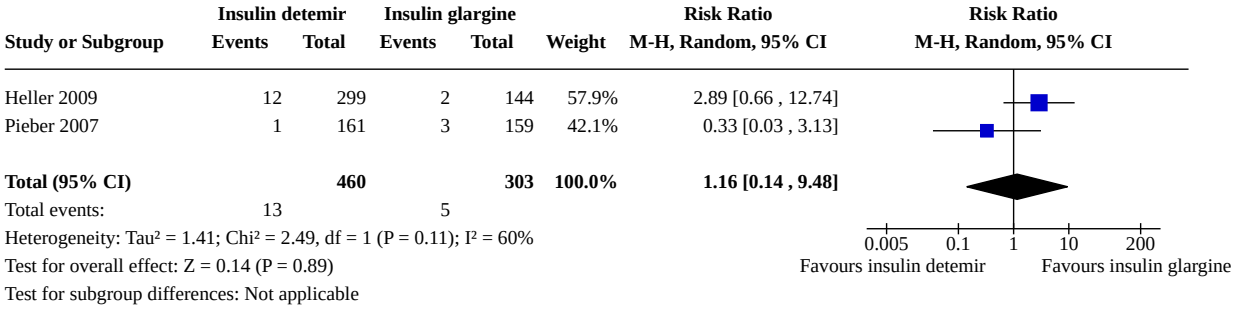
(C) Bias due to missing outcome data: Severe hypoglycaemia (published vs. unpublished data)

(D) Bias in measurement of the outcome: Severe hypoglycaemia (published vs. unpublished data)

(E) Bias in selection of the reported result: Severe hypoglycaemia (published vs. unpublished data)

(F) Overall bias: Severe hypoglycaemia (published vs. unpublished data)

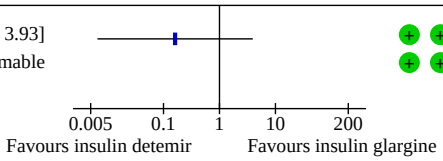
Analysis 3.4. Comparison 3: Insulin detemir versus insulin glargine, Outcome 4: Hypoglycaemia reported as a serious adverse event



Analysis 3.5. Comparison 3: Insulin detemir versus insulin glargine, Outcome 5: Cardiovascular mortality

Study or Subgroup	Insulin detemir Events	Total	Insulin glargine Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Heller 2009	0	299	1	144	0.16 [0.01 , 3.93]	+ + + + + +
Pieber 2007	0	161	0	159	Not estimable	+ + + + + +

Test for subgroup differences: Not applicable

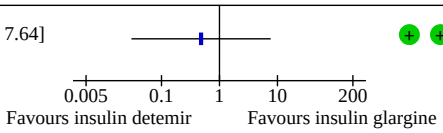


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Cardiovascular mortality
(C) Bias due to missing outcome data: Cardiovascular mortality
(D) Bias in measurement of the outcome: Cardiovascular mortality
(E) Bias in selection of the reported result: Cardiovascular mortality
(F) Overall bias: Cardiovascular mortality

Analysis 3.6. Comparison 3: Insulin detemir versus insulin glargine, Outcome 6: Non-fatal myocardial infarction

Study or Subgroup	Insulin detemir Events	Total	Insulin glargine Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Heller 2009	1	299	1	144	0.48 [0.03 , 7.64]	+ + + + + +

Test for subgroup differences: Not applicable

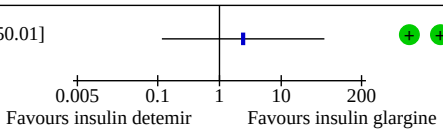


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Non-fatal myocardial infarction
(C) Bias due to missing outcome data: Non-fatal myocardial infarction
(D) Bias in measurement of the outcome: Non-fatal myocardial infarction
(E) Bias in selection of the reported result: Non-fatal myocardial infarction
(F) Overall bias: Non-fatal myocardial infarction

Analysis 3.7. Comparison 3: Insulin detemir versus insulin glargine, Outcome 7: Non-fatal stroke

Study or Subgroup	Insulin detemir Events	Total	Insulin glargine Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Heller 2009	2	299	0	144	2.42 [0.12 , 50.01]	+ + + + + +

Test for subgroup differences: Not applicable

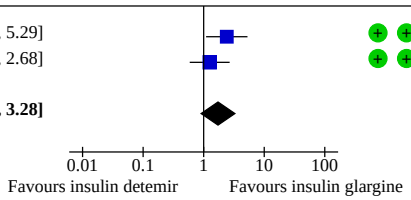


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Non-fatal stroke
(C) Bias due to missing outcome data: Non-fatal stroke
(D) Bias in measurement of the outcome: Non-fatal stroke
(E) Bias in selection of the reported result: Non-fatal stroke
(F) Overall bias: Non-fatal stroke

Analysis 3.8. Comparison 3: Insulin detemir versus insulin glargine, Outcome 8: Serious adverse events

Study or Subgroup	Insulin detemir Events	Total	Insulin glargine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Heller 2009	35	299	7	144	48.7%	2.41 [1.10 , 5.29]
Pieber 2007	14	161	11	159	51.3%	1.26 [0.59 , 2.68]
Total (95% CI)		**460**		**303**	**100.0%**	**1.72 [0.91 , 3.28]**
Total events:	49		18			

Heterogeneity: Tau² = 0.06; Chi² = 1.38, df = 1 (P = 0.24); I² = 27%
Test for overall effect: Z = 1.67 (P = 0.10)
Test for subgroup differences: Not applicable

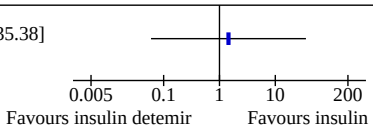


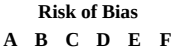
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Serious adverse events
(C) Bias due to missing outcome data: Serious adverse events
(D) Bias in measurement of the outcome: Serious adverse events
(E) Bias in selection of the reported result: Serious adverse events
(F) Overall bias: Serious adverse events

Analysis 3.9. Comparison 3: Insulin detemir versus insulin glargine, Outcome 9: Diabetic ketoacidosis

Study or Subgroup	Insulin detemir Events	Total	Insulin glargine Events	Total	Risk Ratio M-H, Fixed, 95% CI
Heller 2009	1	299	0	144	1.45 [0.06 , 35.38]

Test for subgroup differences: Not applicable



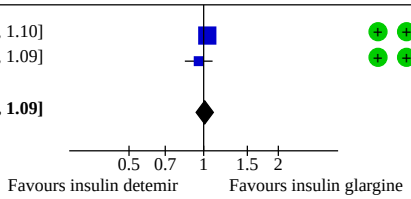


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Diabetic ketoacidosis
(C) Bias due to missing outcome data: Diabetic ketoacidosis
(D) Bias in measurement of the outcome: Diabetic ketoacidosis
(E) Bias in selection of the reported result: Diabetic ketoacidosis
(F) Overall bias: Diabetic ketoacidosis

Analysis 3.10. Comparison 3: Insulin detemir versus insulin glargine, Outcome 10: Non-serious adverse events

Study or Subgroup	Insulin detemir Events	Total	Insulin glargine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Heller 2009	277	299	129	144	70.3%	1.03 [0.97 , 1.10]
Pieber 2007	117	161	121	159	29.7%	0.95 [0.84 , 1.09]
Total (95% CI)		**460**		**303**	**100.0%**	**1.01 [0.93 , 1.09]**
Total events:	394		250			

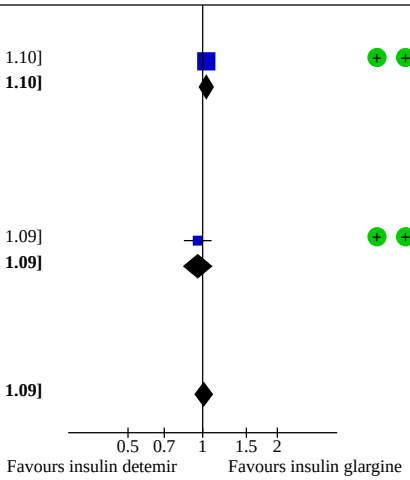
Heterogeneity: Tau² = 0.00; Chi² = 1.48, df = 1 (P = 0.22); I² = 33%
Test for overall effect: Z = 0.24 (P = 0.81)
Test for subgroup differences: Not applicable

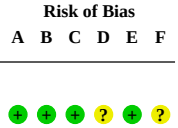


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Non-serious adverse events
(C) Bias due to missing outcome data: Non-serious adverse events
(D) Bias in measurement of the outcome: Non-serious adverse events
(E) Bias in selection of the reported result: Non-serious adverse events
(F) Overall bias: Non-serious adverse events

Analysis 3.11. Comparison 3: Insulin detemir versus insulin glargine, Outcome 11: Non-serious adverse events (published vs. unpublished data)

Study or Subgroup	Insulin detemir Events	Total	Insulin glargine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.11.1 Published						
Heller 2009	277	299	129	144	70.3%	1.03 [0.97 , 1.10]
Subtotal (95% CI)		**299**		**144**	**70.3%**	**1.03 [0.97 , 1.10]**
Total events:	277		129			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.02 (P = 0.31)						
3.11.2 Unpublished						
Pieber 2007	117	161	121	159	29.7%	0.95 [0.84 , 1.09]
Subtotal (95% CI)		**161**		**159**	**29.7%**	**0.95 [0.84 , 1.09]**
Total events:	117		121			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.48)						
Total (95% CI)		**460**		**303**	**100.0%**	**1.01 [0.93 , 1.09]**
Total events:	394		250			
Heterogeneity: Tau² = 0.00; Chi² = 1.48, df = 1 (P = 0.22); I² = 33%						
Test for overall effect: Z = 0.24 (P = 0.81)						
Test for subgroup differences: Chi² = 1.18, df = 1 (P = 0.28), I² = 15.2%						





Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions: Non-serious adverse events (published vs. unpublished data)

(C) Bias due to missing outcome data: Non-serious adverse events (published vs. unpublished data)

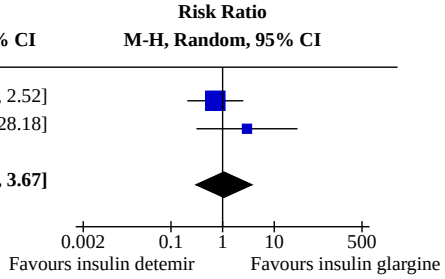
(D) Bias in measurement of the outcome: Non-serious adverse events (published vs. unpublished data)

(E) Bias in selection of the reported result: Non-serious adverse events (published vs. unpublished data)

(F) Overall bias: Non-serious adverse events (published vs. unpublished data)

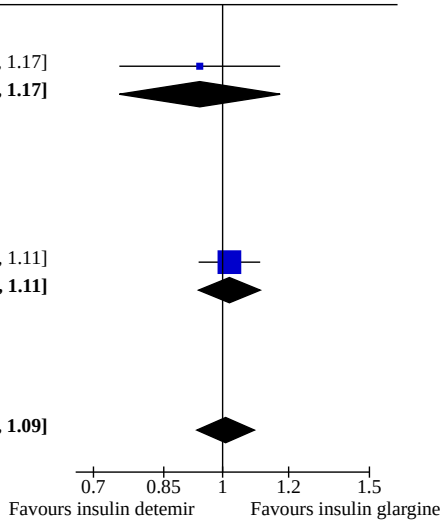
Analysis 3.12. Comparison 3: Insulin detemir versus insulin glargine, Outcome 12: Withdrawals due to adverse events

Study or Subgroup	Insulin detemir Events	Total	Insulin glargine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Heller 2009	6	299	4	144	72.7%	0.72 [0.21 , 2.52]
Pieber 2007	3	161	1	159	27.3%	2.96 [0.31 , 28.18]
Total (95% CI)		**460**		**303**	**100.0%**	**1.06 [0.31 , 3.67]**
Total events:	9		5			
Heterogeneity: Tau² = 0.14; Chi² = 1.17, df = 1 (P = 0.28); I² = 14%						
Test for overall effect: Z = 0.10 (P = 0.92)						
Test for subgroup differences: Not applicable						



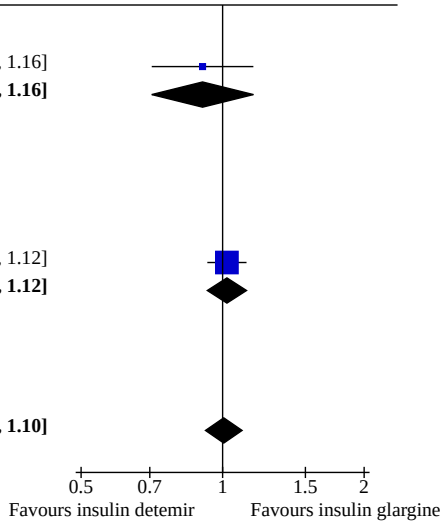
Analysis 3.13. Comparison 3: Insulin detemir versus insulin glargine, Outcome 13: Any nocturnal hypoglycaemia

Study or Subgroup	Insulin detemir Events	Total	Insulin glargine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.13.1 Published						
Pieber 2007	77	161	81	159	12.8%	0.94 [0.75 , 1.17]
Subtotal (95% CI)		**161**		**159**	**12.8%**	**0.94 [0.75 , 1.17]**
Total events:	77		81			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.56 (P = 0.58)						
3.13.2 Unpublished						
Heller 2009	256	299	121	144	87.2%	1.02 [0.94 , 1.11]
Subtotal (95% CI)		**299**		**144**	**87.2%**	**1.02 [0.94 , 1.11]**
Total events:	256		121			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.43 (P = 0.67)						
Total (95% CI)		**460**		**303**	**100.0%**	**1.01 [0.93 , 1.09]**
Total events:	333		202			
Heterogeneity: Tau² = 0.00; Chi² = 0.61, df = 1 (P = 0.43); I² = 0%						
Test for overall effect: Z = 0.20 (P = 0.84)						
Test for subgroup differences: Chi² = 0.46, df = 1 (P = 0.50), I² = 0%						



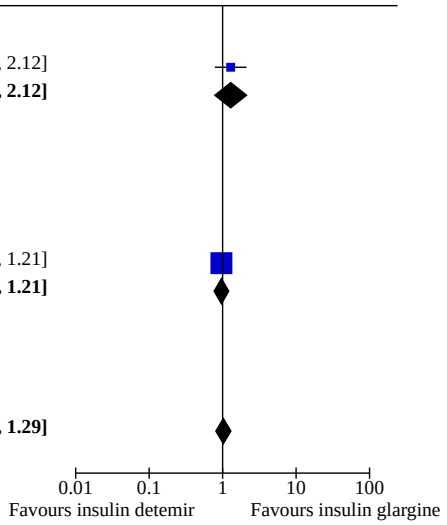
Analysis 3.14. Comparison 3: Insulin detemir versus insulin glargine, Outcome 14: Confirmed nocturnal hypoglycaemia (PG < 3.1 mmol/L and no assistance)

Study or Subgroup	Insulin detemir Events	Total	Insulin glargine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.14.1 Published						
Pieber 2007	67	161	73	159	12.9%	0.91 [0.71 , 1.16]
Subtotal (95% CI)		**161**		**159**	**12.9%**	**0.91 [0.71 , 1.16]**
Total events:	67		73			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.77 (P = 0.44)						
3.14.2 Unpublished						
Heller 2009	246	299	116	144	87.1%	1.02 [0.93 , 1.12]
Subtotal (95% CI)		**299**		**144**	**87.1%**	**1.02 [0.93 , 1.12]**
Total events:	246		116			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.43 (P = 0.67)						
Total (95% CI)		**460**		**303**	**100.0%**	**1.01 [0.92 , 1.10]**
Total events:	313		189			
Heterogeneity: Tau² = 0.00; Chi² = 0.98, df = 1 (P = 0.32); I² = 0%						
Test for overall effect: Z = 0.12 (P = 0.90)						
Test for subgroup differences: Chi² = 0.77, df = 1 (P = 0.38), I² = 0%						



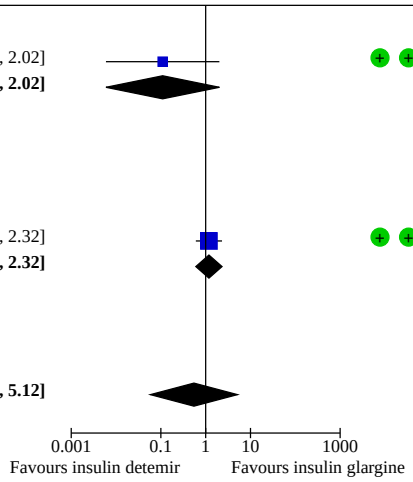
Analysis 3.15. Comparison 3: Insulin detemir versus insulin glargine, Outcome 15: Symptomatic nocturnal hypoglycaemia (PG ≥ 3.1 or no PG and no assistance required)

Study or Subgroup	Insulin detemir Events	Total	Insulin glargine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.15.1 Published						
Pieber 2007	30	161	23	159	20.8%	1.29 [0.78 , 2.12]
Subtotal (95% CI)		**161**		**159**	**20.8%**	**1.29 [0.78 , 2.12]**
Total events:	30		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.00 (P = 0.32)						
3.15.2 Unpublished						
Heller 2009	126	299	63	144	79.2%	0.96 [0.77 , 1.21]
Subtotal (95% CI)		**299**		**144**	**79.2%**	**0.96 [0.77 , 1.21]**
Total events:	126		63			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.32 (P = 0.75)						
Total (95% CI)		**460**		**303**	**100.0%**	**1.02 [0.81 , 1.29]**
Total events:	156		86			
Heterogeneity: Tau² = 0.00; Chi² = 1.12, df = 1 (P = 0.29); I² = 11%						
Test for overall effect: Z = 0.19 (P = 0.85)						
Test for subgroup differences: Chi² = 1.09, df = 1 (P = 0.30), I² = 7.9%						



Analysis 3.16. Comparison 3: Insulin detemir versus insulin glargine, Outcome 16: Severe nocturnal hypoglycaemia

Study or Subgroup	Insulin detemir Events	Total	Insulin glargine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
3.16.1 Published							
Pieber 2007	0	161	4	159	32.4%	0.11 [0.01 , 2.02]	+ + + + + +
Subtotal (95% CI)		**161**		**159**	**32.4%**	**0.11 [0.01 , 2.02]**	
Total events:	0		4				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.49 (P = 0.14)							
3.16.2 Unpublished							
Heller 2009	27	299	11	144	67.6%	1.18 [0.60 , 2.32]	+ + + + + +
Subtotal (95% CI)		**299**		**144**	**67.6%**	**1.18 [0.60 , 2.32]**	
Total events:	27		11				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.49 (P = 0.63)							
Total (95% CI)		**460**		**303**	**100.0%**	**0.55 [0.06 , 5.12]**	
Total events:	27		15				
Heterogeneity: Tau² = 1.81; Chi² = 2.55, df = 1 (P = 0.11); I² = 61%							
Test for overall effect: Z = 0.53 (P = 0.60)							
Test for subgroup differences: Chi² = 2.43, df = 1 (P = 0.12), I² = 58.8%							

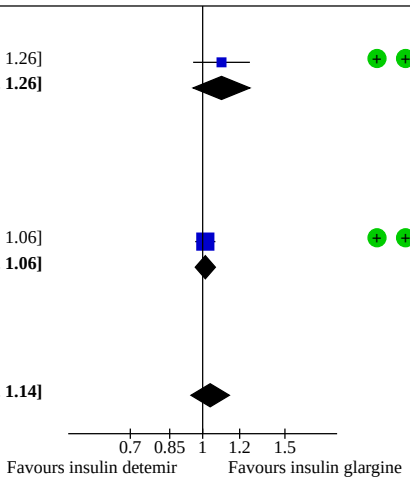


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Severe nocturnal hypoglycaemia
(C) Bias due to missing outcome data: Severe nocturnal hypoglycaemia
(D) Bias in measurement of the outcome: Severe nocturnal hypoglycaemia
(E) Bias in selection of the reported result: Severe nocturnal hypoglycaemia
(F) Overall bias: Severe nocturnal hypoglycaemia

Analysis 3.17. Comparison 3: Insulin detemir versus insulin glargine, Outcome 17: Mild/moderate hypoglycaemia

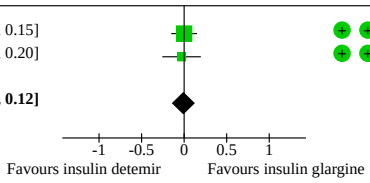
Study or Subgroup	Insulin detemir Events	Total	Insulin glargine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.17.1 Published						
Pieber 2007	120	161	108	159	29.9%	1.10 [0.95 , 1.26]
Subtotal (95% CI)		**161**		**159**	**29.9%**	**1.10 [0.95 , 1.26]**
Total events:	120		108			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.30 (P = 0.19)						
3.17.2 Unpublished						
Heller 2009	284	299	135	144	70.1%	1.01 [0.96 , 1.06]
Subtotal (95% CI)		**299**		**144**	**70.1%**	**1.01 [0.96 , 1.06]**
Total events:	284		135			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.52 (P = 0.61)						
Total (95% CI)		**460**		**303**	**100.0%**	**1.04 [0.94 , 1.14]**
Total events:	404		243			
Heterogeneity: Tau² = 0.00; Chi² = 1.94, df = 1 (P = 0.16); I² = 48%						
Test for overall effect: Z = 0.77 (P = 0.44)						
Test for subgroup differences: Chi² = 1.11, df = 1 (P = 0.29), I² = 10.0%						



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Mild/moderate hypoglycaemia
(C) Bias due to missing outcome data: Mild/moderate hypoglycaemia
(D) Bias in measurement of the outcome: Mild/moderate hypoglycaemia
(E) Bias in selection of the reported result: Mild/moderate hypoglycaemia
(F) Overall bias: Mild/moderate hypoglycaemia

Analysis 3.18. Comparison 3: Insulin detemir versus insulin glargine, Outcome 18: HbA1c

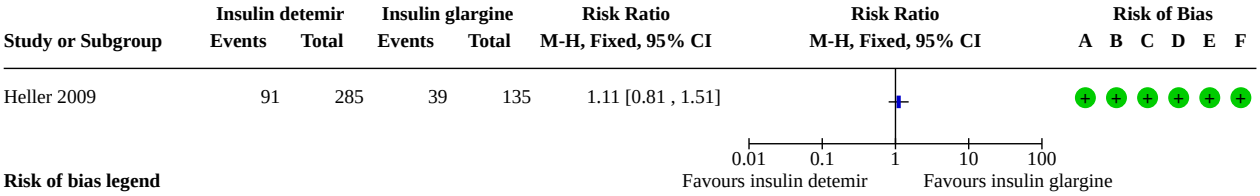
Study or Subgroup	Insulin detemir Mean	SD	Total	Insulin glargine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Heller 2009 (1)	7.6	0.8	283	7.6	0.7	134	69.3%	0.00 [-0.15 , 0.15]
Pieber 2007 (1)	8.16	1	149	8.19	1	151	30.7%	-0.03 [-0.26 , 0.20]
Total (95% CI)			**432**			**285**	**100.0%**	**-0.01 [-0.13 , 0.12]**
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.83); I² = 0%								
Test for overall effect: Z = 0.14 (P = 0.89)								
Test for subgroup differences: Not applicable								



Footnotes
(1) SD calculated from SE

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: HbA1c
(C) Bias due to missing outcome data: HbA1c
(D) Bias in measurement of the outcome: HbA1c
(E) Bias in selection of the reported result: HbA1c
(F) Overall bias: HbA1c

Analysis 3.19. Comparison 3: Insulin detemir versus insulin glargine, Outcome 19: Individuals with HbA1c < 7% without severe hypoglycaemia



Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions: Individuals with HbA1c < 7% without severe hypoglycaemia

(C) Bias due to missing outcome data: Individuals with HbA1c < 7% without severe hypoglycaemia

(D) Bias in measurement of the outcome: Individuals with HbA1c < 7% without severe hypoglycaemia

(E) Bias in selection of the reported result: Individuals with HbA1c < 7% without severe hypoglycaemia

(F) Overall bias: Individuals with HbA1c < 7% without severe hypoglycaemia

Comparison 4. Insulin degludec versus insulin detemir

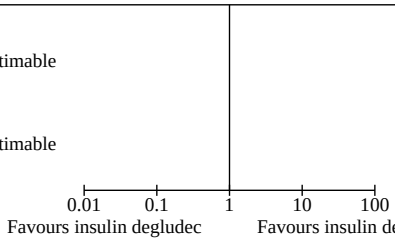
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 All-cause mortality	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1.1 Adults	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1.2 Children	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.2 Health-related quality of life	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.2.1 Physical health score	1	454	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-1.83, 0.63]
4.2.2 Mental health score	1	454	Mean Difference (IV, Fixed, 95% CI)	-3.00 [-4.44, -1.56]
4.3 Severe hypoglycaemia	2	802	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.81, 1.69]
4.3.1 Adults	1	453	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.57, 1.78]
4.3.2 Children	1	349	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.80, 2.12]
4.4 Hypoglycaemia reported as a serious adverse event	2	802	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.37, 2.32]
4.4.1 Adults	1	453	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.29, 1.69]
4.4.2 Children	1	349	Risk Ratio (M-H, Random, 95% CI)	2.01 [0.37, 10.84]
4.5 Cardiovascular mortality	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.5.1 Adults	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.5.2 Children	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.6 Non-fatal myocardial infarction	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.7 Non-fatal stroke	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.8 End stage renal disease	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.9 Blindness	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.10 Serious adverse events	2	802	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.76, 2.05]
4.10.1 Adults	1	453	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.67, 3.17]
4.10.2 Children	1	349	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.60, 2.15]
4.11 Diabetic ketoacidosis	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.11.1 Adults	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.11.2 Children	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.12 Non-serious adverse events	2	802	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.96, 1.08]
4.12.1 Adults	1	453	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.88, 1.11]
4.12.2 Children	1	349	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.97, 1.10]
4.13 Withdrawals due to adverse events	2	802	Risk Ratio (M-H, Random, 95% CI)	2.32 [0.38, 14.18]
4.13.1 Adults	1	453	Risk Ratio (M-H, Random, 95% CI)	1.51 [0.16, 14.44]
4.13.2 Children	1	349	Risk Ratio (M-H, Random, 95% CI)	5.03 [0.24, 103.99]
4.14 Nocturnal hypoglycaemia	2	802	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.94, 1.15]
4.14.1 Adults	1	453	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.85, 1.18]
4.14.2 Children	1	349	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.94, 1.21]
4.15 Mild nocturnal hypoglycaemia	2	802	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.86, 1.10]
4.15.1 Adults	1	453	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.85, 1.16]
4.15.2 Children	1	349	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.79, 1.15]
4.16 Nocturnal hypoglycaemia (symptomatic)	2	802	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.15, 3.59]
4.16.1 Adults	1	453	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.20, 0.72]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.16.2 Children	1	349	Risk Ratio (M-H, Random, 95% CI)	2.01 [0.37, 10.84]
4.17 Nocturnal hypoglycaemia (asymptomatic)	2	802	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.80, 1.03]
4.17.1 Adults	1	453	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.70, 1.23]
4.17.2 Children	1	349	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.79, 1.04]
4.18 Severe nocturnal hypoglycaemia	2	802	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.51, 2.46]
4.18.1 Adults	1	453	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.43, 3.38]
4.18.2 Children	1	349	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.30, 3.41]
4.19 Mild/moderate hypoglycaemia	2	802	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.99, 1.05]
4.19.1 Adults	1	453	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.96, 1.08]
4.19.2 Children	1	349	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.99, 1.06]
4.20 HbA1c	2	805	Mean Difference (IV, Random, 95% CI)	0.05 [-0.08, 0.18]
4.20.1 Adults	1	455	Mean Difference (IV, Random, 95% CI)	0.00 [-0.18, 0.18]
4.20.2 Children	1	350	Mean Difference (IV, Random, 95% CI)	0.11 [-0.08, 0.30]
4.21 Individuals with HbA1c < 7% without severe hypoglycaemia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4: Insulin degludec versus insulin detemir, Outcome 1: All-cause mortality

Study or Subgroup	Insulin degludec Events	Total	Insulin detemir Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
4.1.1 Adults							
Davies 2014	0	301	0	152	Not estimable		+ + + + + +
4.1.2 Children							
BEGIN Young	0	174	0	175	Not estimable		+ + + + + +



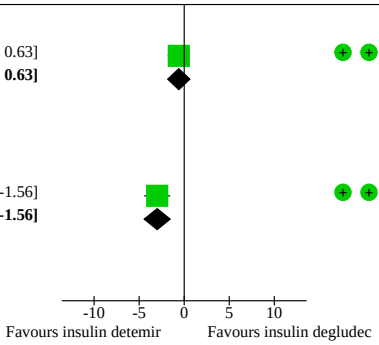
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: All-cause mortality
(C) Bias due to missing outcome data: All-cause mortality
(D) Bias in measurement of the outcome: All-cause mortality
(E) Bias in selection of the reported result: All-cause mortality
(F) Overall bias: All-cause mortality

Analysis 4.2. Comparison 4: Insulin degludec versus insulin detemir, Outcome 2: Health-related quality of life

Study or Subgroup	Insulin degludec Mean	SD	Total	Insulin detemir Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
4.2.1 Physical health score										
Davies 2014	51.9	6.8	301	52.5	6.1	153	100.0%	-0.60 [-1.83 , 0.63]		+ + + ? + ?
Subtotal (95% CI)			**301**			**153**	**100.0%**	**-0.60 [-1.83 , 0.63]**		
Heterogeneity: Not applicable										
Test for overall effect: Z = 0.95 (P = 0.34)										
4.2.2 Mental health score										
Davies 2014	49.5	9.5	301	52.5	6.1	153	100.0%	-3.00 [-4.44 , -1.56]		+ + + ? + ?
Subtotal (95% CI)			**301**			**153**	**100.0%**	**-3.00 [-4.44 , -1.56]**		
Heterogeneity: Not applicable										
Test for overall effect: Z = 4.07 (P < 0.0001)										

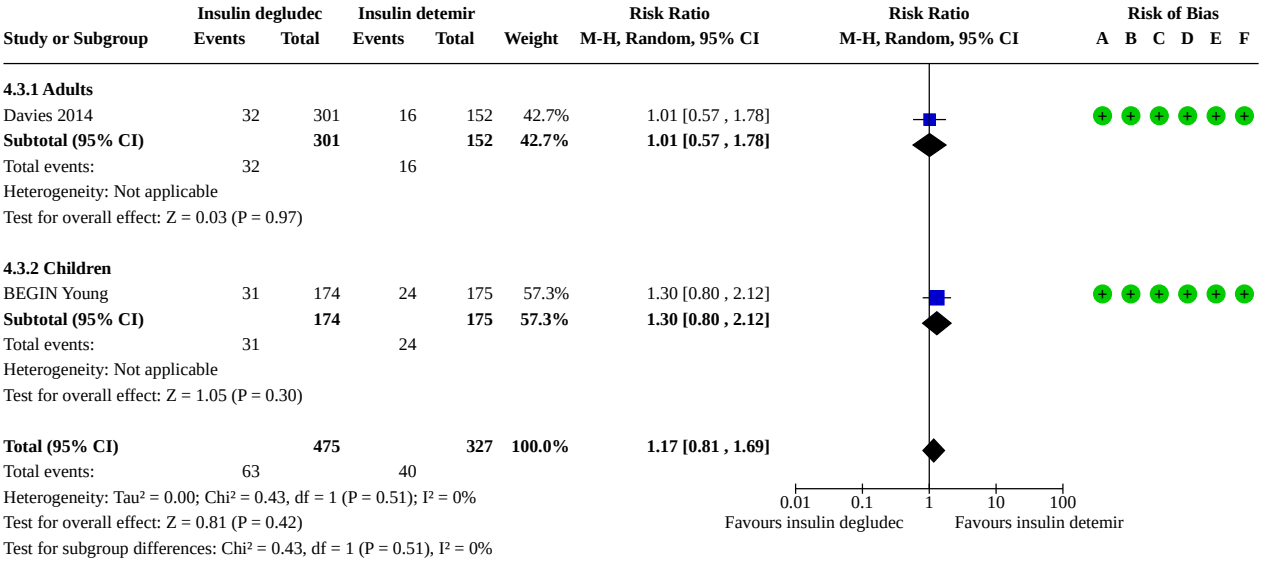
Test for subgroup differences: Chi² = 6.13, df = 1 (P = 0.01), I² = 83.7%



Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Health-related quality of life
(C) Bias due to missing outcome data: Health-related quality of life
(D) Bias in measurement of the outcome: Health-related quality of life
(E) Bias in selection of the reported result: Health-related quality of life
(F) Overall bias: Health-related quality of life

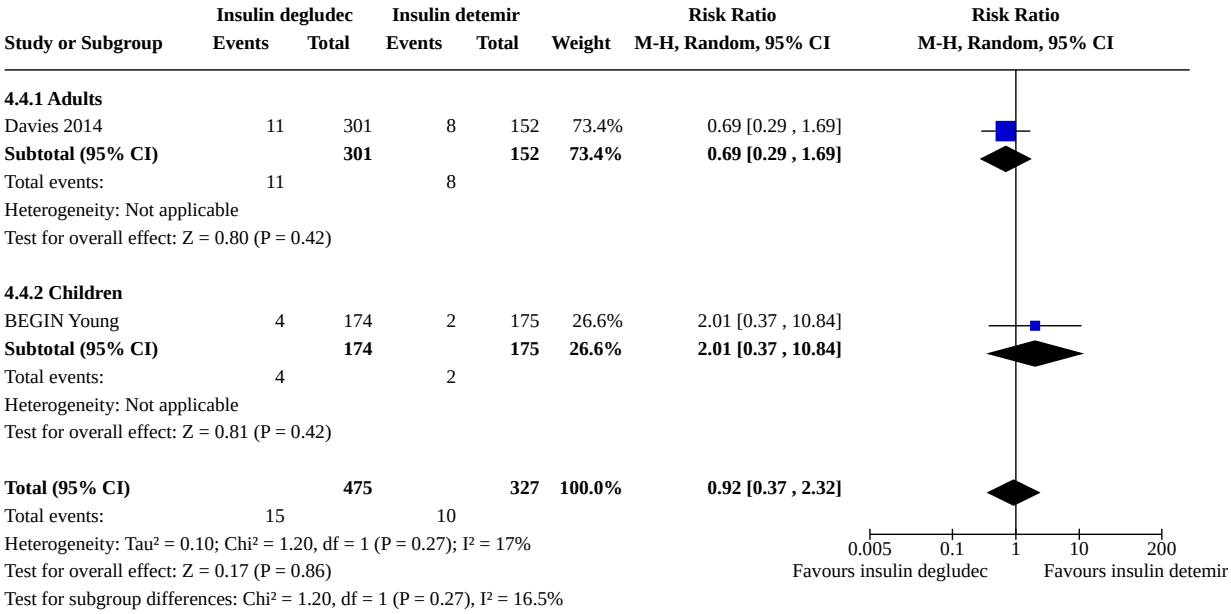
Analysis 4.3. Comparison 4: Insulin degludec versus insulin detemir, Outcome 3: Severe hypoglycaemia



Risk of bias legend

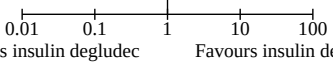
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Severe hypoglycaemia
(C) Bias due to missing outcome data: Severe hypoglycaemia
(D) Bias in measurement of the outcome: Severe hypoglycaemia
(E) Bias in selection of the reported result: Severe hypoglycaemia
(F) Overall bias: Severe hypoglycaemia

Analysis 4.4. Comparison 4: Insulin degludec versus insulin detemir, Outcome 4: Hypoglycaemia reported as a serious adverse event



Analysis 4.5. Comparison 4: Insulin degludec versus insulin detemir, Outcome 5: Cardiovascular mortality

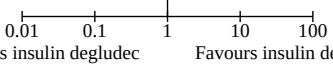
Study or Subgroup	Insulin degludec Events	Total	Insulin detemir Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
4.5.1 Adults							
Davies 2014	0	301	0	152	Not estimable		+ + + + + +
4.5.2 Children							
BEGIN Young	0	174	0	175	Not estimable		+ + + + + +



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Cardiovascular mortality
(C) Bias due to missing outcome data: Cardiovascular mortality
(D) Bias in measurement of the outcome: Cardiovascular mortality
(E) Bias in selection of the reported result: Cardiovascular mortality
(F) Overall bias: Cardiovascular mortality

Analysis 4.6. Comparison 4: Insulin degludec versus insulin detemir, Outcome 6: Non-fatal myocardial infarction

Study or Subgroup	Insulin degludec Events	Total	Insulin detemir Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Davies 2014 (1)	0	301	0	152	Not estimable		+ + + + + +

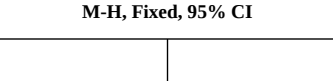


Footnotes
(1) Data provided by study authors

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Non-fatal myocardial infarction
(C) Bias due to missing outcome data: Non-fatal myocardial infarction
(D) Bias in measurement of the outcome: Non-fatal myocardial infarction
(E) Bias in selection of the reported result: Non-fatal myocardial infarction
(F) Overall bias: Non-fatal myocardial infarction

Analysis 4.7. Comparison 4: Insulin degludec versus insulin detemir, Outcome 7: Non-fatal stroke

Study or Subgroup	Insulin degludec Events	Total	Insulin detemir Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Davies 2014 (1)	0	301	0	152	Not estimable		+ + + + + +

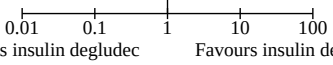


Footnotes
(1) Data provided by study authors

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Non-fatal stroke
(C) Bias due to missing outcome data: Non-fatal stroke
(D) Bias in measurement of the outcome: Non-fatal stroke
(E) Bias in selection of the reported result: Non-fatal stroke
(F) Overall bias: Non-fatal stroke

Analysis 4.8. Comparison 4: Insulin degludec versus insulin detemir, Outcome 8: End stage renal disease

Study or Subgroup	Insulin degludec Events	Total	Insulin detemir Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
Davies 2014 (1)	0	301	0	152	Not estimable		+	+	+	+	+	+

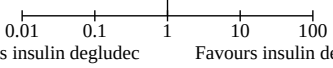


Footnotes
(1) Data provided by study authors

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: End stage renal disease
(C) Bias due to missing outcome data: End stage renal disease
(D) Bias in measurement of the outcome: End stage renal disease
(E) Bias in selection of the reported result: End stage renal disease
(F) Overall bias: End stage renal disease

Analysis 4.9. Comparison 4: Insulin degludec versus insulin detemir, Outcome 9: Blindness

Study or Subgroup	Insulin degludec Events	Total	Insulin detemir Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
Davies 2014 (1)	0	301	0	152	Not estimable		+	+	+	+	+	+

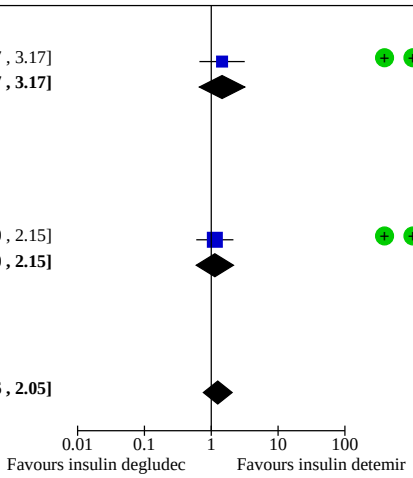


Footnotes
(1) Data provided by study authors

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Blindness
(C) Bias due to missing outcome data: Blindness
(D) Bias in measurement of the outcome: Blindness
(E) Bias in selection of the reported result: Blindness
(F) Overall bias: Blindness

Analysis 4.10. Comparison 4: Insulin degludec versus insulin detemir, Outcome 10: Serious adverse events

Study or Subgroup	Insulin degludec Events	Total	Insulin detemir Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.10.1 Adults						
Davies 2014 (1)	23	301	8	152	40.2%	1.45 [0.67 , 3.17]
Subtotal (95% CI)		**301**		**152**	**40.2%**	**1.45 [0.67 , 3.17]**
Total events:	23		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.94 (P = 0.35)						
4.10.2 Children						
BEGIN Young	18	174	16	175	59.8%	1.13 [0.60 , 2.15]
Subtotal (95% CI)		**174**		**175**	**59.8%**	**1.13 [0.60 , 2.15]**
Total events:	18		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.38 (P = 0.71)						
Total (95% CI)		**475**		**327**	**100.0%**	**1.25 [0.76 , 2.05]**
Total events:	41		24			
Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 1 (P = 0.63); I² = 0%						
Test for overall effect: Z = 0.89 (P = 0.38)						
Test for subgroup differences: Chi² = 0.23, df = 1 (P = 0.63), I² = 0%						



Footnotes

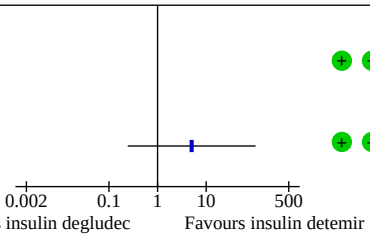
(1) Data after 26 weeks of follow-up

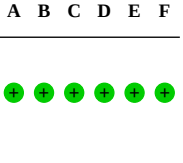
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Serious adverse events
(C) Bias due to missing outcome data: Serious adverse events
(D) Bias in measurement of the outcome: Serious adverse events
(E) Bias in selection of the reported result: Serious adverse events
(F) Overall bias: Serious adverse events

Analysis 4.11. Comparison 4: Insulin degludec versus insulin detemir, Outcome 11: Diabetic ketoacidosis

Study or Subgroup	Insulin degludec Events	Total	Insulin detemir Events	Total	Risk Ratio M-H, Random, 95% CI
4.11.1 Adults					
Davies 2014	0	301	0	152	Not estimable
4.11.2 Children					
BEGIN Young	2	174	0	175	5.03 [0.24 , 103.99]



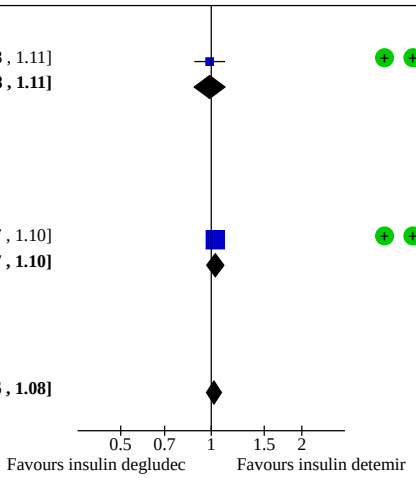


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Diabetic ketoacidosis
(C) Bias due to missing outcome data: Diabetic ketoacidosis
(D) Bias in measurement of the outcome: Diabetic ketoacidosis
(E) Bias in selection of the reported result: Diabetic ketoacidosis
(F) Overall bias: Diabetic ketoacidosis

Analysis 4.12. Comparison 4: Insulin degludec versus insulin detemir, Outcome 12: Non-serious adverse events

Study or Subgroup	Insulin degludec Events	Total	Insulin detemir Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.12.1 Adults						
Davies 2014	219	301	112	152	23.7%	0.99 [0.88 , 1.11]
Subtotal (95% CI)		**301**		**152**	**23.7%**	**0.99 [0.88 , 1.11]**
Total events:	219		112			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.21 (P = 0.83)						
4.12.2 Children						
BEGIN Young	161	174	157	175	76.3%	1.03 [0.97 , 1.10]
Subtotal (95% CI)		**174**		**175**	**76.3%**	**1.03 [0.97 , 1.10]**
Total events:	161		157			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.92 (P = 0.36)						
Total (95% CI)		**475**		**327**	**100.0%**	**1.02 [0.96 , 1.08]**
Total events:	380		269			
Heterogeneity: Tau² = 0.00; Chi² = 0.54, df = 1 (P = 0.46); I² = 0%						
Test for overall effect: Z = 0.70 (P = 0.48)						
Test for subgroup differences: Chi² = 0.40, df = 1 (P = 0.53), I² = 0%						

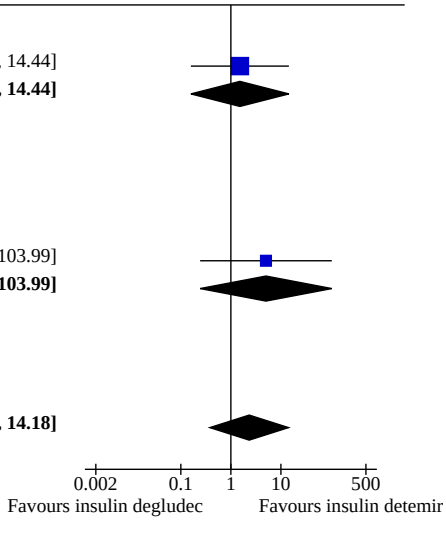


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Non-serious adverse events
(C) Bias due to missing outcome data: Non-serious adverse events
(D) Bias in measurement of the outcome: Non-serious adverse events
(E) Bias in selection of the reported result: Non-serious adverse events
(F) Overall bias: Non-serious adverse events

Analysis 4.13. Comparison 4: Insulin degludec versus insulin detemir, Outcome 13: Withdrawals due to adverse events

Study or Subgroup	Insulin degludec Events	Total	Insulin detemir Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.13.1 Adults						
Davies 2014 (1)	3	301	1	152	64.3%	1.51 [0.16 , 14.44]
Subtotal (95% CI)		**301**		**152**	**64.3%**	**1.51 [0.16 , 14.44]**
Total events:	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.36 (P = 0.72)						
4.13.2 Children						
BEGIN Young	2	174	0	175	35.7%	5.03 [0.24 , 103.99]
Subtotal (95% CI)		**174**		**175**	**35.7%**	**5.03 [0.24 , 103.99]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.30)						
Total (95% CI)		**475**		**327**	**100.0%**	**2.32 [0.38 , 14.18]**
Total events:	5		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.39, df = 1 (P = 0.53); I² = 0%						
Test for overall effect: Z = 0.91 (P = 0.36)						
Test for subgroup differences: Chi² = 0.39, df = 1 (P = 0.53), I² = 0%						

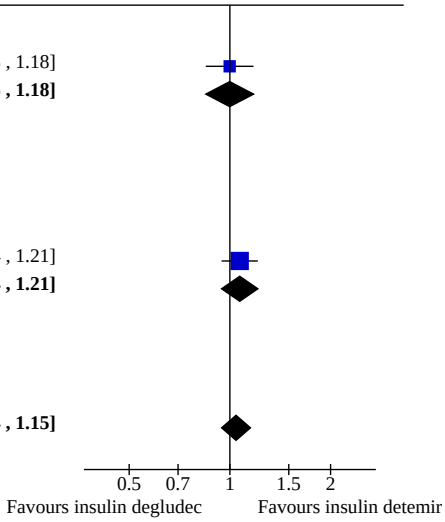


Footnotes

(1) Data reported after 26 weeks of intervention

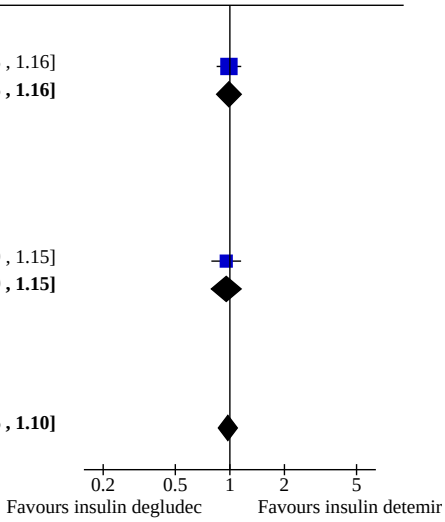
Analysis 4.14. Comparison 4: Insulin degludec versus insulin detemir, Outcome 14: Nocturnal hypoglycaemia

Study or Subgroup	Insulin degludec Events	Total	Insulin detemir Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.14.1 Adults						
Davies 2014	176	301	89	152	36.6%	1.00 [0.85 , 1.18]
Subtotal (95% CI)		**301**		**152**	**36.6%**	**1.00 [0.85 , 1.18]**
Total events:	176		89			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.02 (P = 0.99)						
4.14.2 Children						
BEGIN Young	133	174	125	175	63.4%	1.07 [0.94 , 1.21]
Subtotal (95% CI)		**174**		**175**	**63.4%**	**1.07 [0.94 , 1.21]**
Total events:	133		125			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
Total (95% CI)		**475**		**327**	**100.0%**	**1.04 [0.94 , 1.15]**
Total events:	309		214			
Heterogeneity: Tau² = 0.00; Chi² = 0.46, df = 1 (P = 0.50); I² = 0%						
Test for overall effect: Z = 0.84 (P = 0.40)						
Test for subgroup differences: Chi² = 0.43, df = 1 (P = 0.51), I² = 0%						



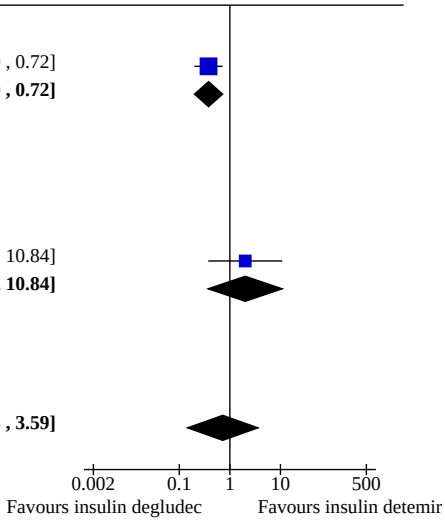
Analysis 4.15. Comparison 4: Insulin degludec versus insulin detemir, Outcome 15: Mild nocturnal hypoglycaemia

Study or Subgroup	Insulin degludec Events	Total	Insulin detemir Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.15.1 Adults						
Davies 2014	182	301	93	152	59.4%	0.99 [0.85 , 1.16]
Subtotal (95% CI)		**301**		**152**	**59.4%**	**0.99 [0.85 , 1.16]**
Total events:	182		93			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.15 (P = 0.88)						
4.15.2 Children						
BEGIN Young	94	174	99	175	40.6%	0.95 [0.79 , 1.15]
Subtotal (95% CI)		**174**		**175**	**40.6%**	**0.95 [0.79 , 1.15]**
Total events:	94		99			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.48 (P = 0.63)						
Total (95% CI)		**475**		**327**	**100.0%**	**0.97 [0.86 , 1.10]**
Total events:	276		192			
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%						
Test for overall effect: Z = 0.42 (P = 0.67)						
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.78), I² = 0%						



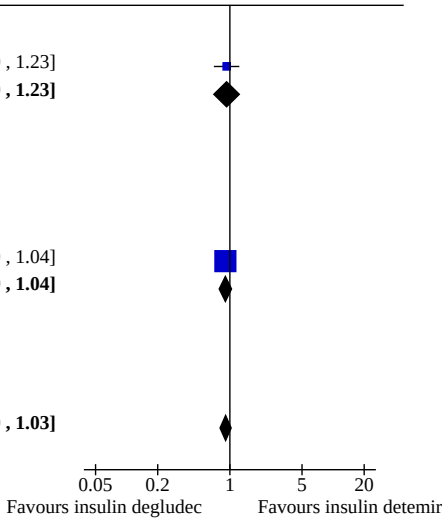
Analysis 4.16. Comparison 4: Insulin degludec versus insulin detemir, Outcome 16: Nocturnal hypoglycaemia (symptomatic)

Study or Subgroup	Insulin degludec Events	Total	Insulin detemir Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.16.1 Adults						
Davies 2014	15	301	20	152	61.2%	0.38 [0.20 , 0.72]
Subtotal (95% CI)		**301**		**152**	**61.2%**	**0.38 [0.20 , 0.72]**
Total events:	15		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.97 (P = 0.003)						
4.16.2 Children						
BEGIN Young	4	174	2	175	38.8%	2.01 [0.37 , 10.84]
Subtotal (95% CI)		**174**		**175**	**38.8%**	**2.01 [0.37 , 10.84]**
Total events:	4		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.81 (P = 0.42)						
Total (95% CI)		**475**		**327**	**100.0%**	**0.72 [0.15 , 3.59]**
Total events:	19		22			
Heterogeneity: Tau² = 0.98; Chi² = 3.33, df = 1 (P = 0.07); I² = 70%						
Test for overall effect: Z = 0.40 (P = 0.69)						
Test for subgroup differences: Chi² = 3.30, df = 1 (P = 0.07), I² = 69.7%						



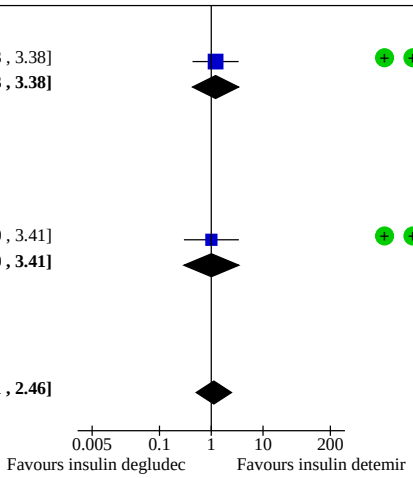
Analysis 4.17. Comparison 4: Insulin degludec versus insulin detemir, Outcome 17: Nocturnal hypoglycaemia (asymptomatic)

Study or Subgroup	Insulin degludec Events	Total	Insulin detemir Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.17.1 Adults						
Davies 2014	92	301	50	152	19.0%	0.93 [0.70 , 1.23]
Subtotal (95% CI)		**301**		**152**	**19.0%**	**0.93 [0.70 , 1.23]**
Total events:	92		50			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.51 (P = 0.61)						
4.17.2 Children						
BEGIN Young	116	174	129	175	81.0%	0.90 [0.79 , 1.04]
Subtotal (95% CI)		**174**		**175**	**81.0%**	**0.90 [0.79 , 1.04]**
Total events:	116		129			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.43 (P = 0.15)						
Total (95% CI)		**475**		**327**	**100.0%**	**0.91 [0.80 , 1.03]**
Total events:	208		179			
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%						
Test for overall effect: Z = 1.51 (P = 0.13)						
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.87), I² = 0%						



Analysis 4.18. Comparison 4: Insulin degludec versus insulin detemir, Outcome 18: Severe nocturnal hypoglycaemia

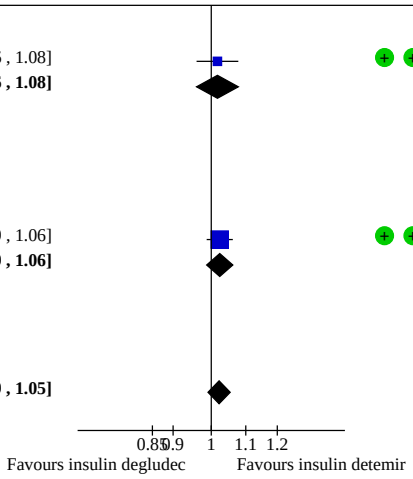
Study or Subgroup	Insulin degludec Events	Total	Insulin detemir Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
4.18.1 Adults							
Davies 2014	12	301	5	152	58.7%	1.21 [0.43 , 3.38]	+ + + + + +
Subtotal (95% CI)		**301**		**152**	**58.7%**	**1.21 [0.43 , 3.38]**	
Total events:	12		5				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.37 (P = 0.71)							
4.18.2 Children							
BEGIN Young	5	174	5	175	41.3%	1.01 [0.30 , 3.41]	+ + + + + +
Subtotal (95% CI)		**174**		**175**	**41.3%**	**1.01 [0.30 , 3.41]**	
Total events:	5		5				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.01 (P = 0.99)							
Total (95% CI)		**475**		**327**	**100.0%**	**1.12 [0.51 , 2.46]**	
Total events:	17		10				
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%							
Test for overall effect: Z = 0.29 (P = 0.77)							
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.82), I² = 0%							



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Severe nocturnal hypoglycaemia
(C) Bias due to missing outcome data: Severe nocturnal hypoglycaemia
(D) Bias in measurement of the outcome: Severe nocturnal hypoglycaemia
(E) Bias in selection of the reported result: Severe nocturnal hypoglycaemia
(F) Overall bias: Severe nocturnal hypoglycaemia

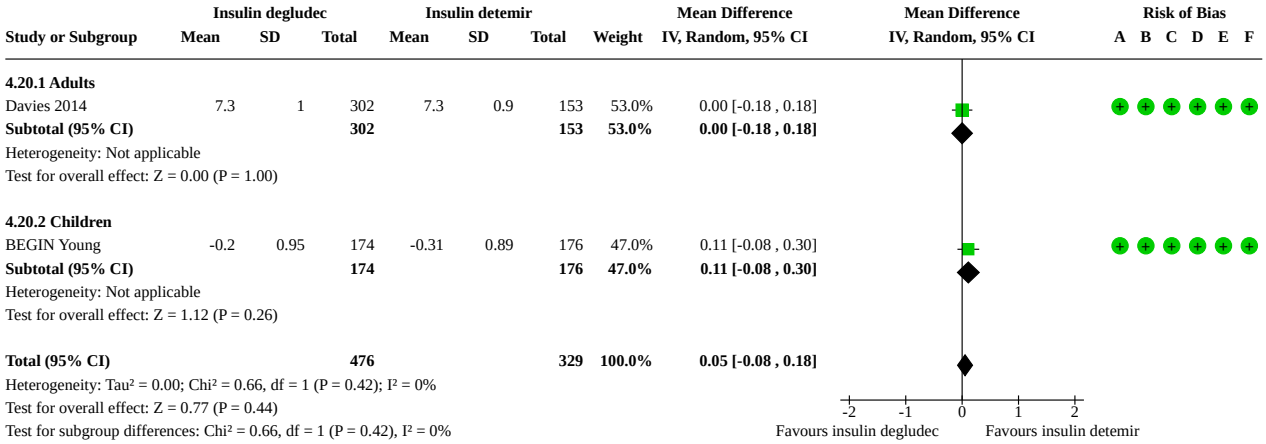
Analysis 4.19. Comparison 4: Insulin degludec versus insulin detemir, Outcome 19: Mild/moderate hypoglycaemia

Study or Subgroup	Insulin degludec Events	Total	Insulin detemir Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
4.19.1 Adults							
Davies 2014	280	301	139	152	28.2%	1.02 [0.96 , 1.08]	+ + + ? + ?
Subtotal (95% CI)		**301**		**152**	**28.2%**	**1.02 [0.96 , 1.08]**	
Total events:	280		139				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.58 (P = 0.56)							
4.19.2 Children							
BEGIN Young	171	174	168	175	71.8%	1.02 [0.99 , 1.06]	+ + + ? + ?
Subtotal (95% CI)		**174**		**175**	**71.8%**	**1.02 [0.99 , 1.06]**	
Total events:	171		168				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.27 (P = 0.20)							
Total (95% CI)		**475**		**327**	**100.0%**	**1.02 [0.99 , 1.05]**	
Total events:	451		307				
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%							
Test for overall effect: Z = 1.39 (P = 0.17)							
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.85), I² = 0%							



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Mild/moderate hypoglycaemia
(C) Bias due to missing outcome data: Mild/moderate hypoglycaemia
(D) Bias in measurement of the outcome: Mild/moderate hypoglycaemia
(E) Bias in selection of the reported result: Mild/moderate hypoglycaemia
(F) Overall bias: Mild/moderate hypoglycaemia

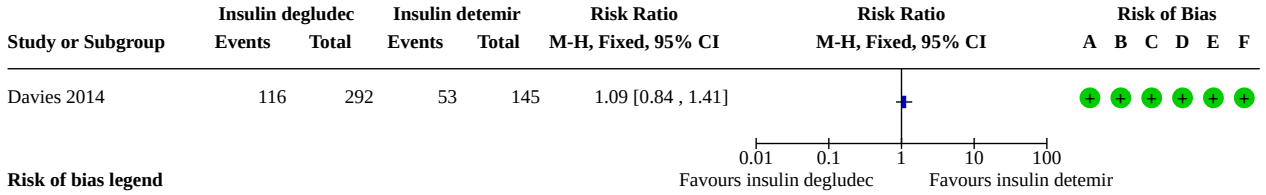
Analysis 4.20. Comparison 4: Insulin degludec versus insulin detemir, Outcome 20: HbA1c



Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: HbA1c
(C) Bias due to missing outcome data: HbA1c
(D) Bias in measurement of the outcome: HbA1c
(E) Bias in selection of the reported result: HbA1c
(F) Overall bias: HbA1c

Analysis 4.21. Comparison 4: Insulin degludec versus insulin detemir, Outcome 21: Individuals with HbA1c < 7% without severe hypoglycaemia



Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Individuals with HbA1c < 7% without severe hypoglycaemia
(C) Bias due to missing outcome data: Individuals with HbA1c < 7% without severe hypoglycaemia
(D) Bias in measurement of the outcome: Individuals with HbA1c < 7% without severe hypoglycaemia
(E) Bias in selection of the reported result: Individuals with HbA1c < 7% without severe hypoglycaemia
(F) Overall bias: Individuals with HbA1c < 7% without severe hypoglycaemia

Comparison 5. Insulin degludec versus insulin glargine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 All-cause mortality	3	973	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.34 [0.15, 11.93]
5.2 All-cause mortality (published vs. unpublished data)	3	973	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.17, 7.65]
5.2.1 Published	1	626	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.06, 7.15]
5.2.2 Unpublished	2	347	Risk Ratio (M-H, Random, 95% CI)	2.98 [0.12, 72.67]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.3 Health-related quality of life (physical health)	2	1043	Mean Difference (IV, Random, 95% CI)	-0.04 [-1.21, 1.13]
5.3.1 Published	1	629	Mean Difference (IV, Random, 95% CI)	0.50 [-0.93, 1.93]
5.3.2 Unpublished	1	414	Mean Difference (IV, Random, 95% CI)	-0.70 [-2.30, 0.90]
5.4 Health-related quality of life (mental health)	2	1539	Mean Difference (IV, Random, 95% CI)	-0.09 [-1.03, 0.85]
5.4.1 Published	1	629	Mean Difference (IV, Random, 95% CI)	0.40 [-1.33, 2.13]
5.4.2 Unpublished	1	910	Mean Difference (IV, Random, 95% CI)	-0.30 [-1.42, 0.82]
5.5 Severe hypoglycaemia	3	970	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.82, 1.82]
5.5.1 Adults	2	952	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.82, 1.82]
5.5.2 Children	1	18	Risk Ratio (M-H, Random, 95% CI)	Not estimable
5.6 Hypoglycaemia reported as a serious adverse event	4	1884	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.40, 1.66]
5.6.1 Adults	3	1866	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.40, 1.66]
5.6.2 Children	1	18	Risk Ratio (M-H, Random, 95% CI)	Not estimable
5.7 Cardiovascular mortality	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.7.1 Adults	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.7.2 Children	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.8 Non-fatal myocardial infarction	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.8.1 Adults	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.8.2 Children	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.9 Non-fatal stroke	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.10 Serious adverse events	3	970	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.58, 1.46]
5.10.1 Adults	2	952	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.58, 1.46]
5.10.2 Children	1	18	Risk Ratio (M-H, Random, 95% CI)	Not estimable
5.11 Diabetic ketoacidosis	3	970	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.05, 6.89]

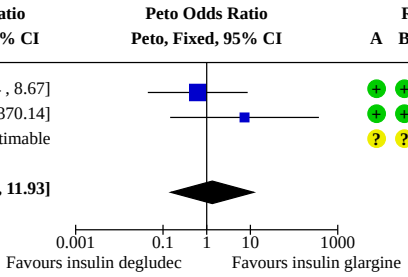
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.11.1 Adults	2	952	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.05, 6.89]
5.11.2 Children	1	18	Risk Ratio (M-H, Random, 95% CI)	Not estimable
5.12 Diabetic ketoacidosis (published vs. unpublished data)	3	970	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.05, 6.89]
5.12.1 Published	1	626	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.04, 1.29]
5.12.2 Unpublished	2	344	Risk Ratio (M-H, Random, 95% CI)	2.93 [0.12, 71.34]
5.13 Non-serious adverse events	3	970	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.95, 1.10]
5.13.1 Adults	2	952	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.95, 1.10]
5.13.2 Children	1	18	Risk Ratio (M-H, Random, 95% CI)	Not estimable
5.14 Withdrawals due to adverse events	2	955	Risk Ratio (M-H, Random, 95% CI)	2.47 [0.72, 8.43]
5.15 Nocturnal hypoglycaemia	3	970	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.91, 1.07]
5.15.1 Adults	2	952	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.91, 1.08]
5.15.2 Chlidren	1	18	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.12, 2.08]
5.16 Mild nocturnal hypoglycaemia	2	952	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.90, 1.07]
5.17 Nocturnal hypoglycaemia (asymptomatic)	2	952	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.71, 1.00]
5.18 Nocturnal hypoglycaemia (symptomatic)	2	952	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.72, 2.07]
5.19 Severe nocturnal hypoglycaemia	3	970	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.59, 3.27]
5.20 Mild/moderate hypoglycaemia	3	970	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.99, 1.04]
5.20.1 Adults	2	952	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.99, 1.04]
5.20.2 Children	1	18	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.82, 1.22]
5.21 HbA1c	4	1388	Mean Difference (IV, Random, 95% CI)	0.10 [0.00, 0.21]
5.21.1 Adults	3	1370	Mean Difference (IV, Random, 95% CI)	0.11 [0.00, 0.21]

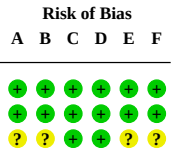
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.21.2 Children	1	18	Mean Difference (IV, Random, 95% CI)	0.00 [-0.55, 0.55]
5.22 HbA1c (published vs. unpublished data)	4	1388	Mean Difference (IV, Random, 95% CI)	0.10 [0.00, 0.21]
5.22.1 Published	3	847	Mean Difference (IV, Random, 95% CI)	0.14 [0.02, 0.25]
5.22.2 Unpublished	1	541	Mean Difference (IV, Random, 95% CI)	0.00 [-0.21, 0.21]
5.23 Individuals with HbA1c < 7% without severe hypoglycaemia	2	911	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.78, 1.10]

Analysis 5.1. Comparison 5: Insulin degludec versus insulin glargine, Outcome 1: All-cause mortality

Study or Subgroup	Insulin degludec Events	Total	Insulin glargine Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
BEGIN Basal-Bolus Type 1	2	472	1	154	68.9%	0.62 [0.04 , 8.67]
BEGIN Flex T1	1	165	0	164	31.1%	7.34 [0.15 , 370.14]
Urakami 2017 (1)	0	9	0	9		Not estimable
Total (95% CI)		**646**		**327**	**100.0%**	**1.34 [0.15 , 11.93]**
Total events:	3		1			

Heterogeneity: Chi² = 1.05, df = 1 (P = 0.31); I² = 5%
Test for overall effect: Z = 0.26 (P = 0.79)
Test for subgroup differences: Not applicable



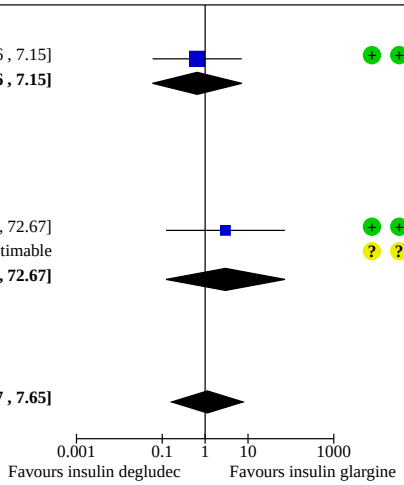


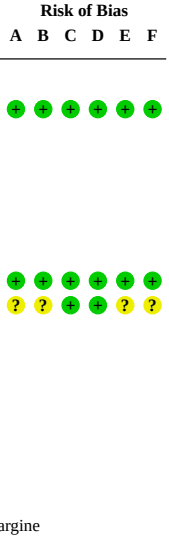
Footnotes
(1) Data from study author

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: All-cause mortality
(C) Bias due to missing outcome data: All-cause mortality
(D) Bias in measurement of the outcome: All-cause mortality
(E) Bias in selection of the reported result: All-cause mortality
(F) Overall bias: All-cause mortality

Analysis 5.2. Comparison 5: Insulin degludec versus insulin glargine, Outcome 2: All-cause mortality (published vs. unpublished data)

Study or Subgroup	Insulin degludec Events	Total	Insulin glargine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
5.2.1 Published						
BEGIN Basal-Bolus Type 1	2	472	1	154	64.0%	0.65 [0.06 , 7.15]
Subtotal (95% CI)		**472**		**154**	**64.0%**	**0.65 [0.06 , 7.15]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.35 (P = 0.73)						
5.2.2 Unpublished						
BEGIN Flex T1	1	165	0	164	36.0%	2.98 [0.12 , 72.67]
Urakami 2017 (1)	0	9	0	9		Not estimable
Subtotal (95% CI)		**174**		**173**	**36.0%**	**2.98 [0.12 , 72.67]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.50)						
Total (95% CI)		**646**		**327**	**100.0%**	**1.13 [0.17 , 7.65]**
Total events:	3		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.57, df = 1 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.12 (P = 0.90)						
Test for subgroup differences: Chi² = 0.56, df = 1 (P = 0.46), I² = 0%						





Footnotes

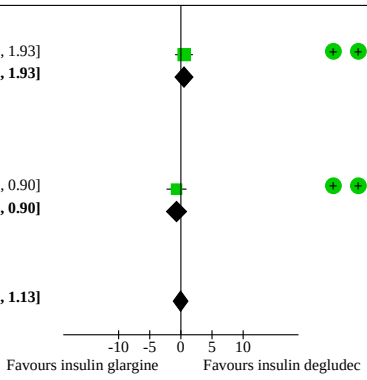
(1) Data from study author

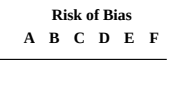
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: All-cause mortality (published vs. unpublished data)
(C) Bias due to missing outcome data: All-cause mortality (published vs. unpublished data)
(D) Bias in measurement of the outcome: All-cause mortality (published vs. unpublished data)
(E) Bias in selection of the reported result: All-cause mortality (published vs. unpublished data)
(F) Overall bias: All-cause mortality (published vs. unpublished data)

Analysis 5.3. Comparison 5: Insulin degludec versus insulin glargine, Outcome 3: Health-related quality of life (physical health)

Study or Subgroup	Insulin degludec Mean	SD	Total	Insulin glargine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
5.3.1 Published								
BEGIN Basal-Bolus Type 1	52.3	7.3	472	51.8	8.1	157	54.7%	0.50 [-0.93 , 1.93]
Subtotal (95% CI)			**472**			**157**	**54.7%**	**0.50 [-0.93 , 1.93]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.69 (P = 0.49)								
5.3.2 Unpublished								
SWITCH 1	49.9	8.1	209	50.6	8.5	205	45.3%	-0.70 [-2.30 , 0.90]
Subtotal (95% CI)			**209**			**205**	**45.3%**	**-0.70 [-2.30 , 0.90]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.86 (P = 0.39)								
Total (95% CI)			**681**			**362**	**100.0%**	**-0.04 [-1.21 , 1.13]**
Heterogeneity: Tau² = 0.12; Chi² = 1.20, df = 1 (P = 0.27); I² = 17%								
Test for overall effect: Z = 0.07 (P = 0.94)								
Test for subgroup differences: Chi² = 1.20, df = 1 (P = 0.27), I² = 16.9%								



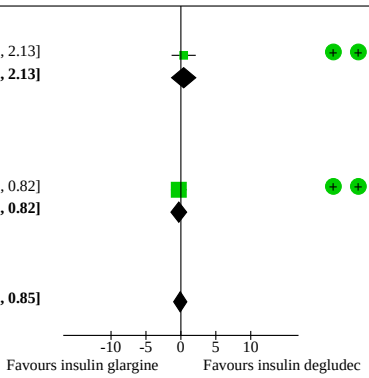


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Health-related quality of life (physical health)
(C) Bias due to missing outcome data: Health-related quality of life (physical health)
(D) Bias in measurement of the outcome: Health-related quality of life (physical health)
(E) Bias in selection of the reported result: Health-related quality of life (physical health)
(F) Overall bias: Health-related quality of life (physical health)

Analysis 5.4. Comparison 5: Insulin degludec versus insulin glargine, Outcome 4: Health-related quality of life (mental health)

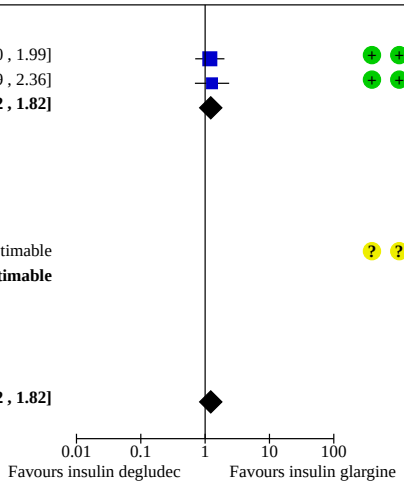
Study or Subgroup	Insulin degludec Mean	SD	Total	Insulin glargine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
5.4.1 Published								
BEGIN Basal-Bolus Type 1	50.3	9.5	472	49.9	9.6	157	29.7%	0.40 [-1.33 , 2.13]
Subtotal (95% CI)			**472**			**157**	**29.7%**	**0.40 [-1.33 , 2.13]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.45 (P = 0.65)								
5.4.2 Unpublished								
SWITCH 1	50.1	8.7	409	50.4	8.5	501	70.3%	-0.30 [-1.42 , 0.82]
Subtotal (95% CI)			**409**			**501**	**70.3%**	**-0.30 [-1.42 , 0.82]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.52 (P = 0.60)								
Total (95% CI)			**881**			**658**	**100.0%**	**-0.09 [-1.03 , 0.85]**
Heterogeneity: Tau² = 0.00; Chi² = 0.44, df = 1 (P = 0.51); I² = 0%								
Test for overall effect: Z = 0.19 (P = 0.85)								
Test for subgroup differences: Chi² = 0.44, df = 1 (P = 0.51), I² = 0%								

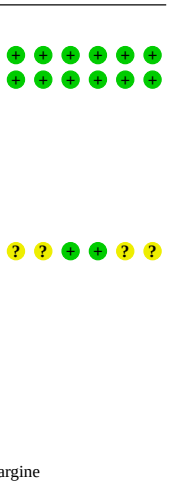


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Health-related quality of life (mental health)
(C) Bias due to missing outcome data: Health-related quality of life (mental health)
(D) Bias in measurement of the outcome: Health-related quality of life (mental health)
(E) Bias in selection of the reported result: Health-related quality of life (mental health)
(F) Overall bias: Health-related quality of life (mental health)

Analysis 5.5. Comparison 5: Insulin degludec versus insulin glargine, Outcome 5: Severe hypoglycaemia

Study or Subgroup	Insulin degludec Events	Total	Insulin glargine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
5.5.1 Adults						
BEGIN Basal-Bolus Type 1	58	472	16	154	57.9%	1.18 [0.70 , 1.99]
BEGIN Flex T1	21	165	16	161	42.1%	1.28 [0.69 , 2.36]
Subtotal (95% CI)		**637**		**315**	**100.0%**	**1.22 [0.82 , 1.82]**
Total events:	79		32			
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.99 (P = 0.32)						
5.5.2 Children						
Urakami 2017	0	9	0	9		Not estimable
Subtotal (95% CI)		**9**		**9**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**646**		**324**	**100.0%**	**1.22 [0.82 , 1.82]**
Total events:	79		32			
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.99 (P = 0.32)						
Test for subgroup differences: Not applicable						

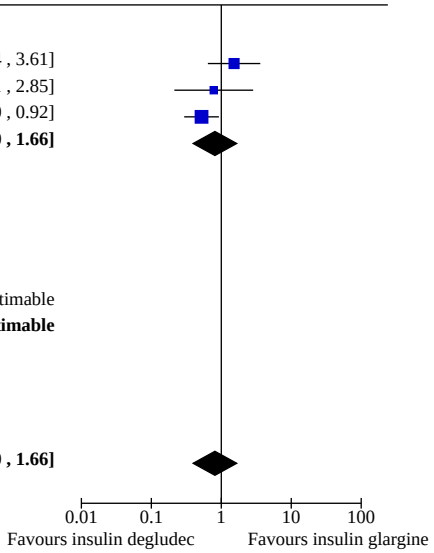




Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Severe hypoglycaemia
(C) Bias due to missing outcome data: Severe hypoglycaemia
(D) Bias in measurement of the outcome: Severe hypoglycaemia
(E) Bias in selection of the reported result: Severe hypoglycaemia
(F) Overall bias: Severe hypoglycaemia

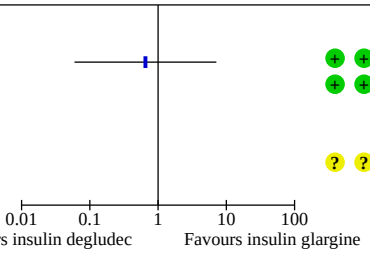
Analysis 5.6. Comparison 5: Insulin degludec versus insulin glargine, Outcome 6: Hypoglycaemia reported as a serious adverse event

Study or Subgroup	Insulin degludec Events	Total	Insulin glargine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
5.6.1 Adults						
BEGIN Basal-Bolus Type 1	28	472	6	154	33.4%	1.52 [0.64 , 3.61]
BEGIN Flex T1	4	165	5	161	20.7%	0.78 [0.21 , 2.85]
SWITCH 1	17	454	33	460	45.9%	0.52 [0.30 , 0.92]
Subtotal (95% CI)		**1091**		**775**	**100.0%**	**0.81 [0.40 , 1.66]**
Total events:	49		44			
Heterogeneity: Tau² = 0.21; Chi² = 4.13, df = 2 (P = 0.13); I² = 52%						
Test for overall effect: Z = 0.57 (P = 0.57)						
5.6.2 Children						
Urakami 2017	0	9	0	9		Not estimable
Subtotal (95% CI)		**9**		**9**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**1100**		**784**	**100.0%**	**0.81 [0.40 , 1.66]**
Total events:	49		44			
Heterogeneity: Tau² = 0.21; Chi² = 4.13, df = 2 (P = 0.13); I² = 52%						
Test for overall effect: Z = 0.57 (P = 0.57)						
Test for subgroup differences: Not applicable						



Analysis 5.7. Comparison 5: Insulin degludec versus insulin glargine, Outcome 7: Cardiovascular mortality

Study or Subgroup	Insulin degludec Events	Total	Insulin glargine Events	Total	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
5.7.1 Adults						
BEGIN Basal-Bolus Type 1	2	472	1	154	0.65 [0.06 , 7.15]	+ + + + + +
BEGIN Flex T1	0	165	0	161	Not estimable	+ + + + + +
5.7.2 Children						
Urakami 2017 (1)	0	9	0	9	Not estimable	? ? + + ? ?

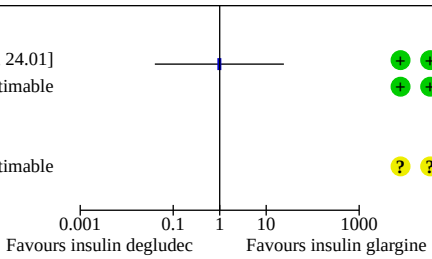


Footnotes
(1) Data from study author

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Cardiovascular mortality
(C) Bias due to missing outcome data: Cardiovascular mortality
(D) Bias in measurement of the outcome: Cardiovascular mortality
(E) Bias in selection of the reported result: Cardiovascular mortality
(F) Overall bias: Cardiovascular mortality

Analysis 5.8. Comparison 5: Insulin degludec versus insulin glargine, Outcome 8: Non-fatal myocardial infarction

Study or Subgroup	Insulin degludec Events	Total	Insulin glargine Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
5.8.1 Adults							
BEGIN Basal-Bolus Type 1	1	472	0	154	0.98 [0.04 , 24.01]		+ + + + + +
BEGIN Flex T1	0	165	0	161	Not estimable		+ + + + + +
5.8.2 Children							
Urakami 2017 (1)	0	9	0	9	Not estimable		? ? + + ? ?



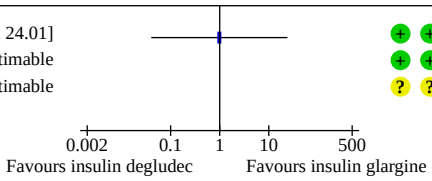
Footnotes
(1) Data from study author

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Non-fatal myocardial infarction
(C) Bias due to missing outcome data: Non-fatal myocardial infarction
(D) Bias in measurement of the outcome: Non-fatal myocardial infarction
(E) Bias in selection of the reported result: Non-fatal myocardial infarction
(F) Overall bias: Non-fatal myocardial infarction

Analysis 5.9. Comparison 5: Insulin degludec versus insulin glargine, Outcome 9: Non-fatal stroke

Study or Subgroup	Insulin degludec Events	Total	Insulin glargine Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
BEGIN Basal-Bolus Type 1	1	472	0	154	0.98 [0.04 , 24.01]		+ + + + + +
BEGIN Flex T1	0	165	0	161	Not estimable		+ + + + + +
Urakami 2017 (1)	0	9	0	9	Not estimable		? ? + + ? ?

Test for subgroup differences: Not applicable

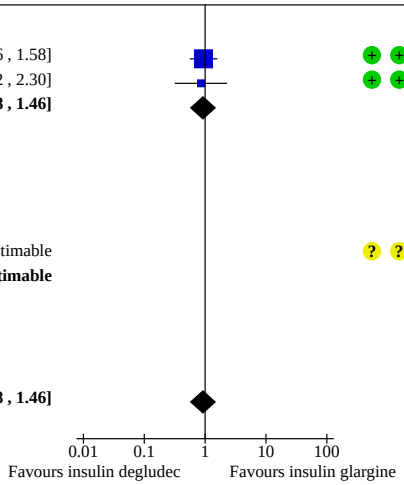


Footnotes
(1) Data from study author

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Non-fatal stroke
(C) Bias due to missing outcome data: Non-fatal stroke
(D) Bias in measurement of the outcome: Non-fatal stroke
(E) Bias in selection of the reported result: Non-fatal stroke
(F) Overall bias: Non-fatal stroke

Analysis 5.10. Comparison 5: Insulin degludec versus insulin glargine, Outcome 10: Serious adverse events

Study or Subgroup	Insulin degludec Events	Total	Insulin glargine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
5.10.1 Adults							
BEGIN Basal-Bolus Type 1	49	472	17	154	78.4%	0.94 [0.56 , 1.58]	+ + + + + +
BEGIN Flex T1	7	165	8	161	21.6%	0.85 [0.32 , 2.30]	+ + + + + +
Subtotal (95% CI)		**637**		**315**	**100.0%**	**0.92 [0.58 , 1.46]**	
Total events:	56		25				
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0%							
Test for overall effect: Z = 0.35 (P = 0.73)							
5.10.2 Children							
Urakami 2017 (1)	0	9	0	9		Not estimable	? ? + + ? ?
Subtotal (95% CI)		**9**		**9**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total (95% CI)		**646**		**324**	**100.0%**	**0.92 [0.58 , 1.46]**	
Total events:	56		25				
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0%							
Test for overall effect: Z = 0.35 (P = 0.73)							
Test for subgroup differences: Not applicable							



Footnotes

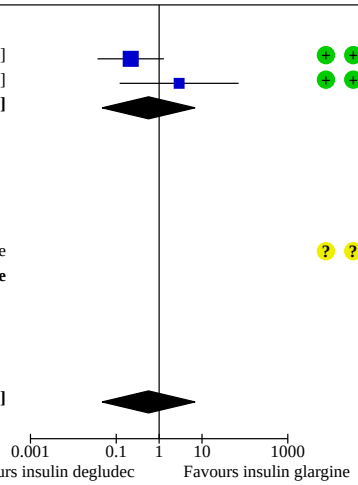
(1) Data from study author

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Serious adverse events
(C) Bias due to missing outcome data: Serious adverse events
(D) Bias in measurement of the outcome: Serious adverse events
(E) Bias in selection of the reported result: Serious adverse events
(F) Overall bias: Serious adverse events

Analysis 5.11. Comparison 5: Insulin degludec versus insulin glargine, Outcome 11: Diabetic ketoacidosis

Study or Subgroup	Insulin degludec Events	Total	Insulin glargine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
5.11.1 Adults							
BEGIN Basal-Bolus Type 1	2	472	3	154	63.1%	0.22 [0.04 , 1.29]	+ + + + + +
BEGIN Flex T1	1	165	0	161	36.9%	2.93 [0.12 , 71.34]	+ + + + + +
Subtotal (95% CI)		**637**		**315**	**100.0%**	**0.57 [0.05 , 6.89]**	
Total events:	3		3				
Heterogeneity: Tau² = 1.75; Chi² = 2.00, df = 1 (P = 0.16); I² = 50%							
Test for overall effect: Z = 0.44 (P = 0.66)							
5.11.2 Children							
Urakami 2017 (1)	0	9	0	9		Not estimable	? ? + + ? ?
Subtotal (95% CI)		**9**		**9**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total (95% CI)		**646**		**324**	**100.0%**	**0.57 [0.05 , 6.89]**	
Total events:	3		3				
Heterogeneity: Tau² = 1.75; Chi² = 2.00, df = 1 (P = 0.16); I² = 50%							
Test for overall effect: Z = 0.44 (P = 0.66)							
Test for subgroup differences: Not applicable							



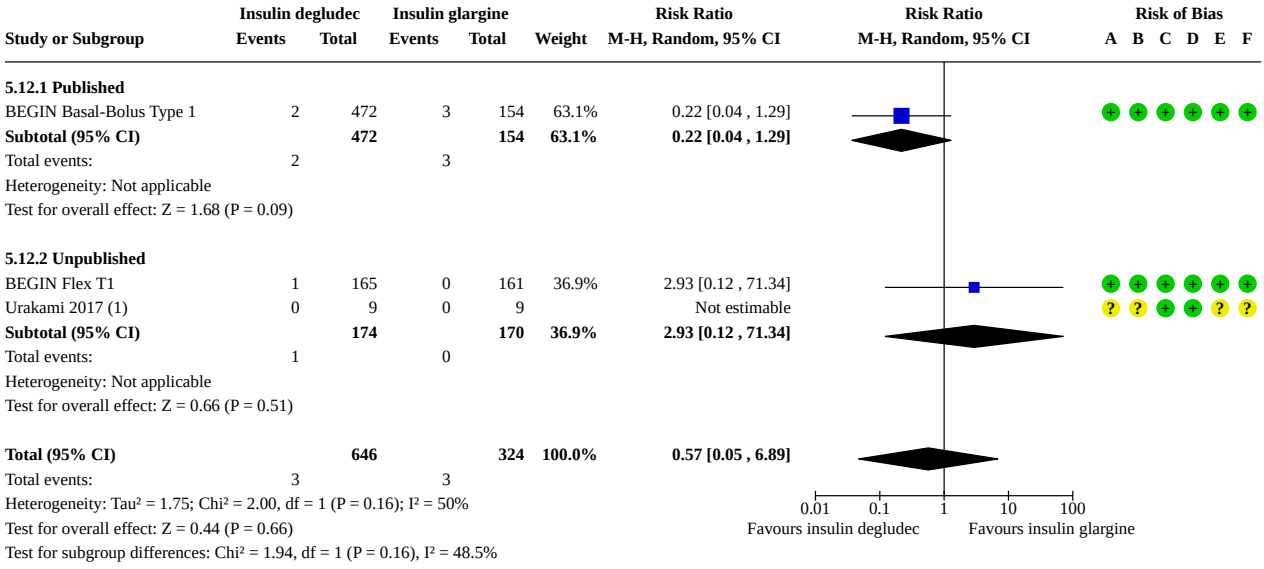
Footnotes

(1) Data from study author

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Diabetic ketoacidosis
(C) Bias due to missing outcome data: Diabetic ketoacidosis
(D) Bias in measurement of the outcome: Diabetic ketoacidosis
(E) Bias in selection of the reported result: Diabetic ketoacidosis
(F) Overall bias: Diabetic ketoacidosis

Analysis 5.12. Comparison 5: Insulin degludec versus insulin glargine, Outcome 12: Diabetic ketoacidosis (published vs. unpublished data)



Footnotes

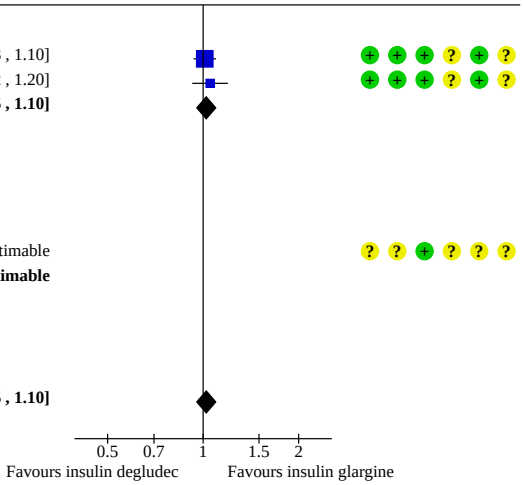
(1) Data from study author

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Diabetic ketoacidosis (published vs. unpublished data)
(C) Bias due to missing outcome data: Diabetic ketoacidosis (published vs. unpublished data)
(D) Bias in measurement of the outcome: Diabetic ketoacidosis (published vs. unpublished data)
(E) Bias in selection of the reported result: Diabetic ketoacidosis (published vs. unpublished data)
(F) Overall bias: Diabetic ketoacidosis (published vs. unpublished data)

Analysis 5.13. Comparison 5: Insulin degludec versus insulin glargine, Outcome 13: Non-serious adverse events

Study or Subgroup	Insulin degludec Events	Total	Insulin glargine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
5.13.1 Adults						
BEGIN Basal-Bolus Type 1	397	472	128	154	71.7%	1.01 [0.93 , 1.10]
BEGIN Flex T1	125	165	116	161	28.3%	1.05 [0.92 , 1.20]
Subtotal (95% CI)		**637**		**315**	**100.0%**	**1.02 [0.95 , 1.10]**
Total events:	522		244			
Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 1 (P = 0.61); I² = 0%						
Test for overall effect: Z = 0.65 (P = 0.52)						
5.13.2 Children						
Urakami 2017 (1)	0	9	0	9		Not estimable
Subtotal (95% CI)		**9**		**9**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**646**		**324**	**100.0%**	**1.02 [0.95 , 1.10]**
Total events:	522		244			
Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 1 (P = 0.61); I² = 0%						
Test for overall effect: Z = 0.65 (P = 0.52)						
Test for subgroup differences: Not applicable						



Footnotes

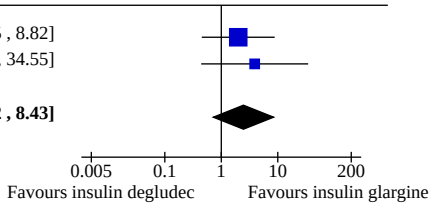
(1) Data from study author

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Non-serious adverse events
(C) Bias due to missing outcome data: Non-serious adverse events
(D) Bias in measurement of the outcome: Non-serious adverse events
(E) Bias in selection of the reported result: Non-serious adverse events
(F) Overall bias: Non-serious adverse events

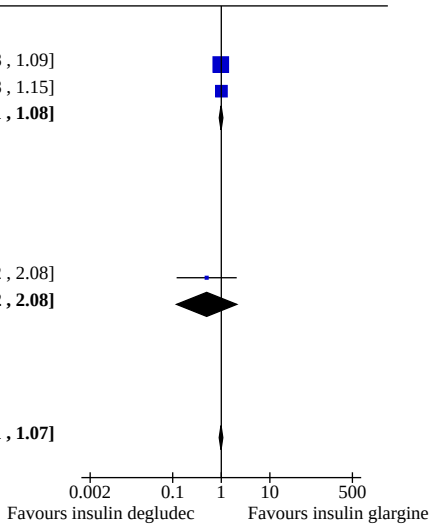
Analysis 5.14. Comparison 5: Insulin degludec versus insulin glargine, Outcome 14: Withdrawals due to adverse events

Study or Subgroup	Insulin degludec Events	Total	Insulin glargine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
BEGIN Basal-Bolus Type 1	12	472	2	157	68.3%	2.00 [0.45 , 8.82]
BEGIN Flex T1	4	165	1	161	31.7%	3.90 [0.44 , 34.55]
Total (95% CI)		**637**		**318**	**100.0%**	**2.47 [0.72 , 8.43]**
Total events:	16		3			
Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 1 (P = 0.62); I² = 0%						
Test for overall effect: Z = 1.44 (P = 0.15)						
Test for subgroup differences: Not applicable						



Analysis 5.15. Comparison 5: Insulin degludec versus insulin glargine, Outcome 15: Nocturnal hypoglycaemia

Study or Subgroup	Insulin degludec Events	Total	Insulin glargine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
5.15.1 Adults						
BEGIN Basal-Bolus Type 1	341	472	114	154	59.3%	0.98 [0.88 , 1.09]
BEGIN Flex T1	121	165	117	161	40.4%	1.01 [0.88 , 1.15]
Subtotal (95% CI)		**637**		**315**	**99.7%**	**0.99 [0.91 , 1.08]**
Total events:	462		231			
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%						
Test for overall effect: Z = 0.25 (P = 0.80)						
5.15.2 Chlidren						
Urakami 2017 (1)	2	9	4	9	0.3%	0.50 [0.12 , 2.08]
Subtotal (95% CI)		**9**		**9**	**0.3%**	**0.50 [0.12 , 2.08]**
Total events:	2		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.95 (P = 0.34)						
Total (95% CI)		**646**		**324**	**100.0%**	**0.99 [0.91 , 1.07]**
Total events:	464		235			
Heterogeneity: Tau² = 0.00; Chi² = 1.03, df = 2 (P = 0.60); I² = 0%						
Test for overall effect: Z = 0.31 (P = 0.76)						
Test for subgroup differences: Chi² = 0.88, df = 1 (P = 0.35), I² = 0%						

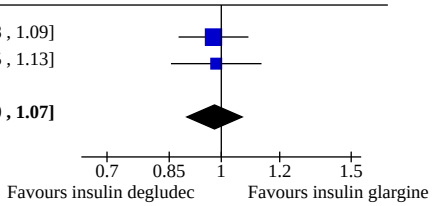


Footnotes

(1) Data provided by study author

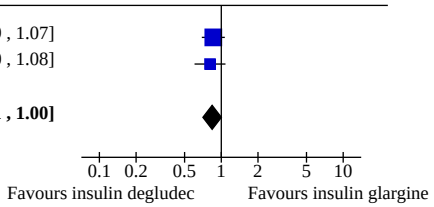
Analysis 5.16. Comparison 5: Insulin degludec versus insulin glargine, Outcome 16: Mild nocturnal hypoglycaemia

Study or Subgroup	Insulin degludec Events	Total	Insulin glargine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
BEGIN Basal-Bolus Type 1	341	472	114	154	62.7%	0.98 [0.88 , 1.09]
BEGIN Flex T1	115	165	114	161	37.3%	0.98 [0.85 , 1.13]
Total (95% CI)		**637**		**315**	**100.0%**	**0.98 [0.90 , 1.07]**
Total events:	456		228			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%						
Test for overall effect: Z = 0.48 (P = 0.63)						
Test for subgroup differences: Not applicable						



Analysis 5.17. Comparison 5: Insulin degludec versus insulin glargine, Outcome 17: Nocturnal hypoglycaemia (asymptomatic)

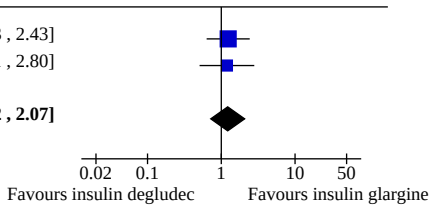
Study or Subgroup	Insulin degludec Events	Total	Insulin glargine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
BEGIN Basal-Bolus Type 1	174	472	66	154	64.4%	0.86 [0.69 , 1.07]
BEGIN Flex T1	53	165	64	161	35.6%	0.81 [0.60 , 1.08]
Total (95% CI)		**637**		**315**	**100.0%**	**0.84 [0.71 , 1.00]**
Total events:	227		130			
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%						
Test for overall effect: Z = 1.94 (P = 0.05)						
Test for subgroup differences: Not applicable						



Analysis 5.18. Comparison 5: Insulin degludec versus insulin glargine, Outcome 18: Nocturnal hypoglycaemia (symptomatic)

Study or Subgroup	Insulin degludec Events	Total	Insulin glargine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
BEGIN Basal-Bolus Type 1	38	472	10	154	61.7%	1.24 [0.63 , 2.43]
BEGIN Flex T1	11	165	9	161	38.3%	1.19 [0.51 , 2.80]
Total (95% CI)		**637**		**315**	**100.0%**	**1.22 [0.72 , 2.07]**
Total events:	49		19			

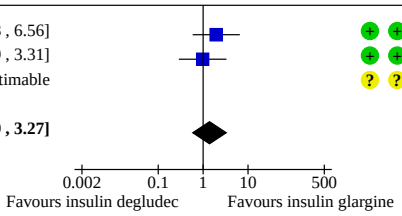
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.74 (P = 0.46)
Test for subgroup differences: Not applicable



Analysis 5.19. Comparison 5: Insulin degludec versus insulin glargine, Outcome 19: Severe nocturnal hypoglycaemia

Study or Subgroup	Insulin degludec Events	Total	Insulin glargine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
BEGIN Basal-Bolus Type 1	18	472	3	154	50.5%	1.96 [0.58 , 6.56]	+ + + + + +
BEGIN Flex T1	5	165	5	161	49.5%	0.98 [0.29 , 3.31]	+ + + + + +
Urakami 2017 (1)	0	9	0	9		Not estimable	? ? + + ? ?
Total (95% CI)		**646**		**324**	**100.0%**	**1.39 [0.59 , 3.27]**	
Total events:	23		8				

Heterogeneity: Tau² = 0.00; Chi² = 0.64, df = 1 (P = 0.42); I² = 0%
Test for overall effect: Z = 0.75 (P = 0.46)
Test for subgroup differences: Not applicable

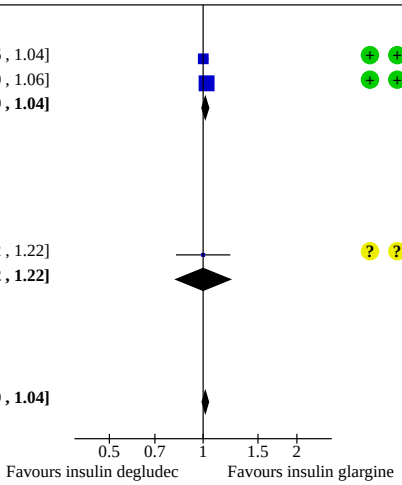


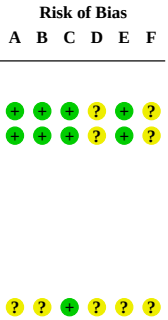
Footnotes
(1) Data from study author

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Severe nocturnal hypoglycaemia
(C) Bias due to missing outcome data: Severe nocturnal hypoglycaemia
(D) Bias in measurement of the outcome: Severe nocturnal hypoglycaemia
(E) Bias in selection of the reported result: Severe nocturnal hypoglycaemia
(F) Overall bias: Severe nocturnal hypoglycaemia

Analysis 5.20. Comparison 5: Insulin degludec versus insulin glargine, Outcome 20: Mild/moderate hypoglycaemia

Study or Subgroup	Insulin degludec Events	Total	Insulin glargine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
5.20.1 Adults						
BEGIN Basal-Bolus Type 1	451	472	147	154	36.1%	1.00 [0.96 , 1.04]
BEGIN Flex T1	164	165	156	161	62.5%	1.03 [1.00 , 1.06]
Subtotal (95% CI)		**637**		**315**	**98.6%**	**1.02 [0.99 , 1.04]**
Total events:	615		303			
Heterogeneity: Tau² = 0.00; Chi² = 1.11, df = 1 (P = 0.29); I² = 10%						
Test for overall effect: Z = 1.24 (P = 0.21)						
5.20.2 Children						
Urakami 2017 (1)	9	9	9	9	1.4%	1.00 [0.82 , 1.22]
Subtotal (95% CI)		**9**		**9**	**1.4%**	**1.00 [0.82 , 1.22]**
Total events:	9		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Total (95% CI)		**646**		**324**	**100.0%**	**1.02 [0.99 , 1.04]**
Total events:	624		312			
Heterogeneity: Tau² = 0.00; Chi² = 1.14, df = 2 (P = 0.56); I² = 0%						
Test for overall effect: Z = 1.34 (P = 0.18)						
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%						





Footnotes

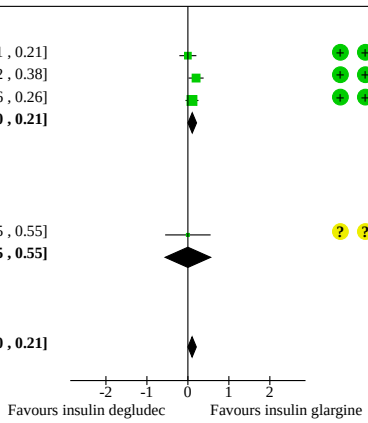
(1) Data from study author

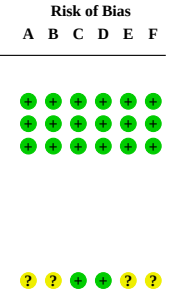
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Mild/moderate hypoglycaemia
(C) Bias due to missing outcome data: Mild/moderate hypoglycaemia
(D) Bias in measurement of the outcome: Mild/moderate hypoglycaemia
(E) Bias in selection of the reported result: Mild/moderate hypoglycaemia
(F) Overall bias: Mild/moderate hypoglycaemia

Analysis 5.21. Comparison 5: Insulin degludec versus insulin glargine, Outcome 21: HbA1c

Study or Subgroup	Insulin degludec Mean	SD	Total	Insulin glargine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
5.21.1 Adults								
BEGIN Basal-Bolus Type 1	7.3	1	402	7.3	1.1	139	24.2%	0.00 [-0.21 , 0.21]
BEGIN Flex T1	7.3	0.9	165	7.1	0.8	164	30.7%	0.20 [0.02 , 0.38]
SWITCH 1	7	0.9	248	6.9	0.9	252	41.7%	0.10 [-0.06 , 0.26]
Subtotal (95% CI)			**815**			**555**	**96.6%**	**0.11 [0.00 , 0.21]**
Heterogeneity: Tau² = 0.00; Chi² = 2.01, df = 2 (P = 0.37); I² = 1%								
Test for overall effect: Z = 2.01 (P = 0.04)								
5.21.2 Children								
Urakami 2017	7.8	0.6	9	7.8	0.6	9	3.4%	0.00 [-0.55 , 0.55]
Subtotal (95% CI)			**9**			**9**	**3.4%**	**0.00 [-0.55 , 0.55]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
Total (95% CI)			**824**			**564**	**100.0%**	**0.10 [0.00 , 0.21]**
Heterogeneity: Tau² = 0.00; Chi² = 2.15, df = 3 (P = 0.54); I² = 0%								
Test for overall effect: Z = 1.98 (P = 0.05)								
Test for subgroup differences: Chi² = 0.14, df = 1 (P = 0.71), I² = 0%								

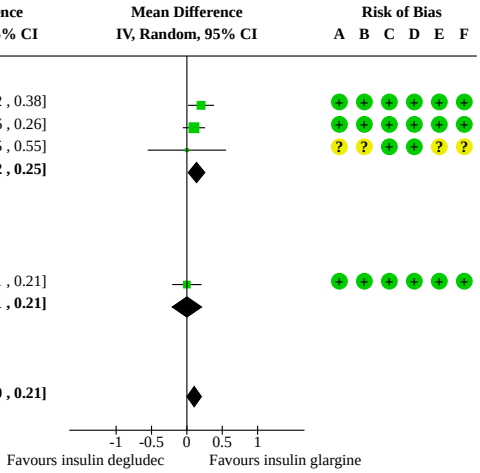




Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: HbA1c
(C) Bias due to missing outcome data: HbA1c
(D) Bias in measurement of the outcome: HbA1c
(E) Bias in selection of the reported result: HbA1c
(F) Overall bias: HbA1c

Analysis 5.22. Comparison 5: Insulin degludec versus insulin glargine, Outcome 22: HbA1c (published vs. unpublished data)

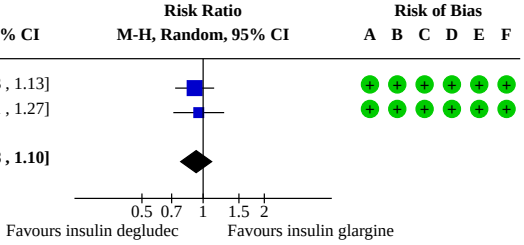


Study or Subgroup	Insulin degludec Mean	SD	Total	Insulin glargine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F
5.22.1 Published									
BEGIN Flex T1	7.3	0.9	165	7.1	0.8	164	30.7%	0.20 [0.02 , 0.38]	+ + + + + +
SWITCH 1	7	0.9	248	6.9	0.9	252	41.7%	0.10 [-0.06 , 0.26]	+ + + + + +
Urakami 2017	7.8	0.6	9	7.8	0.6	9	3.4%	0.00 [-0.55 , 0.55]	? ? + + ? ?
Subtotal (95% CI)			**422**			**425**	**75.8%**	**0.14 [0.02 , 0.25]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.90, df = 2 (P = 0.64); I² = 0%									
Test for overall effect: Z = 2.28 (P = 0.02)									
5.22.2 Unpublished									
BEGIN Basal-Bolus Type 1	7.3	1	402	7.3	1.1	139	24.2%	0.00 [-0.21 , 0.21]	+ + + + + +
Subtotal (95% CI)			**402**			**139**	**24.2%**	**0.00 [-0.21 , 0.21]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.00 (P = 1.00)									
Total (95% CI)			**824**			**564**	**100.0%**	**0.10 [0.00 , 0.21]**	
Heterogeneity: Tau² = 0.00; Chi² = 2.15, df = 3 (P = 0.54); I² = 0%									
Test for overall effect: Z = 1.98 (P = 0.05)									
Test for subgroup differences: Chi² = 1.25, df = 1 (P = 0.26), I² = 20.2%									

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: HbA1c (published vs. unpublished data)
(C) Bias due to missing outcome data: HbA1c (published vs. unpublished data)
(D) Bias in measurement of the outcome: HbA1c (published vs. unpublished data)
(E) Bias in selection of the reported result: HbA1c (published vs. unpublished data)
(F) Overall bias: HbA1c (published vs. unpublished data)

Analysis 5.23. Comparison 5: Insulin degludec versus insulin glargine, Outcome 23: Individuals with HbA1c < 7% without severe hypoglycaemia



Study or Subgroup	Insulin degludec Events	Total	Insulin glargine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
BEGIN Basal-Bolus Type 1	174	453	63	149	62.9%	0.91 [0.73 , 1.13]	+ + + + + +
BEGIN Flex T1	56	153	60	156	37.1%	0.95 [0.71 , 1.27]	+ + + + + +
Total (95% CI)		**606**		**305**	**100.0%**	**0.92 [0.78 , 1.10]**	
Total events:	230		123				
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.80); I² = 0%							
Test for overall effect: Z = 0.88 (P = 0.38)							
Test for subgroup differences: Not applicable							

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Individuals with HbA1c < 7% without severe hypoglycaemia
(C) Bias due to missing outcome data: Individuals with HbA1c < 7% without severe hypoglycaemia
(D) Bias in measurement of the outcome: Individuals with HbA1c < 7% without severe hypoglycaemia
(E) Bias in selection of the reported result: Individuals with HbA1c < 7% without severe hypoglycaemia
(F) Overall bias: Individuals with HbA1c < 7% without severe hypoglycaemia

ADDITIONAL TABLES

Table 1. Overview of study populations

Study ID (study design)	Intervention(s) and comparator(s)	Description of power and sample size calculation	Screened/ eligible (n)	Randomised (n)	Analysed primary outcome) (n)	Finishing study (n)	Randomised finishing study (%)	Follow-up (extended follow-up)[a]
Bartley 2008 (parallel-group non-inferiority RCT)	I: insulin detemir	**Quote**: "A total of 489 patients were needed to obtain 245 evaluable patients on detemir and 123 on NPH to detect a clinically relevant difference of 0.4% in HbA1c with a power of 85%, assuming a standard deviation (SD) for HbA1c of 1.2 and an expected drop-out rate of 25%"	557	331	320	278	84.3	24 months
	C: NPH insulin			166	159	144	86.7	
	total:			497	479	422	85.0	
BEGIN Basal-Bolus Type 1 [b] (parallel-group non-inferiority RCT)	I: insulin degludec	**Quote**: "Sample size was determined by the primary objective with the assumption of a one sided t test at a significance level of 2·5%, a zero mean treatment difference, and an SD of 1·1% for HbA1c. A total of 624 participants were needed for at least 95% power after adjustment for a 15% dropout rate"	722	472	472	404	85.6	52 weeks (104 weeks)
	C: insulin glargine			157	157	137	87.0	
	total:			629	629	541	86.0	
BEGIN Flex T1 [c] (parallel-group non-inferiority RCT)	I: insulin degludec	**Quote**: "Sample size was determined on the basis of the primary objective under the assumption of a 1-sided t test of size 2.5%, a zero mean treatment difference, and standard deviation of 1.1% for HbA1c"	549	165	165	139	84.2	26 weeks (52 weeks)
	C: insulin glargine			164	164	152	92.7	
	total:			329	329	291	88.4	
BEGIN Young [d] (parallel-group non-inferiority RCT)	I: insulin degludec	**Quote**: "The sample size was determined using a t-statistic under the assumption of a one-sided test of size 2.5%, a zero mean treatment difference and standard deviation (SD) of 1.25% for HbA1c. A total of 346 participants had to be randomized to achieve at least 80% or greater power in the evaluation of the per	363	174	174	170	97.7	26 weeks (52 weeks)
	C: insulin detemir			176	176	163	93.7	

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

		protocol (PP) analysis set, after adjustment for a 10% dropout rate"						
	total:			350	350	333	95.1	
Bolli 2009 (parallel-group superiority RCT)	I: insulin glargine	**Quote**: "The expected FBG difference in the two groups at the end of the study treatment was estimated to be 30+/-60 mg/dL. Using a two-sided test with α = 0.01 and ß = 0.1 (i.e., power: 1-ß = 0.9), 240 evaluable patients were to be included. Due to an expected dropout rate of 20% and to the randomization schedule, which was restricted and stratified by centre (26 centres), 312 patients were planned to be enrolled"	213	85	85	78	91.8	24 weeks (30 weeks)
	C: NPH insulin			90	90	74	82.2	
	total:			175	175	152	86.7	
Chase 2008 (parallel-group non-inferiority RCT)	I: insulin glargine	**Quote:** "The primary clinical outcome (the mean change in A1C from baseline [week 0] to endpoint [week 24 or last post randomization assessment]) was compared in the 2 treatment groups using analysis of covariance (ANCOVA), with treatment group, study centre (pooled), CGMS values, sex, and baseline value as covariates (α = 0.05; 2-sided test). The 95% confidence intervals (CIs) were computed for the adjusted mean difference between treatment groups from the ANCOVA to test for noninferiority (defined as an upper bound of the 95% CI for the mean difference in A1C of ≤ 0.4%)"	235	85	84	81	95.3	24 weeks (25 weeks)
	C: NPH insulin/Lente			90	84	76	84.4	
	total:			175	168	157	89.7	
Davies 2014e (parallel-group non-inferiority RCT)	I: insulin degludec	**Quote:** "Assuming a standard deviation (SD) of 1.1% for the primary endpoint, the trial had 90% power with 360 participants randomized 2:1"	512	303	302	283	93.4	26 weeks (52 weeks)
	C: insulin detemir			153	153	138	90.2	
	total:			456	455	421	92.5	

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

Fulcher 2005 (parallel-group non-inferiority RCT)	I: insulin glargine	**Quote**: "The sample size was calculated assuming a 20% dropout rate, so that 118 patients (59 in each group) were enrolled in order to have 96 patients (48 in each group) available for evaluation at end-point. Assuming a SD of 1.2 for HbA1c (based on previous Phase IIIa studies), the study had 80% power to detect a 0.7% difference in HbA1c"	173[f]	62	62	58	94	30 weeks
	C: NPH insulin			63	62	49	78	
	total:			125	124[f]	107	85.6	
Heller 2009 (parallel-group non-inferiority RCT)	I: insulin detemir	**Quote**: "The sample size was determined for 2:1 (detemir:glargine) randomization and based on a 1-sided t test at a 2.5% significance level. Assuming an SD of 1.0% for HbA1c and a dropout rate of 15%, a sample size of 435 patients gave 95% power to demonstrate noninferiority"	515	300	299	263	87.7	52 weeks
	C: insulin glargine			147	144	122	83.0	
	total:			447	443	385	86.1	
Home 2005 (parallel-group superiority RCT)	I: insulin glargine	**Quote from CSR**: "It was planned to treat 520 subjects, 260 subjects in each group. Each investigation site was to randomise 10-20 subjects.The primary efficacy variable for the comparison between HOE 901 and NPH insulin was the change from baseline in GHb at the study endpoint for the individual subject ... The standard deviation for change from baseline in GHb at endpoint was estimated to be 1.6%. Based on 1:1 randomization and using a t-test, a total number of 440 subjects (220 subjects for each group) was required to detect a mean difference of 0.5% GHb between HOE 901 and NPH with a type I error of α = 5% and a statistical power of 90%. With an expected drop-out rate of 15% during the course of the study, a total number of 520 subjects (260 subjects in each group) were to be enrolled in order to have 440 subjects (220 subjects in each group) evaluable at week 28"	655	298	292	276	94.5	28 weeks
	C: NPH insulin			305	293	272	92.8	
	total:			603[g]	585[h]	548	93.6	

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

Kobayashi 2007 (parallel-group non-inferiority RCT)	I: insulin detemir	—	454[i]	197	195	183	93.4	48 weeks
	C: NPH insulin			99	98	91	92.9	
	total:			296	293	274	92.6	
Liu 2016 (parallel-group non-inferiority RCT)	I: insulin glargine	**Quote from CSR**: "The planned sample size was reduced from 366 to 150 patients in view of extremely difficult recruitment progress over the 2 years since first patient's enrolment..."	196	107	108	106	99.1	24 weeks (25 weeks)
	C: NPH insulin			55	54	50	90.9	
	total:			162	161	156	96.3	
NCT00595374[f] (parallel-group non-inferiority RCT)	I: insulin detemir	—	124	75	—	70	93.3	26 weeks
	C: NPH insulin			38	—	34	92.1	
	total:			113	—	104	92.0	
NCT00605137[f] (parallel-group non-inferiority RCT)	I: insulin detemir	**Quote from trial protocol**: "This power calculation is based on a two-sample poisson test at a significance level of 5% for the comparison of the mean rate of nocturnal episodes per four weeks although nocturnal episodes will be analysed as recurrent events using gamma frailty model in the trial analysis"	88	57	55	55	96.5	24 weeks
	C: NPH insulin			29	27	27	93.1	
	total:			86	82	82	95.3	
Pieber 2007 (parallel-group non-inferiority RCT)	I: insulin detemir	**Quote**: "The sample size was determined in order to test non-inferiority in a 1:1 randomization. Assuming a standard deviation for HbA1c of 1.2% and a clinically relevant, absolute difference in HbA1c of 0.4%, a total of 286 randomized participants were needed to achieve a power of 80%. Assuming a 10%	415	161	161	147	91.3	26 weeks
	C: insulin glargine			161	159	146	90.7	

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

		drop-out rate, 159 randomized participants were needed in each group"						
	total:			322	319	293	91.0	
Porcellati 2004 (parallel-group superiority RCT)	I: insulin glargine	**Quote**: "In this design, a total of 120 participants were required to achieve 90% power to detect a difference of 0.3% among the means with group standard deviations of 0.4 at the significance level (alpha) of 5%"	130	61	61	61	100	1 year
	C: NPH insulin			60	60	60	100	
	total:			121	121	121	100	
PRESCHOOL (parallel-group non-inferiority RCT)	I: insulin glargine	**Quote**: "Sample size calculation was based on an expected composite hypoglycemia rate of 0.8 events/100 patient-yr of exposure to insulin glargine or to NPH insulin. The sample size and novel composite outcome was planned to ensure sufficient power so that the upper bound of the two-sided 95% confidence interval (CI) for the insulin glargine:NPH ratio of the mean composite hypoglycemia rates for the comparison of treatment groups would not exceed 1.15. A sample size of 35 completed patients per treatment group was to provide 96% power to demonstrate noninferiority of insulin glargine vs. NPH"	165	61	61	57	93.4	24 weeks (26 weeks)
	C: NPH insulin			64	64	54	84.4	
	total:			125[j]	125	111	88.8	
Ratner 2000 (parallel-group superiority RCT)	I: insulin glargine	**Quote**: "An estimated 440 participants (220 in each treatment group) were required to detect a mean difference of 0.5% in GHb levels between treatment with a type 1 error of α = 5% and a statistical power of 90%"	677[f]	266	256	233	88.3	28 weeks
	C: NPH insulin			274	262	248	91.9	
	total:			540[k]	518	481[f]	90.1	
Robertson 2007 (parallel-group	I: insulin detemir	**Quote**: "The sample size was determined for a 2: 1 randomization based on a two-sided t -test on a 5% significance level. Assuming a SD for HbA 1c of 1.1% and a clinically relevant difference in HbA 1c of 0.4% (absolute), 270	363[f]	232	232	226	97.4	26 weeks
	C: NPH insulin			115	114	109	94.8	

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

non-inferiority RCT)		children were needed to achieve a power of 80%. With an expected drop-out rate of 20%, 338 children were to be allocated to study treatment"						
	total:			347	347	335[f]	96.5	
Russell-Jones 2004 (parallel-group non-inferiority RCT)	I: insulin detemir	**Quote**: "Sample size was based on an SD for HbA1c of 1.4% and the assumption that a 0.4% absolute difference in HbA1c represents a clinically relevant difference" and " All comparisons were 2-tailed tests with a 5% level of significance"	838[f]	492	491	465	94.7	6 months
	C: NPH insulin			257	256	235	91.8	
	total:			749[f]	747	700	93.5	
Schober 2002 (parallel-group superiority RCT)	I: insulin glargine	**Quote**: "The sample size was calculated to detect a mean difference in HbA1C from baseline to endpoint of 0.5% with a statistical power of 90%. Assuming a 20% dropout rate, the minimum sample size required was 360 patients"	385	180	155	169	93.9	28 weeks
	C: NPH insulin			181	156	168	92.8	
	total:			361[l]	311	337[f]	93.4	
Standl 2004 [m] (parallel-group non-inferiority RCT)	I: insulin detemir	**Quote from CSR**: "A total of 440 type 1 participants were planned for randomisation in order to obtain 400 evaluable participants, assuming a dropout rate of approximately 10%"	505[f]	237	210	212	89.5	6 months (12 months)
	C: NPH insulin			224	206	209	93.3	
	total:			461[f]	416[f]	421	91.3	
SWITCH 1 [n] (cross-over non-inferiority RCT)	I: insulin degludec	**Quote**: "The trial was powered to show non-inferiority of the primary end point. Based on the assumption that up to 10% of the randomised patients may not contribute to the analysis, 400 patients needed to contribute to the analysis if 446 patients were randomised to ensure a power of 94%, to demonstrate noninferiority with an expected rate of overall symptomatic hypoglycemia of 5.0 episodes per patient-years' exposure (PYE)"	634	249	249	209	83.9	32 weeks
	C: insulin glargine			252	251	205	81.3	

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

	total:			501	414	414	82.6	
Thalange 2013 (parallel-group non-inferiority RCT)	I: insulin detemir	**Quote**: "The power calculation was analysed on this basis: using a two-sided t-test with a one-sided significance level of 2.5%, assuming SD of 1.1, a non-inferiority criterion of 0.4%, a power of 85% and an expected dropout rate of 20%, a total of 344 children were to be randomized"	381	177	171	164	92.7	52 weeks (104 weeks)
	C: NPH insulin			171	168	161	94.2	
	total:			348	339	325	93.4	
Urakami 2017 [p] (cross-over superiority RCT)	I: insulin degludec	—	—	9	9	9	100	24 weeks
	C: insulin glargine			9	9	9	100	
	total:			18	18	18	100	
Vague 2003 (parallel-group non-inferiority RCT)	I: insulin detemir	**Quote**: "The initial cohort size was calculated to achieve a power of 85% on the basis of non-inferiority testing at the 5% significance level and a 2:1 randomization"	471[f]	301	280	284	94.4	6 months (12 months)
	C: NPH insulin			147	139	141	96.6	
	total:			448	419	425	95.1	
Overall total	**All insulin detemir**			**2889**		**2648**		
	All insulin degludec			**1372**		**1214**		
	All insulin glargine			**2095**		**1890**		
	All NPH insulin			**2428**		**2202**		
	All interventions			**8784**		**7954**		

Table 1. Overview of study populations and comparators *(Continued)*

— denotes not reported

[a]Follow-up under randomised conditions until end of study (= duration of intervention + follow-up post-intervention or identical to 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]Data in the table are for the main period.After 52 weeks, the participants of the initial study were invited to an extension study. 74% in the degludec and 75% in the glargine participated. Of the one included in the extension period, 94% (330/351) participants completed in the degludec group and 96% (113/118) participants in the glargine group.

[c]An additional study arm existed, which was not included in this review.

[d]Data in the table are for the main period. In the insulin degludec group, 152 participants entered the extension study and 151 participants completed; in the insulin detemir group, 128 participants entered the extension study and 122 participants completed.

[e]Data in the table are for the main period. In the insulin degludec group, 248 participants entered the extension study and 242 participants completed (79.9% of those initially randomised); in the insulin detemir group, 122 participants entered the extension study and 115 participants completed (75.2% of those initially randomised).

[f]Data from clinical study report/synopsis.

[g]In the publication, it was only mentioned that 602 participants were randomised, but not explained how these were divided between the intervention groups. This was reported in the clinical study report. In the publication, there was only information about the allocation of the 585 participants who received the intervention.

[h]In the main publication, the number of participants analysed was not clearly described; this number was provided by the clinical study report.

[i]Both people with type 1 diabetes mellitus and type 2 diabetes mellitus were screened.

[j]One participant randomised to NPH insulin was actually treated with insulin glargine, thus the safety population comprised 62 participants for insulin glargine and 63 participants for NPH insulin.

[k]In the main publication, it was stated that 534 participants were randomised (264 participants allocated to insulin glargine; 270 participants allocated to NPH insulin). In the clinical study report, it was stated that a total of 540 participants were randomised, but six were never treated (2 participants in the insulin glargine group; 4 participants in the NPH insulin group).

[l]Of the 361 participants randomised, 12 withdrew their consent before being treated, therefore a total 349 participants were treated: 174 participants in the glargine group compared with 175 participants in the NPH group.

[m]Data in the table are for the main period. In the insulin detemir group, 154 participants entered the extension study and 118 participants completed (49.8% of those initially randomised); in the NPH insulin group, 135 participants entered the extension study and 134 participants completed (59.8% of those initially randomised).

[n]Data from first treatment period before cross-over (32 weeks).

[o]Extension only performed for the detemir group.

[p]Not reported if any participant dropped out during the study. All randomised participants were included in all analyses.

A1c: glycosylated haemoglobin A1c
ANCOVA: analysis of covariance
C: comparator
CGMS: continuous glucose monitoring system
CI: confidence interval
CSR: clinical study report
FBG: fasting blood glucose
GHb: glycated haemoglobin
HbA1c: glycosylated haemoglobin A1c
HOE 901: insulin glargine
I: intervention
NPH: neutral protamine Hagedorn
PYE: patient-years' exposure

RCT: randomised controlled trial
SD: standard deviation
vs: versus

APPENDICES

Appendix 1. Checklist to aid consistency and reproducibility of GRADE assessments: insulin detemir compared with NPH insulin

Items		(1) All-cause mortality	(2) Health-related quality of life	(3) Severe hypoglycaemia	(4) Non-fatal myocardial infarction/stroke	(5) Severe nocturnal hypoglycaemia	(6) Serious adverse events	(7) HbA1c
Study limitations (risk of bias)[a]	Overall risk of bias	Low risk	Some concerns	Low risk	Low risk/not reported	Low risk	Low risk	Low risk
Inconsistency[b]	Point estimates did not vary widely?	Yes	NA	No (↓)	NA	Yes	Yes	Yes
	To what extent did confidence intervals overlap (substantial: all confidence intervals overlap at least one of the included studies point estimate; some: confidence intervals overlap but not all overlap at least one point estimate; no: at least one outlier: where the confidence interval of some of the studies do not overlap with those of most included studies)?	Substantial		Some		Substantial	Substantial	Some
	Was the direction of effect consistent?	Yes		No (↓)		Yes	No (↓)	Yes
	What was the magnitude of statistical heterogeneity (as measured by I^2) - low ($I^2 < 40\%$), moderate (I^2 40%-60%), high $I^2 > 60\%$)?	Low		Low		Moderate	Low	Low
	Was the test for heterogeneity statistically significant ($P < 0.1$)?	Not statistically significant		Not statistically significant		Not statistically significant	Not statistically significant	Not 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	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	Highly applicable
	Was the included outcome not a surrogate outcome?	Yes	Yes	Yes	Yes	Yes	Yes	No (↓)
	Was the outcome timeframe sufficient?	No (↓)	Yes	Yes	No (↓)	Yes	Yes	Yes

(Continued)

	Were the conclusions based on direct comparisons?	Yes	NA	Yes	Yes	Yes	Yes	Yes
Imprecision[c]	Was the confidence interval for the pooled estimate not consistent with benefit and harm?	Yes	NA	Yes	NA	No (↓)	Yes	No (↓)
	What is the magnitude of the median sample size (high: 300 participants, intermediate: 100-300 participants, low: < 100 participants)?[e]	High	High	High	High	High	High	High
	What was the magnitude of the number of included studies (large: > 10 studies, moderate: 5-10 studies, small: < 5 studies)?[e]	Moderate	Small (↓)	Moderate	Small (↓)	Moderate	Moderate	Moderate
	Was the outcome a common event (e.g. occurs more than 1/100)?	No (↓)	NA	Yes	No (↓)	Yes	Yes	NA
Publication bias[d]	Was a comprehensive search conducted?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Was grey literature searched?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Were no restrictions applied to study selection on the basis of language?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	There was no industry influence on studies included in the review?	No	No	No	No	No	No	No
	There was no evidence of funnel plot asymmetry?	NA	NA	NA	NA	NA	NA	NA
	There was no discrepancy in findings between published and unpublished studies?	Yes	Unclear	No (↓)	Unclear	Yes	Yes	Yes

[a]Risk of bias was addressed by the Cochrane 'Risk of bias' 2 tool (RoB 2).
[b]Questions on inconsistency are primarily based on visual assessment of forest plots and prediction intervals.

[c]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.
[d]Questions address comprehensiveness of the search strategy, industry influence, funnel plot asymmetry and discrepancies between published and unpublished studies.
[e]Depends on the context of the systematic review area.

(↓): key item for potential downgrading the certainty of the evidence (GRADE) as shown in the footnotes of the 'Summary of finding' table(s).

(Continued)

HbA1c: glycosylated haemoglobin A1c;**NA:** not applicable.

Appendix 2. Checklist to aid consistency and reproducibility of GRADE assessments: insulin glargine compared with NPH insulin

Items		(1) All-cause mortality	(2) Health-related quality of life	(3) Severe hypoglycaemia	(4) Non-fatal myocardial infarction/stroke	(5) Severe nocturnal hypoglycaemia	(6) Serious adverse events	(7) HbA1c
Study limitations (risk of bias)[a]	Overall risk of bias	Low risk	Some concerns	Low risk	Low risk / low risk	Low risk	Low risk	Low risk
Inconsistency[b]	Point estimates did not vary widely?	NA	Unclear	Yes	NA	Yes	No (↓)	Yes
	To what extent did confidence intervals overlap (substantial: all confidence intervals overlap at least one of the included studies point estimate; some: confidence intervals overlap but not all overlap at least one point estimate; no: at least one outlier: where the confidence interval of some of the studies do not overlap with those of most included studies)?		Substantial	Substantial		Substantial	Some	Some
	Was the direction of effect consistent?		Unclear	Yes		Yes	No (↓)	Yes
	What was the magnitude of statistical heterogeneity (as measured by I^2) - low ($I^2 < 40\%$), moderate (I^2 40%-60%), high $I^2 > 60\%$)?		Low	Low		Low	High	Low
	Was the test for heterogeneity statistically significant ($P < 0.1$)?		Not statistically significant	Not statistically significant		Not statistically significant	Statistically significant	Not 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	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	Highly applicable
	Was the included outcome not a surrogate outcome?	Yes	Yes	Yes	Yes	Yes	Yes	No (↓)
	Was the outcome timeframe sufficient?	No (↓)	Yes	Yes	No (↓)	Yes	Yes	Yes

(Continued)

	Were the conclusions based on direct comparisons?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Imprecision[c]	Was the confidence interval for the pooled estimate not consistent with benefit and harm?	NA	NA	No (↓)	NA	No (↓)	Yes	No (↓)
	What is the magnitude of the median sample size (high: 300 participants, intermediate: 100-300 participants, low: < 100 participants)?[e]	Intermediate	Intermediate	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)?[e]	Small (↓)	Small (↓)	Moderate	Small (↓)	Moderate	Moderate	Moderate
	Was the outcome a common event (e.g. occurs more than 1/100)?	No (↓)	NA	Yes	No (↓)	Yes	Yes	NA
Publication bias[d]	Was a comprehensive search conducted?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Was grey literature searched?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Were no restrictions applied to study selection on the basis of language?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	There was no industry influence on studies included in the review?	No	No	No	No	No	No	No
	There was no evidence of funnel plot asymmetry?	NA	NA	NA	NA	NA	NA	NA
	There was no discrepancy in findings between published and unpublished studies?	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes

[a]Risk of bias was addressed by the Cochrane 'Risk of bias' 2 tool (RoB 2).
[b]Questions on inconsistency are primarily based on visual assessment of forest plots and prediction intervals.

[c]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.
[d]Questions address comprehensiveness of the search strategy, industry influence, funnel plot asymmetry and discrepancies between published and unpublished studies.
[e]Depends on the context of the systematic review area.

(↓): key item for potential downgrading the certainty of the evidence (GRADE) as shown in the footnotes of the 'Summary of finding' table(s).

(Continued)

HbA1c: glycosylated haemoglobin A1c;**NA:** not applicable.

Appendix 3. Checklist to aid consistency and reproducibility of GRADE assessments: insulin detemir compared with insulin glargine

Items		(1) All-cause mortality	(2) Health-related quality of life	(3) Severe hypoglycaemia	(4) Non-fatal myocardial infarction/stroke	(5) Severe nocturnal hypoglycaemia	(6) Serious adverse events	(7) HbA1c
Study limitations (risk of bias)[a]	Overall risk of bias	Low risk	Not reported	Low risk	Low risk / low risk	Low risk	Low risk	Low risk
Inconsistency[b]	Point estimates did not vary widely?	NA		No (↓)	NA	No (↓)	No (↓)	Yes
	To what extent did confidence intervals overlap (substantial: all confidence intervals overlap at least one of the included studies point estimate; some: confidence intervals overlap but not all overlap at least one point estimate; no: at least one outlier: where the confidence interval of some of the studies do not overlap with those of most included studies)?			Some		Substantial	Substantial	Substantial
	Was the direction of effect consistent?			No (↓)		No (↓)	Yes	Yes
	What was the magnitude of statistical heterogeneity (as measured by I^2) - low ($I^2 < 40\%$), moderate (I^2 40%-60%), high $I^2 > 60\%$)?			High		High	Low	Low
	Was the test for heterogeneity statistically significant ($P < 0.1$)?			Statistically significant		Not statistically significant	Not statistically significant	Not 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?	No (↓)		Yes	No (↓)	Yes	Yes	Yes

(Continued)

	Were the conclusions based on direct comparisons?	Yes	Yes	Yes	Yes	Yes	Yes
Imprecision[c]	Was the confidence interval for the pooled estimate not consistent with benefit and harm?	NA	No (↓)	NA	No (↓)	No (↓)	No (↓)
	What is the magnitude of the median sample size (high: 300 participants, intermediate: 100-300 participants, low: < 100 participants)?[e]	Intermediate	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)?[e]	Small (↓)	Small (↓)	Small (↓)	Small (↓)	Small (↓)	Small (↓)
	Was the outcome a common event (e.g. occurs more than 1/100)?	Yes (↓)	Yes	Yes (↓)	Yes	Yes	NA
Publication bias[d]	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 studies?	Unclear	No (↓)	NA	Yes	NA	Yes

[a]Risk of bias was addressed by the Cochrane 'Risk of bias' 2 tool (RoB 2).
[b]Questions on inconsistency are primarily based on visual assessment of forest plots and prediction intervals.

[c]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.
[d]Questions address comprehensiveness of the search strategy, industry influence, funnel plot asymmetry and discrepancies between published and unpublished studies.
[e]Depends on the context of the systematic review area.

(↓): key item for potential downgrading the certainty of the evidence (GRADE) as shown in the footnotes of the 'Summary of finding' table(s).

(Continued)

HbA1c: glycosylated haemoglobin A1c;**NA:** not applicable.

Appendix 4. Checklist to aid consistency and reproducibility of GRADE assessments: insulin degludec compared with insulin detemir

Items		(1) All-cause mortality	(2) Health-related quality of life	(3) Severe hypoglycaemia	(4) Non-fatal myocardial infarction/stroke	(5) Severe nocturnal hypoglycaemia	(6) Serious adverse events	(7) HbA1c
Study limitations (risk of bias)[a]	Overall risk of bias	Low risk	Some concerns	Low risk	Low risk / low risk	Low risk	Low risk	Low risk
Inconsistency[b]	Point estimates did not vary widely?	NA	NA	Yes	NA	Yes	Yes	Yes
	To what extent did confidence intervals overlap (substantial: all confidence intervals overlap at least one of the included studies point estimate; some: confidence intervals overlap but not all overlap at least one point estimate; no: at least one outlier: where the confidence interval of some of the studies do not overlap with those of most included studies)?			Substantial		Substantial	Substantial	Some
	Was the direction of effect consistent?			Yes		Yes	Yes	Yes
	What was the magnitude of statistical heterogeneity (as measured by I^2) - low ($I^2 < 40\%$), moderate (I^2 40%-60%), high $I^2 > 60\%$)?			Low		Low	Low	Low
	Was the test for heterogeneity statistically significant ($P < 0.1$)?			Not statistically significant		Not statistically significant	Not statistically significant	Not 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	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	Highly applicable
	Was the included outcome not a surrogate outcome?	Yes	Yes	Yes	Yes	Yes	Yes	No (↓)
	Was the outcome timeframe sufficient?	No (↓)	Yes	Yes	No (↓)	Yes	Yes	Yes

(Continued)

	Were the conclusions based on direct comparisons?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Imprecision[c]	Was the confidence interval for the pooled estimate not consistent with benefit and harm?	NA	NA	No (↓)	NA	No (↓)	No (↓)	No (↓)
	What is the magnitude of the median sample size (high: 300 participants, intermediate: 100-300 participants, low: < 100 participants)?[e]	Intermediate	Intermediate	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)?[e]	Small (↓)	Small (↓)	Small (↓)	Small (↓)	Small (↓)	Small (↓)	Small (↓)
	Was the outcome a common event (e.g. occurs more than 1/100)?	No (↓)	NA	Yes	NA	Yes	Yes	NA
Publication bias[d]	Was a comprehensive search conducted?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Was grey literature searched?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Were no restrictions applied to study selection on the basis of language?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	There was no industry influence on studies included in the review?	No	No	No	No	No	No	No
	There was no evidence of funnel plot asymmetry?	NA	NA	NA	NA	NA	NA	NA
	There was no discrepancy in findings between published and unpublished studies?	NA	NA	NA	NA	Yes	NA	Yes

[a]Risk of bias was addressed by the Cochrane 'Risk of bias' 2 tool (RoB 2).
[b]Questions on inconsistency are primarily based on visual assessment of forest plots and prediction intervals.

[c]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.
[d]Questions address comprehensiveness of the search strategy, industry influence, funnel plot asymmetry and discrepancies between published and unpublished studies.
[e]Depends on the context of the systematic review area.

(↓): key item for potential downgrading the certainty of the evidence (GRADE) as shown in the footnotes of the 'Summary of finding' table(s).

(Continued)

HbA1c: glycosylated haemoglobin A1c;**NA:** not applicable.

Appendix 5. Checklist to aid consistency and reproducibility of GRADE assessments: insulin degludec compared with insulin glargine

Items		(1) All-cause mortality	(2) Health-related quality of life	(3) Severe hypoglycaemia	(4) Non-fatal myocardial infarction/stroke	(5) Severe nocturnal hypoglycaemia	(6) Serious adverse events	(7) HbA1c
Study limitations (risk of bias)[a]	Overall risk of bias	Low risk	Some concerns	Low risk	Low risk / low risk	Low risk	Low risk	Low risk
Inconsistency[b]	Point estimates did not vary widely?	Yes	Yes	Yes	NA	Yes	Yes	Yes
	To what extent did confidence intervals overlap (substantial: all confidence intervals overlap at least one of the included studies point estimate; some: confidence intervals overlap but not all overlap at least one point estimate; no: at least one outlier: where the confidence interval of some of the studies do not overlap with those of most included studies)?	Substantial	Some	Substantial		Substantial	Substantial	Some
	Was the direction of effect consistent?	No (↓)	No (↓)	Yes		Yes	Yes	Yes
	What was the magnitude of statistical heterogeneity (as measured by I^2) - low ($I^2 < 40\%$), moderate (I^2 40%-60%), high $I^2 > 60\%$)?	Low	Low	Low		Low	Low	Low
	Was the test for heterogeneity statistically significant ($P < 0.1$)?	Not statistically significant	Not statistically significant	Not statistically significant		Not statistically significant	Not statistically significant	Not 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	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	Highly applicable
	Was the included outcome not a surrogate outcome?	Yes	Yes	Yes	Yes	Yes	Yes	No (↓)
	Was the outcome timeframe sufficient?	No (↓)	Yes	Yes	No (↓)	Yes	Yes	Yes

(Continued)

	Were the conclusions based on direct comparisons?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Imprecision[c]	Was the confidence interval for the pooled estimate not consistent with benefit and harm?	Yes	Yes	No (↓)	NA	No (↓)	Yes	No (↓)
	What is the magnitude of the median sample size (high: 300 participants, intermediate: 100-300 participants, low: < 100 participants)?[e]	Intermediate	Intermediate	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)?[e]	Small (↓)	Small (↓)	Small (↓)	Small (↓)	Small (↓)	Small (↓)	Small (↓)
	Was the outcome a common event (e.g. occurs more than 1/100)?	No (↓)	NA	Yes	No (↓)	Yes	Yes	NA
Publication bias[d]	Was a comprehensive search conducted?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Was grey literature searched?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Were no restrictions applied to study selection on the basis of language?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	There was no industry influence on studies included in the review?	No	No	No	No	No	No	No
	There was no evidence of funnel plot asymmetry?	NA	NA	NA	NA	NA	NA	NA
	There was no discrepancy in findings between published and unpublished studies?	Unclear	Unclear	NA	NA	Yes	NA	Yes

[a]Risk of bias was addressed by the Cochrane 'Risk of bias' 2 tool (RoB 2).
[b]Questions on inconsistency are primarily based on visual assessment of forest plots and prediction intervals.

[c]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.
[d]Questions address comprehensiveness of the search strategy, industry influence, funnel plot asymmetry and discrepancies between published and unpublished studies.
[e]Depends on the context of the systematic review area.

(↓): key item for potential downgrading the certainty of the evidence (GRADE) as shown in the footnotes of the 'Summary of finding' table(s).

(Continued)

HbA1c: glycosylated haemoglobin A1c;**NA:** not applicable.

Appendix 6. Search strategies

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
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

(Continued)

MEDLINE (Ovid)

[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.

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

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

23. (NN 1250 or NN1250).mp.

24. or/19-23

25. 10 or 18 or 24

[*Condition: diabetes*]

26. exp Diabetes Mellitus/

27. diabet*.mp.

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

(Continued)

29. or/26-28

[*Combination of intervention and population*]

30. 25 and 29

[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

[*"Phase 3" filter* (Cooper 2019)]

42. Clinical Trial, Phase III/

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

44. 42 or 43

[*RCT or "phase 3" filter*]

45. 41 or 44

[*Combination of intervention, population and filters*]

46. 30 and 45

WHO ICTRP Search Portal (Standard search)

glargine AND diabet* OR

levemir AND diabet* OR

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]

HTA database

(Continued)

(glargine) OR (levemir) OR (detemir) OR (degludec)

Appendix 7. Overview of sources of unpublished additional data

Study ID (Trial ID)	Accessible pages from clinical study report	Accessible pages from clinical study synopsis	Accessible pages from EMA	Accessible pages from FDA
Bartley 2008 (NN304-1595)	731 No appendices	5	—	—
BEGIN Basal-Bolus Type 1 (NN1250-3583)	2581 (+3564 CSR pages of extension trial NN1250-3644) No appendices	17	134	419
BEGIN Flex T1 (NN1250-3770)	1675 (+ 2212 CSR pages of extension trial NN1250-3770-ext) No appendices	9 (12 synopsis of main trial period + extension trial period)	134	559
BEGIN Young (NN1250-3561)	1914 (+ 3350 CSR pages of extension trial NN1250-3561) No appendices	16	81	559
Bolli 2009	—	—	—	—
Chase 2008 (HOE901/4030)	150 No end-of-text tables, no appendices (additional 4182+ pages)	7	—	—
Davies 2014 (NN1250-3585)	1645 (+ 2086 CSR pages of extension trial NN1250-3725) No appendices	16	134	419
Fulcher 2005 (HOE901/4010)	127 No summary tables, no appendices	8	—	—
Heller 2009 (NN304-1430)	386 No appendices	8	—	—
Home 2005 (HOE901/3001)	317 (+ 40 CSR pages on health-related quality of life; + 342 CSR pages on health economics) No appendices	3		34
Kobayashi 2007	3	8	—	—

(Continued)

(NN304-1476)	Translated pages			
Liu 2016 (HOE901; EFC11681)	154 No appendices	9	21	—
NCT00595374 (NN304-1582)	—	4	—	—
NCT00605137 (NN304-1604)	4 (+ 80 CSR protocol pages) Translated pages	6	—	—
Pieber 2007 (NN304-1372)	97 No appendices	4	—	145
Porcellati 2004	—	—	—	—
PRESCHOOL (HOE901; EFC11202)	188 No appendices	7	36	—
Ratner 2000 (HOE301/3004)	331 No appendices, some tables ("participant listing") missing (additional 11.990+ pages)	5	—	34
Robertson 2007 (NN304-1379)	647 (+ 653 CSR pages on extension trial NN304-1690) No appendices	5	—	11
Russell-Jones 2004 (NN304-1335)	314 No appendices	5	29	145
Schober 2002 (HOE901/3003)	330 (+ 196 CSR pages on health economics) No appendices (additional 7087+ pages)	3	—	34
Standl 2004 (NN304-1181)	108 No end-of-text tables, no end-of-text figures, no selected listings, no appendices	5	29	145
SWITCH 1 (NN1250-3995)	3042 No appendices	9	—	559
Thalange 2013 (NN304-1689)	1055 (+653 CSR pages of extension trial NN304-1690) No appendices	7	38	—
Urakami 2017	—	—	—	—
Vague 2003	256	5	29	145

(Continued)

(NN304-1205)	No end-of-text tables, no end-of-text figures, no selected listings, no appendices

—: indicates source not available

CSR: clinical study report; **EMA**: European Medicines Agency; **FDA**: Food and Drug Administration.

Appendix 8. Description of interventions

Bartley 2008	Intervention	Description
Intervention[a]	I: detemir	Once daily at any time during the evening (Levemir®, Novo Nordisk A/S, Bagsvaerd, Denmark 100 U/mL), administered in the thigh, sc, a second basal insulin dose could be added in the morning
	C: NPH	Once daily NPH at any time during the evening (Insulatard®, Novo Nordisk A/S, 100 U/mL), administered in the thigh, sc, a second basal insulin dose could be added in the morning
Titration period	Assuming 12 weeks ("During the first 12 weeks, patients were in weekly contact with the investigator or research team")	
Strength of insulin	Based in titration regimen, then 1 U detemir = 1 unit NPH	
Rapid-acting insulin	Aspart (NovoRapid®, Novo Nordisk A/S, 100 U/mL) was injected immediately before each main meal, administered in the abdomen. Aspart was titrated according to local practice to achieve a post-prandial PG level ≤ 9.0 mmol/L	
Glycaemic targets	Basal insulin was titrated aiming for a PG target ≤ 6.0 mmol/L before breakfast and dinner; post-prandial glucose < 10 mmol/L; BG 2:00-4:00 4-7 mmol/L	
Interval of blood glucose measurement	Participants were asked to measure PG pre-breakfast and pre-dinner on three consecutive days prior to each contact	
Calibration of blood glucose measurement device	Participants were instructed in the use and calibration of blood glucose meters	
Adjusting insulin doses	Patients transferred from a once daily basal insulin regimen started treatment with detemir or NPH at an identical number of units, while those transferred from a twice-daily regimen initiated treatment at 70% of the previous total daily basal insulin dose. If it was necessary to add more than once daily insulin dose, then the additional basal morning dose was initiated at 4 U and titrated according to the same algorithm as used for the evening dose. Algorithm: FPG or pre-evening dinner meal: Insulin adjustment > 15 mmol/L +6 U 10.1–15.0 mmol/L +4 U 6.1–10.0 mmol/L +2 U ≤ 6.0 mmol/L no adjustment	

(Continued)

	If one SMPG measurement: 3.1–4.0 mmol/L −2 U < 3.1 mmol/L −4 U If the FPG target was achieved while pre-dinner PG values remained above target, the basal evening dose could be increased as long as nocturnal hypoglycaemia did not occur. A second basal insulin dose could be added in the morning if the pre-dinner PG target was not achieved with use of the algorithm and after optimisation of bolus insulin.	
Interval for insulin adjustments	After the first 12 weeks, weekly contact between the investigators and the participants. A central surveillance committee reviewed the PG concentrations and the prescribed basal insulin doses throughout the study	
Other concomitant intervention	None	
BEGIN Basal-Bolus Type 1	**Intervention**	**Description**
Intervention	I: degludec	Once daily with main evening meal, 100 U/mL, sc, 3 mL FlexPen®, insulin and insulin pen manufactured by Novo Nordisk, Bagsværd, Denmark, sc, abdomen or deltoid or thigh
	C: glargine	Lantus ®, Once daily at any time, 100 U/mL, sc, 3 mL SoloStar®, Sanofi, Paris, France, sc, abdomen or deltoid or thigh
Titration period	None	
Strength of insulin	If previous basal insulin was used once daily, initial doses were replaced with insulin degludec or insulin glargine in a 1:1 ratio. If more than one daily dose had been taken, the total daily basal dose was calculated and replaced with insulin degludec in a 1:1 ratio, with the recommendation that the dose be reduced by 20% to 30% for participants in the insulin glargine group, and administered once daily	
Rapid-acting insulin	Insulin aspart before each meal (NovoRapid/NovoLog®, 100 U/mL, subcutaneously, 3 mL FlexPen®, Novo Nordisk, Bagsvaerd, Denmark). Additional doses were allowed with a fourth meal and snacks	
Glycaemic targets	Pre-breakfast plasma glucose values of 3.9–4.9 mmol/L	
Interval of blood glucose measurement	Measurements before breakfast, lunch, main evening meal and bedtime. Measurements were preferably performed on 3 consecutive days just before each scheduled visit or telephone contact using the glucose meter provided. a 9-point profile with an additional 4-point profile on the 3 days immediately before some predefined visits	
Calibration of blood glucose measurement device	Glucose meter and instructions for use and calibration for measurement	
Adjusting insulin doses	Changes to basal insulin were recommended before changes to the bolus insulin were considered	
Interval for insulin adjustments	Basal insulin: Pre-breakfast plasma glucose (mmol/L) (footnote: mean of 3 measures before visit) and adjustment of insulin dose < 3.1 Insulin dose: –4 (If dose > 45U, reduce by 10%) 3.1-3.8 Insulin dose: –2 (If dose > 45U, reduce by 5%) 3.9 -< 5.0 Insulin dose: 0 5-9.9 Insulin dose: +2 10-14.9 Insulin dose: +4	

(Continued)

	≥ 15.0 Insulin dose: +6 Titration basal bolus: Pre-prandial/bedtime PG and adjustment of insulin aspart 3.9 –< 5.0 Insulin dose: 0 5.0–7.9 Insulin dose: +2 8.0–9.9 Insulin dose: +3 ≥ 10.0 Insulin dose: +4
Other concomitant intervention	None

BEGIN Flex T1	Intervention	Description
Intervention	I: degludec	Once daily with evening meal, 100 U/mL, 3 mL FlexPen®; Novo Nordisk, Bagsvaerd, Denmark, sc (abdomen or deltoid or thigh)
	C: glargine	Once daily, Lantus®, 100 U/mL, 3 mL SoloStar®, Sanofi, Paris, France, sc (abdomen or deltoid or thigh)
Titration period	None	
Strength of insulin	If once daily regimen, then prescribe same number of units. If prior basal insulin was taken more than once daily, then dose of glargine was reduced by 20% to 30% and degludec reduction based on the investigators decision	
Rapid-acting insulin	Insulin aspart, three-times daily or more	
Glycaemic targets	Basal: pre-breakfast SMPG target of 4.0–5.0 mmol/L; mean premeal SMPG: a mean premeal SMPG target of less than 5.0 mmol/L	
Interval of blood glucose measurement	Daily	
Calibration of blood glucose measurement device	Glucose measurements were performed with drawn capillary blood automatically calibrated to plasma-equivalent glucose values	
Adjusting insulin doses	Titration of basal insulin Previous days' mean pre-breakfast SMPG (mmol/L) and insulin adjustment (U) < 4.0 Insulin dose: -2 4.0–5.0 Insulin dose: 0 > 5.0 Insulin dose: +2 Titration of bolus insulin Pre-prandial (mmol/L) and titration of insulin aspart < 5.0 Insulin dose: 0 5.0-8.0 Insulin dose: +2 8.0-10.0 Insulin dose: +3 ≥ 10 Insulin dose: +4	

(Continued)

Interval for insulin adjustments	Self-adjustment of basal insulin dose was to be performed three-times weekly (Monday, Wednesday, Friday) based on daily pre-breakfast SMPG	
Other concomitant intervention	None	
BEGIN Young	**Intervention**	**Description**
Intervention	I: degludec	Once daily (approximately same time of the day), 100U/mL, Penfill® 3-mL cartridge, Novo Nordisk, Bagsværd, Denmark, sc
	C: detemir	Once or twice daily (approximately same tome of the day), 100U/mL,Penfill®3-mLcartridge; Novo Nordisk, sc
Titration period	—	
Strength of insulin	Participants were to continue on the previous dose of basal insulin if randomised to detemir. Detemir doses were consistently higher than degludec doses	
Rapid-acting insulin	Insulin aspart at meals, 100 U/ml 3 ml Penfill® cartridge. It was aiming for a basal:bolus ratio of between 50:50 and 30:70. The choice of basal:bolus split for each participant was made at the discretion of the investigator	
Glycaemic targets	Pre-breakfast SMPG target of 5–8 mmol/L	
Interval of blood glucose measurement	Daily (morning, premeal and evening). Four-point profiles were performed weekly and 8-point profiles were performed at randomisation, 12, 26, 38 and 52)	
Calibration of blood glucose measurement device	Glucose meters calibrated to plasma values	
Adjusting insulin doses	Basal insulin titration was based on the lowest pre-breakfast SMPG value, on the 3 days prior to each weekly visit/phone contact Current basal dose < 5U 5–15U > 15U Pre-breakfast or pre-dinner PG (mmol/L) Adjustment (U) < 5 −1/2 −1 −2 5.0–8.0 0 0 0 8.1–10.0 +0.5 +1 +2 10.1–15.0 +1 +2 +4 > 15.0 +1.5 +3 +6 Current bolus dose ≤ 5U > 5U Lowest pre-meal or bedtime PG (mmol/L) Adjustment (U) < 5.0 −1 −2 5.0–8.0 0 0 8.1–10.0 +0.5 +1 10.1–15.0 +1 +2 > 15.0 +1.5 +3	

(Continued)

Interval for insulin adjustments	Weekly	
Other concomitant intervention	None	
Bolli 2009 [b]	**Intervention**	**Description**
Intervention	I: glargine	Glargine (Lantus, SanofieAventis) once daily at dinner time by means of pen device (OptiPen pro 1®)
	C: NPH	NPH (Humulin I, Eli Lilly and Co.) twice (or more) daily (bedtime and lunchtime) by pen (Humapen Lilly®)
Titration period	—	
Strength of insulin	—	
Rapid-acting insulin	Lispro	
Glycaemic targets	FBG target value 5.0-6.7 mmol/L; NPH pre-dinner BG 5.0-6.7 mmol/L	
Interval of blood glucose measurement	During the last 2 weeks before the scheduled visits, participants measured BG 2 hours after meals and at 3 a.m., in addition to FBG and pre-prandial BG to provide 7-point BG profile	
Calibration of blood glucose measurement device	—	
Adjusting insulin doses	Long-acting insulin Dinnertime glargine and bedtime NPH were titrated to achieve the FBG target value 5.0-6.7 mmol/L, but avoiding nocturnal hypoglycaemia. The lunchtime dose of NPH was adjusted to a target pre-dinner 5.0-6.7 mmol/L Bolus insulin The dose of lispro was adjusted to a target post-prandial BG of < 7.8 mmol/L. Additional doses (1 or 2 U) of lispro were also used to correct unexpected hyperglycaemia	
Interval for insulin adjustments	—	
Other concomitant intervention	None	
Chase 2008	**Intervention**	**Description**
Intervention	I: glargine	Once daily, sc, before breakfast, 10 mL vial (1 mL contains 100 U)
	C: NPH	Twice daily, sc, before breakfast and in the evening, 10 mL vial (1 mL contains 100 U)[c]
Titration period	—	
Strength of insulin	Anticipated to be 1 U glargine = 1 U NPH. The starting doses of basal insulin were determined by the investigator	

(Continued)

Rapid-acting insulin	Insulin lispro, sc, before each meal based on insulin:carbohydrate ratio and correction factor (proactive sliding scale), 10 mL vial (1 mL contains 100 IU) and 3 mL pen cartridges	
Glycaemic targets	FPG between 3.9 - 5.6 mmol/L	
Interval of blood glucose measurement	CGMS applied to most participants[d]. Everyday (FBG, pre-prandial and bedtime SMBG)	
Calibration of blood glucose measurement device	—	
Adjusting insulin doses	40%-50% of the total daily dose of insulin was basal insulin and 50%-60% of the total daily dose was bolus insulin. The total daily dose of insulin glargine and the evening dose of NPH/Lente were titrated weekly by the investigator to achieve FPG between 3.9 - 5.6 mmol/L. The pre-breakfast dose of NPH was titrated based on the investigator's clinical judgement. The weekly increase in the insulin dose could be divided across 2 or more incremental doses over the course of the week at the investigator's discretion	
Interval for insulin adjustments	Basal dose changes were made at scheduled study visits, titration contacts (weekly) or in the event of unexplained hypoglycaemia	
Other concomitant intervention	None	
Davies 2014	**Intervention**	**Description**
Intervention	I: degludec	Once daily (between evening meal and bedtime), FlexPen®, sc (abdomen or deltoid or thigh), 100 U/mL, 3 mL
	C: detemir	Once daily (between evening meal and bedtime, an additional morning dose could be added) FlexPen®. sc (abdomen or deltoid or thigh), 100 U/mL, 3 mL
Titration period	Not reported, but optimisation of basal insulin dose was to be prioritised the first 8 weeks of the study	
Strength of insulin	1 U of degludec was estimated to have the same BG lowering activity as 1 U detemir. If basal insulin was taken in a once daily regimen prior to the study, the same number of units once daily was prescribed. If basal insulin was taken more than once daily prior to the study, the total daily basal dose was calculated and transferred 1:1 as the once daily starting dose for both degludec and detemir	
Rapid-acting insulin	Insulin aspart was administered immediately prior to breakfast, lunch and dinner, and an additional dose was permitted to cover an additional meal/snack. The dose of insulin aspart was adjusted weekly based on the mean of three self measured pre-prandial PG values	
Glycaemic targets	On the basis of pre-breakfast SMBG (mean value from 3 consecutive days), insulins were titrated individually once a week to a glucose of 3.9–4.9 mmol/L Criteria according for splitting detemir doses in two also pre-dinner: plasma glucose > 6.0mmol/L	
Interval of blood glucose measurement	—	
Calibration of blood glucose measurement device	All capillary blood measurements were calibrated to plasma-equivalent glucose values (SMPG), using the plasma glucose meter and documented by the participant	
Adjusting insulin doses	*Titration algorithm for basal insulin* < 3.1 mmol/L Insulin dose: decrease by 4 U	

(Continued)

	3.1–3.8 mmol/L Insulin dose: decrease by 2 U 3.9–4.9 mmol/L Insulin dose: no adjustment 5.0–9.9 mmol/L Insulin dose: increase by 2 U 10.0–14.9 mmol/L Insulin dose: increase by 4 U ≥ 15.0 mmol/L Insulin dose: increase by 6 U In the insulin detemir group, a second detemir dose could be added if there was inadequate glycaemic control after ≥ 8 weeks of treatment (defined as < 0.5%-point improvement in HbA1c (participants with baseline HbA1c ≥ 8.0% or any deterioration of HbA1c; participants with baseline HbA1c < 8.0% in conjunction with a mean pre-dinner PG > 6.0 mmol/L and no diagnosis of a treatable concurrent disease causing hyperglycaemia) *Titration algorithm for bolus insulin - pre-prandial plasma glucose* < 5.0 mmol/L Insulin dose: no adjustment 5.0–7.9 mmol/L Insulin dose: increase by 2 U 8.0–9.9 mmol/L Insulin dose: increase by 3 U ≥ 10.0 mmol/L Insulin dose: increase by 4 U
Interval for insulin adjustments	Once a week
Other concomitant intervention	None

Fulcher 2005	**Intervention**	**Description**
Intervention	I: glargine	Once daily at bedtime (10 p.m.), sc, delivered by OptiPen Pro® device, cartridge containing 3 mL (1mL contains 100 IU), Aventis Pharma
	C: NPH	Once daily at bedtime (10 p.m.), sc, delivered by HumaPen® device, cartridge containing 3 mL (1mL contains 100 IU), Eli Lilly
Titration period	6 weeks	
Strength of insulin	Based in titration regimen, then 1 U glargine = 1 unit NPH	
Rapid-acting insulin	Lispro (before meals)	
Glycaemic targets	Targets were as follows: FBG = 5.5 mmol/L, pre-prandial BG 3.9–6.7 mmol/L, 2-h post-prandial BG <8 mmol/L and 3 a.m. BG >3.6 mmol/L	
Interval of blood glucose measurement	Not explicit stated, but mentioned that targets were as follows: FBG = 5.5 mmol/L, pre-prandial BG 3.9–6.7 mmol/L, 2-h post-prandial BG < 8 mmol/L and 3 a.m. BG > 3.6 mmol/L, then 7 times a day	
Calibration of blood glucose measurement device	—	
Adjusting insulin doses	Basal insulin dose adjustments were made twice weekly during the titration phase and fortnightly in the treatment follow-up phase based on FBG measurements. Initiation dose: decided by the investigator > 7.7 mmol/L Insulin dose: increased by 4–6 IU 6.6–7.7 mmol/L Insulin dose: increased by 2–4 IU 5.5–6.6 mmol/L Insulin dose: increased by 2 IU	

(Continued)

	All glycaemic measures should be for at least one of the two consecutive days before the visit, no episodes of severe hypoglycaemia or an FBG or overnight BG of = 3.6 mmol/L	
Interval for insulin adjustments	Twice weekly (during titration phase), thereafter every second week	
Other concomitant intervention	None	
Heller 2009	**Intervention**	**Description**
Intervention	I: detemir	Detemir, 100 U/mL (2400 nmol/mL) FlexPen®, initially administered once daily (in the evening). If patients in the detemir arm were achieving the PG target before breakfast but not before dinner, a second daily dose (initially 4 U) administered in the morning was added to the usual evening dose
	C: glargine	Glargine, 100 U/mL (600 nmol/mL) in 3 mL cartridges in Europe and in 10 mL vials in the United States, initially administered once daily (in the evening). In the glargine arm, the dose was administered once daily regardless of the pre-dinner PG measurement
Titration period	—	
Strength of insulin	Based in titration regimen, then 1 U detemir = 1 U glargine. If pre-study basal insulin was administered more than once daily, the total daily basal insulin dose was reduced by 30%	
Rapid-acting insulin	NovoRapid® (insulin aspart), 100 U/mL FlexPen® 3 mL solution for injection in a pre-filled pen (Novo Nordisk, Denmark). The dose was individually titrated and administered as subcutaneous injections	
Glycaemic targets	PG target of ≤ 6.0 mmol/L before breakfast and dinner, with no episodes of significant hypoglycaemia. Post-prandial PG target ≤ 9.0 mmol/L	
Interval of blood glucose measurement	Patients measured their FPG before breakfast and dinner on the 3 days before each study visit using standard glucose meters and test strips calibrated to PG levels. All patients were asked to record a 10-point SMPG profile on a typical day during the weeks before the randomisation visit, the 24-week visit, and the 52-week visit	
Calibration of blood glucose measurement device	Yes	
Adjusting insulin doses	If the pre-trial basal insulin had been administered more frequently, the total daily basal insulin dose was reduced by 30% and given once daily, followed by dose titration Mean pre-breakfast PG values were used for titration of the evening dose; mean pre-dinner PG values were used for titration of the morning dose *Mean PG change in basal insulin dose (without significant hypoglycaemia)* Target: ≤ 6.0 mmol/L (≤ 108 mg/dL) Insulin dose: no adjustment 6.1–10.0 mmol/L (109–180 mg/dL) Insulin dose: + 2 U 10.1–15.0 mmol/L (181–270 mg/dL) Insulin dose: + 4 U > 15.0 mmol/L (> 270 mg/dL) Insulin dose: + 6 U	
Interval for insulin adjustments	The increase of the basal insulin was not to be more frequent than every 2 days	

(Continued)

Other concomitant intervention	None	

Home 2005	Intervention	Description
Intervention	I: glargine	Once daily at bedtime. The dose was determined on the first treatment day by the total basal insulin dose the day before
	C: NPH	NPH according to previous regimen (people who were treated previously with NPH insulin and continued to receive NPH insulin in the study remained on a regimen similar to their previous basal insulin regimen: those on once-daily injections continued on once-daily (bedtime) and those on more than once daily injections were put on a twice-daily injection regimen (morning and at bedtime). Starting evening doses were the same as those on the immediate pre-treatment day
Titration period	—	
Strength of insulin	Not reported, but based on initiation regimen then 1 U glargine = 1 U NPH	
Rapid-acting insulin	Unmodified human insulin was injected before meals according to the participant's habit	
Glycaemic targets	*Titration of basal insulin*: the protocol suggested dose titration by 10% or greater increments, according to self-monitored FBG levels, with a target of 4.4–6.7 mmol/L averaged over at least 2–4 days and an absence of nocturnal hypoglycaemia. All dose adjustments were at the discretion of the investigator/person with diabetes *Titration of bolus insulin:* 4.4–6.7 mmol/L, in the absence of hypoglycaemia	
Interval of blood glucose measurement	Self-measurement of FBG on the 7 consecutive days immediately preceding baseline and the 8-, 20- and 28-week visits. On the day immediately preceding each of these visits, the participants were asked to perform a 24-hour blood glucose profile at 03:00 hours, just prior to and 2 h after breakfast, lunch and dinner, and at bedtime	
Calibration of blood glucose measurement device	—	
Adjusting insulin doses	Given the large number of centres and, therefore, the small number of people per centre, it was recognised that it was premature to enforce any algorithm for insulin dose adjustment	
Interval for insulin adjustments	Insulin dose adjustment was made throughout the study based on advice from the investigators during the scheduled visits (week 1, 4, 8, 12, 20 and 28) and informal contacts, and SMBG results between visits. Basal insulin regulated with at least two days in between	
Other concomitant intervention	None	

Kobayashi 2017	Intervention	Description
Intervention	I: detemir	Detemir, sc once (bedtime) or twice (morning and bedtime) daily, 2400 nmol/mL (100 U/mL), 3 mL Penfill®.
	C: NPH	NPH, sc once (bedtime) or twice (morning and bedtime) daily, 600 nmol/mL (100 U/mL), 3 mL Penfill®
Titration period	4 weeks	

(Continued)

Strength of insulin	All participants in the detemir group started treatment on approximately 70% of basal insulin dose (insulin detemir units) as their pre-study intermediate/long-acting human insulin dose. All participants in NPH group started the treatment on the same basal insulin dose as their pre-study intermediate/long-acting human insulin dose	
Rapid-acting insulin	Insulin aspart as bolus insulin 3 times daily before each main meal	
Glycaemic targets	During the entire study, insulin dose was adjusted in accordance with treatment targets: FPG < 5.6 mmol/L and HbA1c < 6.2%	
Interval of blood glucose measurement	Assumed daily	
Calibration of blood glucose measurement device	—	
Adjusting insulin doses	—	
Interval for insulin adjustments	—	
Other concomitant intervention	—	
Liu 2016	**Intervention**	**Desciption**
Intervention	I: glargine	Lantus®, 100 U/mL, sc, once daily at bedtime (22:00 - 22:00), Solostar® device
	C: NPH	Novolin N®, 100 U/mL, sc, once (at bedtime 20:00 to 22:00) or twice daily in the morning (before breakfast) and at bedtime (20:00 to 22:00). Decided by the investigator if it should be given once or twice daily
Titration period	—	
Strength of insulin	The initial glargine dose for participants whose prestudy regimen was based on NPH insulin was recommended to take entire daily dose of basal insulin as on the pre-treatment day (reduced by 20% if NPH insulin given more than once daily), then adjusted at the discretion of the Investigator to achieve glycaemic targets without an increase of hypoglycaemia	
Rapid-acting insulin	Insulin aspart, 100 U/mL, sc, before each meal. The doses of insulin aspart were adjusted to optimise glycaemic control after basal insulin doses had been optimised and could be reduced as basal insulin doses are increased	
Glycaemic targets	Metabolic control without hypoglycaemia, defined by: FBG 5.0–8.0 mmol/L, bedtime BG 6.7–10.0 mmol/L, nocturnal BG 4.4–9.0 mmol/L and HbA1c < 7.5%	
Interval of blood glucose measurement	Not reported, but probably daily	
Calibration of blood glucose measurement device	—	
Adjusting insulin doses	On the investigators discretion	

(Continued)

Interval for insulin adjustments	Week 1, 2, 4, 6, 8, 10, 12, 16, 20 and 24	
Other concomitant intervention	Diet and lifestyle counselling every 3rd months	
NCT00595374	**Intervention**	**Description**
Intervention	I: detemir	sc, once or twice daily
	C: NPH	sc, once or twice daily
Titration period	6 weeks	
Strength of insulin	The starting dose of basal insulin was equal to previous basal insulin dose	
Rapid-acting insulin	Insulin aspart	
Glycaemic targets	—	
Interval of blood glucose measurement	—	
Calibration of blood glucose measurement device	—	
Adjusting insulin doses	—	
Interval for insulin adjustments	—	
Other concomitant intervention	—	
NCT00605137	**Intervention**	**Description**
Intervention	I: detemir	2400 nmol/mL (100 U/mL), 3 mL cartridge in FlexPen®, sc once daily at bedtime or twice daily before breakfast and at bedtime, according to the same treatment regimen as pre-study basal insulin
	C: NPH	600 nmol/mL (100 IU/mL), 3 mL cartridge, FlexPen®, sconce daily at bedtime or twice daily before breakfast and at bedtime, according to the same treatment regimen as pre-study basal insulin
Titration period	6 weeks	
Strength of insulin	Start of detemir was 70% basal insulin dose (insulin detemir unit) as their pre-study intermediate/long-acting human insulin dose. The start dose of NPH was the same as the pre-study dose	
Rapid-acting insulin	Not reported, probably the same type of rapid-acting insulin as pre-study (insulin aspart and/or soluble human insulin)	

(Continued)

Glycaemic targets[b]	7-12 years; pre-breakfast 4.4 to 8.3 mmol/L; post-prandial (2 hours after meal) < 11.1. mmol/L: HbA1c: 6.5% to 7.4%; 13 years or older; pre-breakfast 4.4 to 7.8 mmol/L; post-prandial (2 hours after meal) < 10.0 mmol/L: HbA1c: 6.5% to 7.4%
Interval of blood glucose measurement	—
Calibration of blood glucose measurement device	—
Adjusting insulin doses[b]	Algorithm for adjustment of the bedtime dose (guidance only) FBG Change in basal insulin dose > 4.4 mmol/L Should be reduced 4.4 to 8.3 mmol/L (7-12 years) Investigators' judgement 4.4 to 7.8 mmol/L (13 years and older) Investigators' judgement > 8.3 to 10 mmol/L (7-12 years) +10% > 7.8 to 10 mmolL (13 years and older) +10% > 10 mmol/L +20% Algorithm for adjustment of the morning dose in participants in twice daily regimen (guidance only) FBG Change in basal insulin dose > 4.4 mmol/L Should be reduced 4.4 to 8.3 mmol/L (7-12 years) Investigators' judgement 4.4 to 7.8 mmol/L (13 years and older) Investigators' judgement > 8.3 to 10 mmol/L (7-12 years) +10% > 7.8 to 10 mmolL (13 years and older) +10% > 10 mmol/L +20%
Interval for insulin adjustments	—
Other concomitant intervention	Throughout the study period, instructions for diet and exercise (if any) therapy to participants was continued

Pieber 2007	**Intervention**	**Description**
Intervention	I: detemir	Detemir (Levemir®), 100 U/mL, morning and bedtime, NovoPen 3®
	C: glargine	Glargine (Lantus®), 100 U/mL, bedtime, OptiPen®
Titration period	6 weeks with contact at least twice a week (during the first 6 weeks, the detemir doses were titrated aiming for a pre-breakfast and pre-evening meal PG of ≤ 7.3 mmol/L, whereas the glargine doses were titrated only to a pre-breakfast PG). The insulin aspart dose was kept constant during the titration period. Based on two 5-point PG profiles and the data recorded on insulin therapy, all participants were instructed about their starting dose of study medication	

(Continued)

Strength of insulin	Detemir with a 30% reduction in both the morning and evening doses from previous regimen. Glargine was initiated at a dose of 20–30% less than the participants previous total basal insulin dose
Rapid-acting insulin	Insulin aspart before meals
Glycaemic targets	Doses were optimised according to the following algorithm: PG ≤ 7.3 mmol/L resulted in no change in dose; PG > 7.3–11.2 mmol/L resulted in a 10% increase in dose; PG > 11.2–16.8 mmol/L resulted in a 20% increase in dose; PG > 16.8 mmol/L resulted in a 25% increase in dose Post-prandial PG target (90 min after a meal) of ≤ 10.1 mmol/L
Interval of blood glucose measurement	Detemir: recommended to measure FPG before breakfast (prior to insulin injection) and before dinner on a normal weekday before the next contact Glargine: recommended to measure FPG before breakfast on a normal weekday before the next contact
Calibration of blood glucose measurement device	Test strips for glucose meters were plasma-calibrated
Adjusting insulin doses	See 'Glycaemic targets'
Interval for insulin adjustments	After titration period, intervals for insulin adjustments were decided by the investigator
Other concomitant intervention	None

Porcellati 2004	**Intervention**	**Description**
Intervention	I: glargine	Glargine was given once daily at dinner time (20:00 h), injected in anterior part of one thigh, either pens or syringes. sc
	C: NPH	NPH was administered 4 times daily (NPH insulin at each meal, and NPH at bedtime), injected in anterior part of one thigh, either pens or syringes[e], sc
Titration period	—	
Strength of insulin	1 U glargine = 1 U NPH	
Rapid-acting insulin	Lispro	
Glycaemic targets	FBG and BG before meals and at bedtime 6.4–7.2 mmol/L, 2 hours after meal 8.0–9.2 mmol/L	
Interval of blood glucose measurement	Every day: capillary BG before meals and bedtime Every other day: BG 2 hours after meals Twice a week: BG at 03.00 o'clock	
Calibration of blood glucose measurement device	—	

(Continued)

Adjusting insulin doses	For the first 2 days of treatment, the daily glargine dose was assumed to be identical to the total daily NPH units of the run-in period. Afterwards, the dose of glargine was varied by 1–2 units every 2–3 days, if necessary, to meet the target FBG. Similar adjustments were made with the NPH treatment *Basal insulin:* participants were advised to decrease or increase the dose of basal insulin if FBG was repeatedly below 6.0 mmol/L or above 7.8 mmol/L, and to decrease or increase the dose of rapid-acting insulin at meals if the 2 hour post-prandial BG was repeatedly below 7.0 mmol/L or above 9.5 mmol/L NPH doses at each meal were adjusted based on BG values observed the previous days prior to meals *Adjusting bolus insulin*: adjustments of lispro dose was made according to carbohydrate content of meal Mealtime doses of lispro were 0.04–0.08 U/kg at breakfast, and 0.10–0.17 U/kg at lunch and dinner. The lispro doses were adjusted daily on the basis of pre-prandial BG, as well as 2 hours after meal BG of previous days, as well as composition and size of meal and physical activity	
Interval for insulin adjustments	Not reported, but probably continuously based on information from publication (all participants were in daily telephone contact with the investigators, and were seen weekly in the outpatient unit).	
Other concomitant intervention	None	
PRESCHOOL	**Intervention**	**Description**
Intervention	I: glargine	Once daily, 100 U/mL, Solostar® each containing 300 U and as 10 mL vials each containing 1000 U, sc
	C: NPH	Once or twice daily, 100 U/mL Huminsulin Basal®, Huminsulin Basal Pen® each containing 300 U and as 10 mL vials each containing 1000 U, sc
Titration period	Best efforts were made to complete the up-titration of both basal insulins by week 12	
Strength of insulin	Estimated to be 1 U glargine = 1 U NPH	
Rapid-acting insulin	Insulin lispro used as the principal bolus insulin; regular human insulin permitted. Administration: multiple injection before meals and/or at bedtime at the discretion of the investigator	
Glycaemic targets	FBG between 5.0 to 8.0 mmol/L; bedtime BG between 6.7 to 10.0 mmol/L; nocturnal BG between 4.4 to 9.0 mmol/L; HbA1c < 7.5%	
Interval of blood glucose measurement	Assuming daily, participants had CGM during the study	
Calibration of blood glucose measurement device	—	
Adjusting insulin doses	Titration schedule not provided	
Interval for insulin adjustments	Doses of insulin glargine and NPH insulin were increased no more often than once a week, but doses could be reduced due to hypoglycaemia at any time	
Other concomitant intervention	None	
Ratner 2000	**Intervention**	**Description**

(Continued)

Intervention	I: glargine	Once daily at bedtime, vial containing 5 mL solution (1 mL contains 100 U), sc
	C: NPH	Once daily at bedtime or twice (at bedtime and before breakfast) depending on pre-trial insulin regimens, vial containing 10 mL suspension (1 mL contains 100 U), sc
Titration period	4 weeks	
Strength of insulin	Switching from insulin glargine to once daily NPH was done 1:1. Slight dose decrease was done when switching from twice-daily NPH to glargine. From clinical study report: investigators were advised at the study initiation meeting to reduce glargine dose with 10% — however, this was not specified in protocol	
Rapid-acting insulin	Recombinant human insulin about 30 min before meals, vial containing 10 mL solution (1 mL contains 100 U)	
Glycaemic targets	Based on capillary FBG; goal was 4.4 to 6.7 mmol/L and a bedtime BG value of 6.7 to 8.0 mmol/L	
Interval of blood glucose measurement	Daily. Glucose measurements were evaluated on 7 consecutive days preceding baseline and visit at week 8, 20 and 28	
Calibration of blood glucose measurement device	—	
Adjusting of insulin doses	Dose increases were made if morning capillary FBG levels were constantly > 6.7 mmol/L with no symptomatic hypoglycaemia. Dose decreases were done if fasting capillary BG were < 4.4 mmol/L or if symptomatic nocturnal hypoglycaemia was present. Glargine: the dose increase was to be at least 10% of the total dose of glargine while not exceeding 4 units. Dose increases were not to be made any more frequently than every 2 to 4 days. Dose decreases were to be made if any pre-breakfast BG was less than 4.4 mmol/L or there had been any symptomatic hypoglycaemia during sleep or BG values less than 5.0 mmol/L during sleep in the last 2 to 4 days. The dose was decreased for the next evening dose following the occurrence of the hypoglycaemia or low pre-breakfast BG. The dose of glargine was generally not lowered because of daytime hypoglycaemia unless repeated episodes of daytime hypoglycaemia had occurred after total elimination of the previous dose of regular insulin. NPH: evening dose adjustments as for glargine The pre-breakfast dose of NPH human insulin, if part of the pre-treatment basal insulin regimen, was administered at a standard time in conjunction with the pre-breakfast dose of regular insulin. If a participants had BG values less than 4.4 mmol/L or symptomatic hypoglycaemia occurred between lunch and dinner, either the morning NPH was lowered, the prelunch regular insulin dose was lowered or the afternoon snack was increased. If the majority of pre-supper BG values were greater than 6.7 mmol/L over a 2- to 4-day period, either the morning NPH was increased, the prelunch regular insulin was increased, or the afternoon snack was decreased	
Interval for insulin adjustments	Baseline, week 8, 20 and 28	
Other concomitant intervention	None	
Robertson 2007	**Intervention**	**Description**
Intervention	I: detemir	Detemir (Levemir®; Novo Nordisk A/S, Bagsvaerd, Denmark; 100 U/mL), once (at bedtime) or twice (morning and bedtime) daily, sc, thigh or abdomen, Penfill

(Continued)

	C: NPH	NPH (NPH, human isophane insulin®; Novo Nordisk A/S; 100 IU/mlL, once (at bedtime) or twice (morning and bedtime) daily, sc, thigh or abdomen, Penfill
Titration period	6 weeks	
Strength of insulin	Equivalence. The initial basal insulin dose was 70% of the prestudy basal insulin dose	
Rapid-acting insulin	Insulin aspart (NovoRapid®/NovoLog®; Novo Nordisk A/S; 100 U/mL) before meals, thigh or abdomen	
Glycaemic targets	FPG was 4.5–7.8 mmol/L and evening basal insulin doses were adjusted by the investigator FPG: < 4.5 mmol/L: adjustment according to local practice FPG 4.5-7.8 mmol/L: no adjustment FPG > 7.8–11.2 mmol/L: bedtime dose increased by 10% FPG > 11.2–16.8 mmol/L: bedtime dose increased by 20% FPG > 16.8 mmol/L: bedtime dose increased by 25% A similar guidance algorithm was used for pre-evening meal plasma glucose for children on a twice-daily regimen to adjust the morning dose of basal insulin During the 20-week maintenance period, the insulin aspart dose was optimised by aiming for a post-prandial (90 min after each meal) plasma glucose guidance level of 6.7–10.1 mmol/L. Further adjustment of basal insulin doses in this period was also allowed	
Interval of blood glucose measurement	The number and regularity of self-measured plasma glucose testing was individualised depending on acceptance by the child and the plasma glucose level, but was at least twice weekly during the 6-week titration period	
Calibration of blood glucose measurement device	Regular calibration	
Adjusting of insulin doses	See glycaemic targets. A change between once-daily and twice-daily regimens during the study was allowed	
Interval for insulin adjustments	In titration period, basal insulins were adjusted twice weekly	
Other concomitant intervention	None	
Russell-Jones 2004	**Intervention**	**Description**
Intervention	I: detemir	Detemir (100 U/mL) at bedtime, 2400 nmol/mL, supplied in 3.0 mL cartridges
	C: NPH	NPH (100 U/mL) at bedtime, supplied in 3.0 mL cartridges
Titration period	During the first two weeks, mealtime bolus insulin doses should (preferably) be kept unchanged and only basal insulin dose was titrated according to treatment goals. The following weeks were used to optimise the dose ratio between mealtime bolus insulin and basal insulin	
Strength of insulin	The starting dose for participants switching to insulin detemir was 50% of the usual pre-trial basal insulin dose. Patients assigned to NPH started on their pre-trial basal insulin dose. Participants randomised to NPH insulin were to continue on the same dose as their pre-trial NPH insulin dose	

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Rapid-acting insulin	Regular human insulin (100 U/mL), supplied in 3.0 mL cartridges	
Glycaemic targets	FBG, pre-breakfast/night 4.0–7.0 mmol/L; 90 minutes post-prandial <10.0 mmol/L	
Interval of blood glucose measurement	Daily; SMBG was performed regularly throughout the study	
Calibration of blood glucose measurement device	Patients were instructed in the calibration and use of blood glucose meters (OneTouch Profile, LifeScan, Inc., Milpitas, California), and were asked to perform SMBG regularly throughout the study to allow continuous adjustment of insulin doses	
Adjusting of insulin doses	—	
Interval for insulin adjustments	—	
Other concomitant intervention	None	
Schober 2002	**Intervention**	**Description**
Intervention	I: glargine	Once daily at bedtime (19:00 – 22:00), cartridge containing 3 mL solution (1 mL contains 100 U)
	C: NPH	Once (at bedtime) or twice daily (before breakfast and bedtime) depending in pre-treatment insulin regimen, cartridge containing 3 mL solution (1 mL contains 100 U)
Titration period	—	
Strength of insulin	1:1	
Rapid-acting insulin	Regular human insulin before meals according to individual habits, premeal goal was 4.4 - 8.8 mmol/L	
Glycaemic targets	Titration of bedtime insulin was FBG 4.4-8.8 mmol/L. Morning dose for NPH adjusted as required (not further specified)	
Interval of blood glucose measurement	Daily	
Calibration of blood glucose measurement device	—	
Adjusting of insulin doses	—	
Interval for insulin adjustments	Increase of basal insulin was not to be more frequent than every 4-5 days; dose decrease was decided by the investigator	
Other concomitant intervention	None	
Standl 2004	**Intervention**	**Description**
Intervention	I: detemir	100 U/mL (100 U = 1200 nmol), Penfill, twice daily

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	C: NPH	100 U/mL, twice daily, only the basal insulins were titrated during the initial 2 weeks
Titration period	First month of study	
Strength of insulin	1 U of detemir was estimated to have the same BG lowering activity as 1 U NPH. At study start, the initial detemir dose was half the unit dose of the patients' previous basal insulin, with the expectation of upward titration	
Rapid-acting insulin	Human soluble insulin (Actrapid) before meals	
Glycaemic targets	FBG < 4–7 mmol/L; 90 minutes post-prandial < 10 mmol/L; at 02:00 and 04:00 a.m. < 4–7 mmol/L	
Interval of blood glucose measurement	Not reported, but based on "aiming for the following targets: fasting, 4–7 mmol/L; 90-min post-prandial < 10 mmol/L; at 0200 and 0400 a.m., 4–7 mmol/L" then 5 times a day	
Calibration of blood glucose measurement device	—	
Adjusting of insulin doses	Doses were adjusted continuously at investigators' discretion based on patients' SMBG measurements	
Interval for insulin adjustments	In titration period every second day, thereafter at week 2, 4, 9, 13, 19 and 26	
Other concomitant intervention	None	
SWITCH 1	**Intervention**	**Description**
Intervention	I: degludec	Degludec® 100 U/mL (Novo Nordisk) (about 50% of the participants were randomised to morning dose (from waking up to breakfast) and 50% to evening dose (from main evening meal to bedtime)), 10 mL vial, sc
	C: glargine	Lantus® 100 U/mL (Sanofi) (about 50% of the participants were randomised to morning dose (from waking up to breakfast) and 50% to evening dose (from main evening meal to bedtime)), 10 mL vial, sc
Titration period	Not clearly stated, but participants had a 16 week wash-out period at initiation of study and after cross-over in order to stabilise HbA1c	
Strength of insulin	The starting dose of basal insulin and total bolus insulin (algorithm users only) was reduced by 20% at randomisation and at cross-over (i.e. after 32 weeks)	
Rapid-acting insulin	Insulin aspart 100 U/mL was administered using a prefilled pen (FlexPen®; Novo Nordisk), 2-4 times/daily, sc	
Glycaemic targets	For basal insulin adjustment: FBG between 4.0–5.0 mmol/L Pre-prandial BG between 3.9 and 6.0 mmol/L[b]	
Interval of blood glucose measurement	Participants were supplied with a blood glucose meter and instructed to measure their BG before breakfast, lunch, main evening meal, and bedtime on all days throughout the study. Their BG levels were also measured whenever a hypoglycaemic episode was suspected	

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Calibration of blood glucose measurement device	—
Adjusting insulin doses	Titration of basal insulin was performed once weekly according to the study algorithm, based on the lowest of 3 previous pre-breakfast SMBGs. Basal insulin titration regimen: lowest pre-breakfast BG measurement (mmol/L) and adjustment (U) < 3.1 Insulin dose: −4 3.1–3.9 Insulin dose: −2 4.0–5.0 Insulin dose: 0 5.1–10.0 Insulin dose: +2 10.1–15.0 Insulin dose: +4 > 15.0 Insulin dose: +6 Titration of bolus insulin was either performed twice weekly based on the previous 3 or 4 days' readings according to the provided algorithm, or several times daily based on the insulin:carbohydrate ratio and insulin sensitivity factor Insulin aspart was titrated individually based either on carbohydrate counting or sliding scale
Interval for insulin adjustments	4-point profiles were evaluated with weekly telephone contacts
Other concomitant intervention	None

Thalange 2013	**Desription**	**Intervention**
Intervention	I: detemir	Levemir®; Novo Nordisk A/S, Bagsvaerd, Denmark; 100 U/mL, sc, once or twice daily, according to pre-trial insulin regimen and dose
	C: NPH	Human isophane insulin®; Novo Nordisk A/S; 100 IU/mL, sc, once or twice daily, according to pre-trial insulin regimen and dose
Titration period	—	
Strength of insulin	Anticipated to be 1 U detemir = 1 U NPH	
Rapid-acting insulin	Insulin aspart (NovoRapid®/NovoLog®; Novo Nordisk A/S; 100 U/ml) 2–4 times daily with main meals, was to be taken 0–15 min prior to or immediately after the meal	
Glycaemic targets	Pre-prandial PG 4.0–7.0 mmol/L; post-prandial PG 5.0–11.0 mmol/L	
Interval of blood glucose measurement	Participants were asked to measure their PG before breakfast and dinner on the last 3 days prior to each contact; nine-point SMPG profiles, including nocturnal plasma glucose at 03.00 o'clock, were assessed by the children on a normal weekday 4–7 days prior to randomisation, and after 26 and 52 weeks of treatment	
Calibration of blood glucose measurement device	Use of test strips calibrated to plasma glucose values ensured that capillary blood concentrations were displayed as plasma glucose values	
Adjusting insulin doses (foot note - only adjustment for dose intervals 5-15 written in table)	Pre-breakfast or pre-dinner plasma glucose Insulin adjustment (varies with insulin dose in intervals < 5 U, 5-15 U, > 15 U) < 4.0 mmol/L Reduce according to local practice	

(Continued)

	4.0-7.0 mmol/L 0 7.1-10.0 mmol/L +1 10.1-15.0 mmol/L +2 > 15 mmol/L +3 Rapid-acting insulin: adjusted according to local practice	
Interval for insulin adjustments	Long-acting insulin: each contact Rapid-acting insulin: adjusted according to local practice	
Other concomitant intervention	None	
Urakami 2017	**Description**	**Intervention**
Intervention	I: degludec	Once daily at bedtime
	C: glargine	Once daily at bedtime
Titration period	One week stabilisation period was reported	
Strength of insulin	—	
Rapid-acting insulin	Insulin aspart or insulin lispro before meals	
Glycaemic targets	—	
Interval of blood glucose measurement	Daily before each meal, at bedtime and if symptoms on hypoglycaemia	
Calibration of blood glucose measurement device	—	
Adjusting insulin doses	—	
Interval for insulin adjustments	—	
Other concomitant intervention	—	
Vague 2003	**Description**	**Intervention**
Intervention	I: detemir	Before breakfast and bedtime, 1200 nmol/mL (1 U = 24 nmol)
	C: NPH	Before breakfast and bedtime, 600 nmol/mL, 100 U/mL
Titration period	1 months	
Strength of insulin	Anticipated to be 1:1[f]	
Rapid-acting insulin	Insulin aspart at main meals	

(Continued)

Glycaemic targets	Fasting/pre-prandial, 4–7 mmol/L; post-prandial < 10 mmol/L; from 02:00 to 04:00, 4–7 mmol/L
Interval of blood glucose measurement	Daily
Calibration of blood glucose measurement device	—
Adjusting insulin doses	In titration phase, basal insulin was titrated every second day. Thereafter, basal and bolus doses were adjusted according to investigator recommendations, based on BG measurements
Interval for insulin adjustments	Continuously during study
Other concomitant intervention	None

—: denotes not reported

[a]37% of participants treated with insulin detemir versus 45% treated with NPH insulin completed the study on a once-daily basal insulin regimen.
[b]Values converted from mg/dL to mmol/L using: https://www.diabetes.co.uk/blood-sugar-converter.html.
[c]Only 3 participants stayed on Lente insulin, remaining on NPH insulin, administered twice daily, before breakfast and in the evening.
[d]75 participants in each intervention group received CGMS at baseline. Data were available for 33participants at baseline and after 24 weeks in the insulin glargine group and 36 participants in the NPH insulin group.
[e]Syringes with Lispro insulin and NPH insulin were mixed and administered together.
[f]Approximately three- to fourfold higher molar dose of insulin detemir was required (resulting in an approximately twofold ratio by volume using the formulation in the study). This result may have further discouraged upward titration of dose, a factor that would not be an issue with the more concentrated and bioequivalent preparation of insulin detemir to be marketed (which has a four times higher molar concentration than that of NPH insulin in order to establish unit-to-unit conversion).

a.m.: ante meridiem; **BG:** blood glucose; **CGM:** continuous glucose measurement;**CGMS:** continuous glucose measurement system;**FBG**: fasting blood glucose; **FPG**: fasting plasma glucose; **HbA1c**: glycosylated haemoglobin A1c; **HSI**: human soluble insulin; **IU:** international unit;**NPH**: neutral protamine Hagedorn insulin; **PG**: plasma glucose; **p.m.**: post meridiem; **sc**: subcutaneous; **SMBG:** self-measured blood glucose; **SMPG**: self-measured plasma glucose; **T1DM**: type 1 diabetes mellitus;**TRIM-HYPO:** treatment-related impact measure - hypoglycaemic events; **U**: units.

Appendix 9. Baseline characteristics (I)

Study ID	Intervention(s) and comparator(s)	Duration of intervention (duration of follow-up)[a]	Description of participants	Study period	Country	Setting	Ethnic groups (%)	Duration of diabetes (mean/ range years (SD))
Bartley 2008	I: detemir	24 months (24 months)	T1DM, adults	June 2004 - September 2006	Argentina, Australia, Bulgaria, Croatia, India, Macedonia, The Former Yugoslav Republic, Malaysia, Romania, South Africa, Turkey	Outpatients	White: 73.7 Black: 0.9 Asian/Pacific Islander: 19.9 Other: 5.4	12.7 (9.4)
	C: NPH						White: 78.7 Black: 0.6 Asian/Pacific Islander: 19.5 Other: 1.2	13.5 (9.9)
BEGIN Basal-Bolus Type 1	I: degludec	52 weeks (104 weeks)	T1DM, adults	September 2009 - November 2010	France, Germany, Russia, South Africa, UK, USA	Outpatients	White: 93 Black: 2 Asian: 1 Other: 4	19.2 (12.2)
	C: glargine						White: 94 Black: 2 Asian: 2 Other: 2	18.2 (11.4)
BEGIN Flex T1	I: degludec	26 weeks (52 weeks)	T1DM, adults	March 2010- November 2010[b]	Belgium, Germany, Norway, Poland, UK, USA	Outpatients	White: 97.6 Black: 1.8 Asian: 0.0 Other: 0.6	20.0 (12.5)

(Continued)

	C: glargine						White: 98.8 Black: 0.6 Asian: 0.6 Other: 0.0	18.2 (11.9)
BEGIN Young	I: degludec	26 weeks (52 weeks)	T1DM, children (1–17 years)	January 2012 - February 2013[b]	Bulgaria, Finland, France, Germany, Italy, Japan, the Netherlands, Republic of Macedonia, Russian Federation, South Africa, UK and USA	Outpatients	White: 78.2 Black: 2.9 Asian: 13.2 Other: 5.7	3.9 (3.6)
	C: detemir						White: 86.0 Black: 2.3 Asian: 2.3 Other: 9.3	4.0 (3.4)
Bolli 2009	I: glargine	24 weeks (30 weeks)	T1DM, adults	—	Italy	Outpatients	—	12.9 (8.3)
	C: NPH						—	14.8 (9.6)
Chase 2008	I: glargine	24 weeks (25 weeks)	T1DM, children (9-17 years)	December 2002 - February 2005	USA, Canada	Outpatients	White: 84.5 Black: 0 Asian: 2.4 Hispanic: 8.3 Multiracial: 2.3 Other: 2.4	5.1 (3.4)
	C: NPH/ Lente						White: 81.0 Black: 8.3 Asian: 2.4	5.4 (3.7)

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							Hispanic: 4.8 Multiracial: 1.2 Other: 2.4	
Davies 2014	I: degludec	26 weeks (52 weeks)	T1DM, adults	February 2010- December 2010	Brazil, Finland, India, Italy, Japan, Macedonia and UK	Outpatient	White: 44.0 Black:0.7 Asian:54.6 Other: 0.7	13.7 (10.6)
	C: detemir						White: 45.8 Black:0.0 Asian: 53.6 Other: 0.7	14.4 (9.7)
Fulcher 2005	I: glargine	30 weeks (30 weeks)	T1DM, adults	November 2000 - November 2001	Australia	Outpatient	White: 98.4	17.9 (10.5)
	C: NPH							17.1 (9.7)
Heller 2009	I: detemir	52 weeks (52 weeks)	T1DM, adults	September 2004 - December 2005	USA, UK, Germany, France, the Netherlands, Finland and Sweden	Outpatient	Black: 2.0[b] Hispanic: 2.3 White: 95.7	17.2 (11.7)
	C: glargine						Black: 1.4 Hispanic: 2.8 White: 95.8	17.3 (10.7)
Home 2005 [c]	I: glargine	28 weeks (28 weeks)	T1DM, adults	August 1997 - August 1998[b]	12 European countries (Austria, Czech Republic, Denmark, Finland, France, Germany, Greece, Netherlands, Norway, Sweden, Switzerland, UK)	Outpatient	White: 99.7[b] Other: 0.3	16 (12)
	C: NPH						White: 99.0 Other: 1.0	15 (9)
Kobayashi 2007	I: detemir	48 weeks (48 weeks)	T1DM, adults	May 2003 - March 2005[b]	Japan	Outpatient	Asian (Japanese): 100	13.4 (8.18)

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	C: NPH						Asian (Japanese): 100	13.01 (8.5)
Liu 2016	I: glargine	24 weeks (25 weeks)	T1DM, children (≥ 6 to < 18 years)	February 2011 - August 2013	China	Outpatient	Asian (Chinese): 100	3.8 (2.9)
	C: NPH						Asian (Chinese): 100	3.6 (2.3)
NCT00595374	I: detemir	26 weeks (26 weeks)	T1DM, adults	December 2003 - October 2004	Netherlands	Outpatients	White: 98.7 Asian/Pacific islander: 1.3	—
	C: NPH						White: 97.4 Asian/Pacific islander: 2.6	—
NCT00605137	I: detemir	24 weeks (24 weeks)	T1DM, children (7 to 18 years)	May 2004 - April 2005	Japan	Outpatients	Asian (Japanese): 100	4.7 (3.2)
	C: NPH						Asian (Japanese): 100	6.5 (4.0)
Pieber 2007	I: detemir	26 weeks (26 weeks)	T1DM, adults	April 2002 - March 2003	Germany, Austria, South Africa	Outpatient	From co-publication: White: 95.3 Other: 4.7	17 (range 1-57)
	C: glargine							16 (range 1-48)
Porcellati 2004	I: glargine	1 year (1 year)	T1DM, adults	—	Italy	Outpatient	—	13 (2.4)[d]
	C: NPH							15 (2.3)
PRESCHOOL	I: glargine	24 weeks (26 weeks)	T1DM, children (1-6 years)	October 2009 - March 2011	Argentina, Austria, Brazik, Chile, Czech Republic, Germany, Hungary, India, Mexico, Peru, Poland, Romania, Russia, South Africa, Spain, USA	Outpatient	White: 86.9 Black: 3.3 Asian: 6.6 Other: 3.3	2.1 (1.2)
	C: NPH						White: 75.0 Black: 3.1 Asian: 17.2 Other: 4.7	2.1 (1.0)

(Continued)

Ratner 2000	I: glargine	28 weeks (28 weeks)	T1DM, adults	June 1997 - June 1998[b]	USA	Outpatient	White: 95.1[b] Black:4.2 Asian: — Hispanic: 3.0 Other: 0.8	17.9 (11.7)
	C: NPH						White: 95.6 Black: 3.0 Asian: — Hispanic: 3.3 Other: —	16.9 (10.0)
Robertson 2007	I: detemir	26 weeks (26 weeks)	T1DM, children (6-17 years)	August 2002 - August 2003	Europe (Belgium, Croatia, Denmark, Finland, Germany, Ireland, Macedonia, Netherlands, Norway, Slovenia, Spain, Sweden, Switzerland, UK) and Israel	Outpatient	White: 99.6 Acian/Pacific islander: 0.4	5.1 (3.1)
	C: NPH						White: 100	4.8 (2.8)
Russell-Jones 2004	I1; detemir	6 months (6 months)	T1DM, adults	February 2001 - November 2001	United Kingdom, France, Sweden, Norway, Australia, Netherlands, Denmark, Finland, Belgium, Ireland and Luxembourg	Outpatient	White: 98.7 Other: 1.3	17.1 (11.3)
	C: NPH							16.4 (9.5)
Schober 2002	I: glargine	28 weeks (28 weeks)	T1DM, Children (5-16 years)	June 1997 - March 1999	Austria, Belgium, Croatia, Czech Republic, Finland, Germany, Switzerland, Netherlands, UK and South Africa	Outpatient	White: 96.6 Black: 0.0 Asian/Oriental: 1.7 Multiracial: 1.7	5.8 (3.02)
	C: NPH						White: 97.1 Black: 0.0 Asian/Oriental: 2.9 Multiracial: 0.0	4.7 (3.08)

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Standl 2004e	I: detemir	6 months (12 months)	T1DM, adults	October 1999 - September 2000[b]	Germany, Switzerland, Austria[f], Australia, New Zealand	Outpatient	White 99[b]	14.9 (9.4)
	C: NPH							15.5 (10.8)
SWITCH 1	I: degludec	32 weeks (32 weeks)	T1DM, adults	January 2014 - January 2016	USA, Poland	Outpatient	White: 93.6 Black: 5.2 Asian: 0.4 Hispanic or Latino: 9.2 Other: 0.8	23.2 (13.5)
	C: glargine						White: 90.9 Black: 7.5 Asian: 0.4 Hispanic or Latino: 11.1 Other: 1.2	23.6 (13.4)
Thalange 2013	I: detemir	52 weeks (104 weeks)	T1DM, children (2-16 years)	February 2007 - September 2008	Bulgaria, Czech Republic, Denmark, Finland, France, Hungary, Macedonia, Poland, Russia, Turkey and UK	Outpatient	White: 98[b] Other: 1	3.7 (2.7)
	C: NPH							3.7 (2.5)
Urakami 2017	I: degludec	24 weeks (24 weeks)	T1DM, children	—	Japan	Outpatient	—	—
	C: glargine							
Vague 2003	I: detemir	6 months (12 months)	T1DM, adults	November 1999 - October 2000[b]	France, Belgium. Luxembourg, Netherlands, Norway	Outpatient	White: 99.5[b]	17.1 (9.9)
	C: NPH							17.4 (11.0)

—: denotes not reported

[a]Follow-up under randomised conditions until end of study (= duration of intervention + follow-up post-intervention or identical to duration of intervention).
[b]Data from clinical study report/synopsis.
[c]Baseline characteristics only available for the 585 participants who were treated with study medication (292 participants with insulin glargine and 293 participants with NPH).
[d]Not reported if SD or standard error was provided. Assumed to be standard error, so SD was calculated from anticipated standard error.

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[e]In publication, baseline characteristics were only available for the participants completing the 6 months treatment period and participating in the 6 months extension period (NPH; N = 135; Detemir; N = 154). Data on randomised participants available from clinical study report.
[f]In publication, just stated that Europe - countries in Europa provided by clinical study report.

C: comparator; **I**: intervention; **NPH**: neutral protamine Hagedorn; **SD**: standard deviation; **T1DM**: type 1 diabetes mellitus; **UK**: United Kingdom; **USA**: United States of America.

Appendix 10. Baseline characteristics (II)

Study ID	Intervention(s) and comparator(s)	Sex (% women)	Age (mean/range years (SD))	HbA1c (mean % (SD))	BMI (mean kg/m² (SD))	Comedications/cointerventions (% of participants)	Comorbidities (% of participants)
Bartley 2008	I: detemir	44.4	35 (12)	8.3 (1.2)	24.7 (3.7)	Enalapril 5.4[a] Acetylsalicyl acid 6.9 Paracetamol 2.4	Concomitant illness 57.1[a] Hypertension 16.0 Metabolism and nutrition disorder 14.2 Eye disorder 7.6 Cardiac disorder 7.9
	C: NPH	47.0	35 (11)	8.4 (1.3)	24.7 (3.7)	Enalapril 8.5 Acetylsalicyl acid 4.3 Paracetamol 6.1	Concomitant illness 55.5 Hypertension 14.6 Metabolism and nutrition disorder 14.0 Eye disorder 11.0 Cardiac disorder 7.3
BEGIN Basal-Bolus Type 1	I: degludec	41.1	42.8 (13.7)	7.7 (0.9)	26.3 (3.7)	Simvastatin 14.4[a] Lisonipril 13.8 Acetylsalicyl acid 28.0	Ophthalmic complications 18.6[a] Neurological complications 14.0 Renal complications 7.6 Cardiovascular complications 0.8 Hypothyroidism 13.6
	C: glargine	42.7	43.7 (13.3)	7.7 (1.0)	26.4 (4.2)	Simvastatin 12.1 Lisonipril 12.7 Acetylsalicyl acid 25.5	Ophthalmic complications 17.2 Neurological complications 12.1 Renal complications 6.4 Cardiovascular complications 1.3 Hypothyroidism 19.1
BEGIN Flex T1	I: degludec	43.0	44.5 (13.1)	7.7 (0.9)	—	Acetylsalicyl acid 21.8[a]	Ophthalmic complications 9.1[a]

(Continued)

						Simvastatin 21.2 Lisonopril 11.5	Neurological complications 7.3 Renal complications 4.8
	C: glargine	46.3	44.1 (12.6)	7.7 (0.9)	—	Acetylsalicyl acid 24.4 Simvastatin 20.7 Lisonopril 11.0	Ophthalmic complications 6.7 Neurological complications 6.7 Renal complications 3.7
BEGIN Young	I: degludec	44.8	10.0 (4.4)	8.2 (1.1)	18.7 (3.6)	Ibuprofen 9.3[a] Paracetamol 5.2 Salbutamol 3.4 Loratadine 3.4	Diabetes complications 0.6[a] Seasonal allergy 8.0 Asthma 2.9
	C: detemir	44.3	10.0 (4.4)	8.0 (1.1)	18.5 (3.6)	Ibuprofen 2.3 Paracetamol 4.0 Salbutamol 2.3 Loratadine 1.7	Diabetes complications 0.3 Seasonal allergy 6.3 Asthma 3.4
Bolli 2009	I: glargine	43.5	35.5 (10.6)	7.8 (0.7)	23.3 (2.0)	—	—
	C: NPH	45.6	37.0 (9.4)	7.8 (0.6)	23.6 (1.9)	—	—
Chase 2008	I: glargine	53.6	13.1 (2.4)	7.8 (0.8)	22.6 (3.8)	—	Neuropathy 0[a] Nephropathy 2.4 Retinopathy 0 Hypertension 1.2 Hyperlipidaemia 1.2
	C: NPH/Lente	52.4	13.4 (2.4)	8.0 (0.8)	22.9 (5.0)	—	Neuropathy 0 Nephropathy 3.3 Retinopathy 0 Hypertension: 3.3

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							Hyperlipidaemia 5.6
Davies 2014	I: degludec	50.3	41.1. (14.9)	8.0 (1.0)	24.0 (3.5)	Acetylsalicyl acid 7.3[a] Ramipril 4.0 Simvastatin 6.3	Diabetic complications 26.2[a] Hypertension 28.2
	C: detemir	43.8	41.7 (14.4)	8.0 (0.9)	23.7 (3.4)	Acetylsalicyl acid 7.8 Ramipril 3.9 Simvastatin 7.2	Diabetic complications 28.8 Hypertension 21.6
Fulcher 2005	I: glargine	61.3	41.6 (12.9)	9.2 (1.1)	27.0 (3.6)	—	—
	C: NPH	60.3	39.3 (13.9)	9.7 (1.3)	26.0 (3.9)	—	—
Heller 2009	I: detemir	44.1	42 (13)	8.1 (1.1)	26.5 (4.0)	Acetylsalicyl acid 11.7[a] Levothyroxine 11.4 Simvastatin 10.0	Retinopathy 26.8[a] Neuropathy 17.7 Nephropathy 10.0 Macroangiopathy 3.3
	C: glargine	43.8	41 (12)	8.1 (1.2)	26.3 (3.9)	Acetylsalicyl acid 11.1 Levothyroxine 9.7 Simvastatin 11.1	Retinopathy 27.1 Neuropathy 10.4 Nephropathy 6.9 Macroangiopathy 0.7
Home 2005	I: glargine	45.2	39 (12)	7.9 (1.2)	24.6 (3.1)		Retinopathy 31.2[a] Neuropathy 17.5 Nephropathy 6.2 Macroangiopathy 3.1
	C: NPH	43.3	39 (12)	8.0 (1.2)	25.1 (3.3)		Retinopathy 29.4 Neuropathy 16.7 Nephropathy 7.2

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							Macroangiopathy 3.4
Kobayashi 2007	I: detemir	58.7	42.4 (14.2)	7.4 (1.0)	22.4 (1.7)	—	—
	C: NPH	50	41.8 (13.5)	7.4 (1.2)	22.4 (2.7)	—	—
Liu 2016	I: glargine	58.6	12.2 (3.2)	8.9 (1.2)	18.7 (2.9)	Unspecified herbal and traditional medicine 32.7[a] Anti-infective for systemic use 25.2	Retinopathy 0 Nephropathy 0 Neuropathy 0
	C: NPH	64.8	12.2 (3.5)	9.1 (1.3)	18.2 (2.6)	Unspecified herbal and traditional medicine 47.3 Anti-infective for systemic use 23.6	Retinopathy 0 Nephropathy 1.9 Neuropathy 0
NCT00595374	I: detemir	49.3	39 (13.3)	8.5 (0.9)	—	—	Diabetic complications 25.3
	C: NPH	36.8	42.8 (12.7)	8.3 (1.0)	—	—	Diabetic complications 34.2
NCT00605137	I: detemir	63.6	13.2 (2.5)	7.2 (0.9)	20.5 (3.5)	—	—
	C: NPH	40.7	14.1 (2.5)	7.5 (1.3)	20.8 (3.7)	—	—
Pieber 2007	I: detemir	45.3	40 (range 18-79)	8.9 (range 7.6 - 11.9)	25.6 (range 18.2 - 35.1)	Acetylsalicylic acid 17[a] Paracetamol 13 Ibuprofen 7	From co-publication: Angina pectoris 2.4 Myocardial infarction 0.3 Heart failure 0.3 Stroke 0.4 Atrial fibrillation 0.5 Microalbuminuria 27.2
	C: glargine	52.2	41 (range 18-70)	8.8 (range 7.6-11.9)	15.5 (range 16.8 - 34.4)		
Porcellati 2004 [b]	I: glargine	44.3	36 (7.8)	7.1 (0.8)	22.9 (0.4)	—	Smoker: 17.4 Cardiovascular disease: 11.0
	C: NPH	45.0	34 (7.8)	7.1 (1.6)	23.2 (1.2)	—	

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PRESCHOOL	I: glargine	47.5	4.3 (0.9)	8.0 (1.0)	—	Dermatologicals 23[a] Cardiovascular system 23 Repiratory system 13.1	Diabetic retinopathy 0[a] Motor neuropathy 0 Autonomic neuropathy 1.6 Nephropathy 0 Albuminuria 3.3
	C: NPH	53.1	4.1 (1.0)	8.2 (1.4)	—	Dermatologicals 15.6 Cardiovascular system 12.5 Repiratory system 15.6	Diabetic retinopathy 0 Motor neuropathy 0 Autonomic neuropathy 1.6 Nephropathy 0 Albuminuria 1.6
Ratner 2000	I: glargine	46.6	38.2 (12.2)	7.7 (1.2)	25.6 (4.0)	—	Smoker 14.1 Cardiovascular disease 10.4
	C: NPH	52.2	38.9 (11.9)	7.7 (1.1)	25.9 (4.6)	—	
Robertson 2007	I: detemir	48.7	11.9 (2.8)	8.8 (1.2)	19.2[c]	Paracetamol 49.6[a] Ibuprofen 15.1 Acetylsalicyl acid 5.6	Retinopathy 0[a] Neuropathy 0 Nephropathy 0.4
	C: NPH	52.2	11.7 (2.7)	8.7 (1.1)	19.1	Paracetamol 46.1 Ibuprofen 11.3 Acetylsalicyl acid 7.0	Retinopathy 1.7 Neuropathy 0 Nephropathy 0.9
Russell-Jones 2004	I: detemir	34.4	40.9 (12.4)	8.4 (1.2)	25.1 (3.4)	Paracetamol 35.6[a] Ibuprofen 12.6 Acetylsalicylic acid 7.4	Essential hypertension 13 Retinal disorders 11 Disorder of lipid metabolism 10
	C: NPH	38.7	39.8 (12.3)	8.4 (1.2)	25.4 (3.4)		
Schober 2002	I: glargine	44.3	11.8 (2.5)	8.5 (1.4)	18.8 (2.8)	Concomitant medication other than glucose-lowering drugs 52.6[a]	One patient presented with macroalbuminuria and three presented with microalbuminuria at study entry

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	C: NPH	52.0	11.5 (2.4)	8.8 (1.4)	18.9 (2.9)	Concomitant medication other than glucose-lowering drugs 56.6	
Standl 2004 [d]	I: detemir	38.6	38.6 (13.4)	7.6 (1.2)	25.3 (3.2)	Paracetamol 20[a] Acetylsalicylic acid 17	Neuropathy 9 Both groups: Essential hypertension 21 Retinal disorders 5 Neuropathy 13 Disorders of the lipoid metabolism 10
	C: NPH	36.6	39.8 (12.2)	7.7 (1.2)	25.2 (3.3)		Neuropathy 16
SWITCH 1	I: degludec	49.4	45.4 (13.7)	7.7 (1.0)	27.9 (5.1)	—	—
	C: glargine	43.3	46.4 (14.6)	7.5 (1.0)	27.0 (4.5)	—	—
Thalange 2013	I: detemir	53.1	10.0 (4.1)	8.4 (1.1)	18 (2.7)[a]	Paracetamol 37.3[a] Ibuprofen 19.2	Diabetic nephropathy 1.7[a] Diabetic neuropathy 2.3 Diabetic retinopathy 1.7 Macroangiopathy 0
	C: NPH	42.9	9.8 (3.9)	8.4 (1.1)	18 (2.7)	Paracetamol 34.7 Ibuprofen 19.4	Diabetic nephropathy 1.8 Diabetic neuropathy 2.4 Diabetic retinopathy 0 Macroangiopathy 0
Urakami 2017	I: degludec	30.0	10 (1.5)	7.7 (0.9)	16.0 (4.5)	—	None had microvascular complications
	C: glargine	44.4	11 (1.5)	7.8 (0.9)			
Vague 2003	I: detemir	46.2	38.9 (13.3)	8.18 (1.14)	24.5 (3.2)	—	—
	C: NPH	49.3	41.8 (14.2)	8.11 (1.12)	24.6 (3.4)	—	—

(Continued)

—: denotes not reported

[a]Data from clinical study report/synopsis. Additional information available in clinical study report/synopsis.
[b]Not reported if SD or standard error was provided. Assumed to be standard error, so SD was calculated from anticipated standard error.
[c]Data from Food and Drug Administration medical review.
[d]In publication, baseline characteristics were only available for the participants completing the 6 months treatment period and participating in the 6 months extension period (NPH; N = 135; Detemir; N = 154). Data on randomised participants available from clinical study report.

BMI: body mass index; **C**: comparator; **HbA1c**: glycosylated haemoglobin A1c; **I**: intervention; **NPH**: neutral protamine Hagedorn; **SD**: standard deviation.

Appendix 11. Study endpoints and timing of outcome measurement

Study ID	Review's primary and secondary outcomes	Timing of outcome measurement in study
Bartley 2008	Hypoglycaemia and safety data	At each visit (baseline, 4 weeks, 8 weeks, 12 weeks, 24 weeks, 36 weeks, 52 weeks, 64 weeks, 76 weeks, 88 weeks, 104 weeks)[a]
	HbA1c	Baseline, 12 weeks, 24 weeks, 36 weeks, 52 weeks, 64 weeks, 76 weeks, 88 weeks, 104 weeks[a]
BEGIN Basal-Bolus Type 1	Hypoglycaemia and safety data	Baseline, every second week during study (main study) (for extension study every 4th week)[a]
	HbA1c	Baseline, 12 weeks, 16 weeks, 26 weeks
BEGIN Flex T1	Hypoglycaemia and safety	Baseline, every second week during study
	HbA1c	Baseline, 12 weeks, 16 weeks, 26 weeks
BEGIN Young	Hypoglycaemia and safety	Every visit (i.e. every third week during study)
	HbA1c	Baseline, 12 weeks, 16 weeks, 38 weeks, 52 weeks
Bolli 2009	Quality of life	Baseline, 12 weeks, 24 weeks
	HbA1c	Baseline, 8 weeks, 16 weeks, 24 weeks
	Safety	At each visit (number of visits not described)
Chase 2008	Quality of life	Baseline, 2 weeks, 6 weeks, 12 weeks, 18 weeks, 24 weeks[a]
	HbA1c and hypoglycaemia	During clinical visits at 6 weeks, 12 weeks, 18 weeks, 24 weeks
	Adverse events	Every 1 week of follow-up
Davies 2014	Quality of life	Baseline, 12 weeks, 26 weeks
	Adverse events and hypoglycaemia	Baseline, 1 week, 2 weeks and thereafter every second week
	HbA1c	Baseline, 12 weeks, 16 weeks, 26 weeks
Fulcher 2005 [a]	Quality of life	Baseline, 14 weeks, 30 weeks
	Adverse events	6 weeks, 12 weeks, 18 weeks, 14 weeks, 30 weeks
	HbA1c	6 weeks, 14 weeks, 22 weeks, 30 weeks
	Hypoglycaemia	6 weeks, 12 weeks, 18 weeks, 14 weeks, 30 weeks
	Economic data	14 weeks, 30 weeks
Heller 2009	Hypoglycaemic and adverse events	Baseline, 2 weeks, 4 weeks, 6 weeks, 8 weeks, 12 weeks, 18 weeks, 24 weeks, 50 weeks, 36 weeks, 44 weeks, 52 weeks

(Continued)

	HbA1c	Baseline, 12 weeks, 24 weeks, 36 weeks, 52 weeks
Home 2005	Quality of life	Baseline, 8 weeks, 20 weeks, 28 weeks
	Hypoglycaemia, adverse events, HbA1c	Baseline, 1 week, 4 weeks, 8 weeks, 12 weeks, 20 weeks, 28 weeks
Kobayashi 2007	Hypoglycaemia, adverse events, HbA1c	Baseline, 48 weeks
Liu 2016	HbA1c	Baseline, 12 weeks, 24 weeks
	Hypoglycaemia, safety	Baseline, 1 week, 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks, 16 weeks, 20 weeks, 24 weeks, 25 weeks[a]
NCT00595374	Mortality, adverse events	—
NCT00605137	Hypoglycaemia, adverse events	Baseline, 1 week, 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks, 14 weeks, 16 weeks, 18 weeks, 20 weeks, 22 weeks, 24 weeks
	HbA1c	Baseline, 4 weeks, 8 weeks, 12 weeks, 16 weeks, 20 weeks, 24 weeks
Pieber 2007	Hypoglycaemia and adverse events	Baseline, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 8 weeks, 14 weeks, 20 weeks, 26 weeks
	HbA1c	Baseline, 20 weeks, 26 weeks
Porcellati 2004	Hypoglycaemia	—
	HbA1c	Not reported, but based on figure 2 in main publication, then every second month (0, 2, 4, 6, 8, 10, 12 months)
PRESCHOOL	Adverse events, hypoglycaemia	Baseline, 1 week, 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks, 16 weeks, 20 weeks, 24 weeks, 26 weeks
	HbA1c	Baseline, 12 weeks, 24 weeks
Ratner 2000	Hypoglycaemia and adverse events	Baseline, 1 week, 4 weeks, 8 weeks, 12 weeks, 20 weeks, 28 weeks[a]
	Quality of life	Baseline, 8 weeks, 20 weeks, 28 weeks[a]
	Pharmacoeconomic assessment	Baseline, 1 week, 4 weeks, 8 weeks, 12 weeks, 20 weeks, 28 weeks[a]
	HbA1c	Baseline, 8 weeks, 20 weeks, 28 weeks
Robertson 2007 [a]	Hypoglycaemia and safety	Baseline, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 10 weeks, 18 weeks, 26 weeks
	HbA1c	Baseline, 18 weeks, 24 weeks
Russell-Jones 2004	Hypoglycaemia and adverse events	Baseline, 2 weeks, 4 weeks, 9 weeks, 13 weeks, 19 weeks, 26 weeks
	HbA1c	Baseline, 3 months, 6 months

(Continued)

Schober 2002	Hypoglycaemia and adverse events	Baseline, 4 weeks, 16 weeks, 28 weeks
	HbA1c	Baseline, 4 weeks, 16 weeks, 28 weeks
Standl 2004	Quality of life	Baseline, 13 weeks, 26 weeks
	Safety and hypoglycaemia	Baseline, 3 months, 6 months (extension: 9 months, 12 months)
	HbA1c	Baseline, 3 months, 6 months (extension: 9 months, 12 months)
SWITCH 1	Quality of life	Baseline, 32 weeks
	Hypoglycaemia/adverse events	Weekly during study period
	HbA1c	Baseline, 8 weeks, 12 weeks, 16 weeks, 20 weeks, 24 weeks, 28 weeks, 32 weeks
Thalange 2013	Adverse events, hypoglycaemia	Collected during the study
	HbA1c	Baseline, 12 weeks, 24 weeks, 38 weeks, 52 weeks
Urakami 2017	HbA1c and hypoglycaemia	Baseline, 4 weeks, 12 weeks, 24 weeks
Vague 2003 [a]	Hypoglycaemia, safety	Baseline, 2 weeks, 4 weeks, 9 weeks, 13 weeks, 19 weeks, 26 weeks, 27 weeks
	HbA1c	Baseline, 13 weeks, 26 weeks

—: denotes not reported
[a]Information retrieved from clinical study report.

HbA1c: glycosylated haemoglobin A1c.

Appendix 12. Matrix of study endpoints (publications and trial documents)

Study ID	
Bartley 2008	**Endpoints quoted in trial registers**[a]
	Source: NCT00184665
	Primary outcome measure(s): HbA1c
	Secondary outcome measure(s): adverse events, body weight, antibodies, body composition, blood glucose, hypoglycaemia
	Other outcome measure(s): —
	Trial results available in trials register: yes
	Endpoints quoted in publication(s)[a,b]

(Continued)

	Primary outcome measure(s): HbA1c **Secondary outcome measure(s)**: FPG, nocturnal hypoglycaemia, weight, safety, insulin antibodies **Other outcome measure(s)**: —
	Endpoints quoted in abstract of publication(s)[a,b]
	Primary outcome measure(s): HbA1c **Secondary outcome measure(s)**: FPG, nocturnal hypoglycaemia, weight, safety **Other outcome measure(s)**: —
BEGIN Basal-Bolus Type 1	**Endpoints quoted in trial registers[a]**
	Source: NCT00982228 (main study); NCT00982228 (extension) **Primary outcome measure(s)**: Main study: change in HbA1c after 52 weeks Extension: adverse events from week 0 to 104 + 7 days, confirmed hypoglycaemic episodes from week 0 to 104 + 7 days, cross-reacting antibodies to human insulin (extension study) **Secondary outcome measure(s)**: Main study: confirmed hypoglycaemic episodes, nocturnal confirmed hypoglycaemic episodes, mean of 9-point SMBG profile at week 52 Extension: nocturnal confirmed hypoglycaemic episodes, change in HbA1c after 104 weeks, mean of 9-point SMPG profile at week 104 **Other outcome measure(s)**: — **Trial results available in trials register**: no
	Endpoints quoted in publication(s)[a,b]
	Primary outcome measure(s): Main study: HbA1c Extension: hypoglycaemia, AEs **Secondary outcome measure(s)**: Main study: all predefined outcomes Extension: all predefined outcomes **Other outcome measure(s)**: Main study: adverse events, QoL Extension: insulin dose
	Endpoints quoted in abstract of publication(s)[a,b]
	Primary outcome measure(s): main study: HbA1c, extension study: hypoglycaemia

(Continued)

	Secondary outcome measure(s): main study: hypoglycaemia, extension study: glycaemic measures **Other outcome measure(s)**: main study: adverse events, extension study: insulin dose
BEGIN Flex T1	**Endpoints quoted in trial registers**[a]
	Source: NCT01079234 **Primary outcome measure(s)**: Main study: HbA1c Extension: confirmed hypoglycaemic episodes, nocturnal confirmed hypoglycaemic episodes **Secondary outcome measure(s)**: Main study: FPG Extension: HbA1c, FPG **Other outcome measure(s)**: — **Trial results available in trials register**: yes
	Endpoints quoted in publication(s)[a,b]
	Primary outcome measure(s): main study: HbA1c, extension study: rate of confirmed hypoglycaemic episodes, rate of nocturnal confirmed hypoglycaemic episodes **Secondary outcome measure(s)**: main study: FPG; extension study: HbA1c, FPG **Other outcome measure(s)**: safety, insulin dose, weight
	Endpoints quoted in abstract of publication(s)[a,b]
	Primary outcome measure(s): main study: HbA1c, extension study: rate of confirmed hypoglycaemic episodes, rate of nocturnal confirmed hypoglycaemic episodes **Secondary outcome measure(s)**: — **Other outcome measure(s)**: —
BEGIN Young	**Endpoints quoted in trial registers**[a]
	Source: NCT01513473 **Primary outcome measure(s)**: change in HbA1c at 26 weeks **Secondary outcome measure(s)**: change in HbA1c at 52 weeks, change in FPG at 26 weeks and 52 weeks, adverse events at 26 weeks and 52 weeks, hypoglycaemia at 26 weeks and 52 weeks, self-measured hyperglycaemia at 26 and 52 weeks, episodes with blood ketones above 1.5 mmol/L at 26 weeks and 52 weeks, steady-state plasma concentrations of insulin during study, insulin antibodies **Other outcome measure(s)**: — **Trial results available in trials register**: yes
	Endpoints quoted in publication(s)[a,b]
	Primary outcome measure(s): main publication: HbA1c

(Continued)

	Secondary outcome measure(s): main publication: FPG, hypoglycaemia, adverse events, hyperglycaemia with ketosis **Other outcome measure(s)**: insulin dose
	Endpoints quoted in abstract of publication(s)[a,b]
	Primary outcome measure(s): HbA1c **Secondary outcome measure(s)**: FPG, hypoglycaemia, adverse events, hyperglycaemia with ketosis **Other outcome measure(s)**: insulin dose
Bolli 2009	**Endpoints quoted in trial registers[a]**
	Source: NT
	Endpoints quoted in publication(s)[a,b]
	Primary outcome measure(s): glycaemic measures **Secondary outcome measure(s)**: QoL, safety **Other outcome measure(s)**: —
	Endpoints quoted in abstract of publication(s)[a,b]
	Primary outcome measure(s): glycaemic measures **Secondary outcome measure(s)**: safety **Other outcome measure(s)**: —
Chase 2008	**Endpoints quoted in trial registers[a]**
	Source: NCT00046501 **Primary outcome measure(s)**: HbA1c from baseline to end of follow-up **Secondary outcome measure(s)**: HbA1c at different time points, percentage achieving HbA1c target, change in SMBG, albumin/creatinine ratio, insulin dose, lipids, hypoglycaemia, adverse events, weight **Other outcome measure(s)**: — **Trial results available in trials register**: no
	Endpoints quoted in publication(s)[a,b]
	Primary outcome measure(s): HbA1c **Secondary outcome measure(s)**: hypoglycaemia, blood glucose, insulin dose, SAEs, percentage achieving HbA1c target **Other outcome measure(s):** —
	Endpoints quoted in abstract of publication(s)[a,b]
	Primary outcome measure(s): HbA1c

(Continued)

	Secondary outcome measure(s): hypoglycaemia **Other outcome measure(s):** —
Davies 2014	**Endpoints quoted in trial registers**[a]
	Source: NCT01074268 **Primary outcome measure(s)**: Main study: change from baseline in HbA1c after 26 weeks of treatment Extension: adverse events **Secondary outcome measure(s)**: Main study: mean of 9-point SMPG profile, change in FPG, confirmed hypoglycaemic episodes, nocturnal confirmed hypoglycaemic episodes Extension: change in HbA1c, mean of 9-point SMPG profile, change in FPG, confirmed hypoglycaemic episodes, nocturnal confirmed hypoglycaemic episodes **Other outcome measure(s)**: none **Trial results available in trials register**: yes
	Endpoints quoted in publication(s)[a,b]
	Primary outcome measure(s): Main publication: change in HbA1c Extension: adverse events **Secondary outcome measure(s)**: Main study: FPG, 9-point SMPG profiles and doses of basal and mealtime insulin Extension: hypoglycaemia, immunogenicity, insulin dose and body weight **Other outcome measure(s)**: safety variables included number of hypoglycaemic episodes, adverse events, body weight, standard clinical and laboratory assessments (including insulin antibodies), electrocardiogram, fundoscopy/fundus photography and injection-site reactions
	Endpoints quoted in abstract of publication(s)[a,b]
	Primary outcome measure(s): HbA1c **Secondary outcome measure(s)**: FPG **Other outcome measure(s)**: hypoglycaemia, adverse events
Fulcher 2005	**Endpoints quoted in trial registers**[a]
	Source: NT
	Endpoints quoted in publication(s)[a,b]
	Primary outcome measure(s): change in HbA1c **Secondary outcome measure(s)**: FBG, FBG variability, HbA1c response rates, hypoglycaemia, body weight, lipid profiles, adverse events

(Continued)

	Other outcome measure(s): insulin dose, titration index
	Endpoints quoted in abstract of publication(s)[a,b]
	Primary outcome measure(s): HbA1c **Secondary outcome measure(s)**: FBG, hypoglycaemia **Other outcome measure(s)**: —
Heller 2009	**Endpoints quoted in trial registers[a]**
	Source: NCT00095082; Eudra-CT 2004-000086-35 **Primary outcome measure(s)**: HbA1c **Secondary outcome measure(s)**: adverse events, body weight, hypoglycaemia, blood glucose, insulin treatment satisfaction (clinical trials register EU: proportion of participants with HbA1c ≤ 7.0 % without any episodes of major hypoglycaemia during the last month of treatment) **Other outcome measure(s)**: — **Trial results available in trials register**: no
	Endpoints quoted in publication(s)[a,b]
	Primary outcome measure(s): HbA1c **Secondary outcome measure(s)**: FPG; within-patient variation in SMPG before breakfast and dinner; and 10-point SMPG profiles, hypoglycaemia, adverse events, weight, proportion of participants with HbA1c ≤ 7.0 % without any episodes of major hypoglycaemia during the last month of treatment **Other outcome measure(s)**: —
	Endpoints quoted in abstract of publication(s)[a,b]
	Primary outcome measure(s): HbA1c **Secondary outcome measure(s)**: withdrawal due to adverse events, nocturnal hypoglycaemia, proportion of participants with HbA1c ≤ 7.0 % without any episodes of major hypoglycaemia during the last month of treatment **Other outcome measure(s)**: insulin dose
Home 2005	**Endpoints quoted in trial registers[a]**
	Source: NT
	Endpoints quoted in publication(s)[a,b]
	Primary outcome measure(s): HbA1c **Secondary outcome measure(s)**: plasma glucose, SMBG and hypoglycaemia **Other outcome measure(s)**: retinopathy, insulin antibodies, adverse events
	Endpoints quoted in abstract of publication(s)[a,b]
	Primary outcome measure(s): HbA1c

(Continued)

	Secondary outcome measure(s): FBG, hypoglycaemia **Other outcome measure(s)**: adverse events, clamp investigations
Kobayashi 2007	**Endpoints quoted in trial registers[a]**
	Source: NCT00604344 **Primary outcome measure(s)**: HbA1c **Secondary outcome measure(s)**: blood glucose, hypoglycaemia, adverse events, body weight, insulin antibodies **Other outcome measure(s)**: — (from synopsis: insulin treatment questionnaire (questions concerning glycaemic control, insulin therapy related QoL at night [ITR-QOLN] and insulin treatment satisfaction questionnaire Japan [ITSQ-J])) **Trial results available in trials register**: no
	Endpoints quoted in publication(s)[a,b]
	Primary outcome measure(s): HbA1c **Secondary outcome measure(s)**: blood glucose, hypoglycaemia, adverse events, body weight, insulin antibodies **Other outcome measure(s)**: —
	Endpoints quoted in abstract of publication(s)[a,b]
	Primary outcome measure(s): HbA1c **Secondary outcome measure(s)**: blood glucose, hypoglycaemia, adverse events, body weight **Other outcome measure(s)**: —
Liu 2016	**Endpoints quoted in trial registers[a]**
	Source: NCT01223131; Eudra-CT 2014-004640-35 **Primary outcome measure(s)**: HbA1c over 24 weeks **Secondary outcome measure(s)**: percentage achieving HbA1c < 7.5%, blood glucose, SMBG, insulin dose, hypoglycaemia, safety, antibodies, pharmacokinetics **Other outcome measure(s)**: — **Trial results available in trials register**: yes (EudraCT)
	Endpoints quoted in publication(s)[a,b]
	Primary outcome measure(s): HbA1c **Secondary outcome measure(s)**: percentage achieving HbA1c < 7.5%, blood glucose, SMBG, insulin dose, hypoglycaemia, safety, antibodies, pharmacokinetics **Other outcome measure(s)**: —
	Endpoints quoted in abstract of publication(s)[a,b]
	Primary outcome measure(s): HbA1c

(Continued)

	Secondary outcome measure(s): hypoglycaemia **Other outcome measure(s)**: —
NCT00595374	**Endpoints quoted in trial registers[a]**
	Source: NCT00595374 **Primary outcome measure(s)**: HbA1c **Secondary outcome measure(s)**: hypoglycaemia, adverse events, blood glucose, body weight, QoL **Other outcome measure(s)**: — **Trial results available in trials register**: no
	Endpoints quoted in publication(s)[a,b]
	Primary outcome measure(s): — **Secondary outcome measure(s)**: — **Other outcome measure(s)**: —
	Endpoints quoted in abstract of publication(s)[a,b]
	Primary outcome measure(s): — **Secondary outcome measure(s)**: — **Other outcome measure(s)**: —
NCT00605137	**Endpoints quoted in trial registers[a]**
	Source: NCT00605137 **Primary outcome measure(s)**: safety profile (incidence of hypoglycaemia, adverse events, laboratory assessments, BMI, blood pressure, fundoscopy) **Secondary outcome measure(s)**: laboratory assessments and other safety endpoints, HbA1c, blood glucose **Other outcome measure(s)**: height, insulin dose **Trial results available in trials register**: no
	Endpoints quoted in publication(s)[a,b]
	Primary outcome measure(s): — **Secondary outcome measure(s)**: — **Other outcome measure(s)**: —
	Endpoints quoted in abstract of publication(s)[a,b]
	Primary outcome measure(s): — **Secondary outcome measure(s)**: — **Other outcome measure(s)**: —

(Continued)

Pieber 2007	**Endpoints quoted in trial registers[a]**
	Source: NCT00312104
	Primary outcome measure(s): HbA1c
	Secondary outcome measure(s): hypoglycaemia, adverse events, blood glucose (from CSR: treatment satisfaction and pain perception)
	Other outcome measure(s):
	Trial results available in trials register: no
	Endpoints quoted in publication(s)[a,b]
	Primary outcome measure(s): HbA1c
	Secondary outcome measure(s): hypoglycaemia, adverse events, blood glucose
	Other outcome measure(s): insulin dose, weight
	Endpoints quoted in abstract of publication(s)[a,b]
	Primary outcome measure(s): HbA1c
	Secondary outcome measure(s): hypoglycaemia, adverse events, blood glucose
	Other outcome measure(s): insulin dose, weight
Porcellati 2004	**Endpoints quoted in trial registers[a]**
	Source: NT
	Endpoints quoted in publication(s)[a,b]
	Primary outcome measure(s): HbA1c
	Secondary outcome measure(s): —
	Other outcome measure(s): glycaemic control, hypoglycaemia, clamp data, weight (co-publication: well-being and treatment satisfaction)
	Endpoints quoted in abstract of publication(s)[a,b]
	Primary outcome measure(s): HbA1c
	Secondary outcome measure(s): —
	Other outcome measure(s): glycaemic control, hypoglycaemia (co-publication: well-being and treatment satisfaction)
PRESCHOOL	**Endpoints quoted in trial registers[a]**
	Source: NCT00993473; Eudra CT 2009-011231-12
	Primary outcome measure(s): all hypoglycaemia
	Secondary outcome measure(s): symptomatic hypoglycaemia, severe hypoglycaemia, nocturnal hypoglycaemia, severe nocturnal hypoglycaemia, HbA1c, percentage with HbA1c < 7.5%, CGM
	Other outcome measure(s): —

(Continued)

	Trial results available in trials register: yes
	Endpoints quoted in publication(s)[a,b]
	Primary outcome measure(s): all hypoglycaemia **Secondary outcome measure(s)**: symptomatic hypoglycaemia, severe hypoglycaemia, nocturnal hypoglycaemia, severe nocturnal hypoglycaemia, HbA1c, percentage with HbA1c < 7.5%, CGM **Other outcome measure(s)**: treatment emergent adverse events
	Endpoints quoted in abstract of publication(s)[a,b]
	Primary outcome measure(s): all hypoglycaemia **Secondary outcome measure(s)**: symptomatic hypoglycaemia, severe hypoglycaemia, nocturnal hypoglycaemia, severe nocturnal hypoglycaemia, HbA1c, CGM **Other outcome measure(s)**: —
Ratner 2000	**Endpoints quoted in trial registers[a]**
	Source: NT
	Endpoints quoted in publication(s)[a,b]
	Primary outcome measure(s): glycaemic control and hypoglycaemia **Secondary outcome measure(s)**: — **Other outcome measure(s)**: safety, insulin dose
	Endpoints quoted in abstract of publication(s)[a,b]
	Primary outcome measure(s): glycaemic control, hypoglycaemia **Secondary outcome measure(s)**: — **Other outcome measure(s)**: —
Robertson 2007	**Endpoints quoted in trial registers[a]**
	Source: NCT00312156 **Primary outcome measure(s)**: HbA1c **Secondary outcome measure(s)**: adverse events, body weight, antibodies, blood glucose, hypoglycaemia (in CSR also: incidence of diabetic ketoacidosis requiring hospitalisation) **Other outcome measure(s)**: — **Trial results available in trials register**: no
	Endpoints quoted in publication(s)[a,b]
	Primary outcome measure(s): HbA1c **Secondary outcome measure(s)**: adverse events, body weight, antibodies, blood glucose, hypoglycaemia, (ketoacidosis) **Other outcome measure(s)**: —

(Continued)

	Endpoints quoted in abstract of publication(s)[a,b]
	Primary outcome measure(s): HbA1c **Secondary outcome measure(s)**: adverse events, blood glucose, hypoglycaemia **Other outcome measure(s)**: —
Russell-Jones 2004	**Endpoints quoted in trial registers[a]**
	Source: NCT03220425 **Primary outcome measure(s)**: HbA1c **Secondary outcome measure(s)**: (from CSR: blood glucose, hypoglycaemia, safety profile, antibodies) **Other outcome measure(s)**: — **Trial results available in trials register**: no
	Endpoints quoted in publication(s)[a,b]
	Primary outcome measure(s): HbA1c **Secondary outcome measure(s)**: — **Other outcome measure(s)**: FPG, nocturnal hypoglycaemia, weight, adverse events
	Endpoints quoted in abstract of publication(s)[a,b]
	Primary outcome measure(s): HbA1c **Secondary outcome measure(s)**: — **Other outcome measure(s)**: FPG, nocturnal hypoglycaemia, weight, adverse events
Schober 2002	**Endpoints quoted in trial registers[a]**
	Source: NT
	Endpoints quoted in publication(s)[a,b]
	Primary outcome measure(s): no study protocol available, but HbA1c described as primary outcome in main publication **Secondary outcome measure(s)**: no study protocol available, but FBG and hypoglycaemia described as secondary outcomes in main publication **Other outcome measure(s)**: antibodies, adverse events
	Endpoints quoted in abstract of publication(s)[a,b]
	Primary outcome measure(s): HbA1c **Secondary outcome measure(s)**: FBG and hypoglycaemia **Other outcome measure(s)**: adverse events
Standl 2004	**Endpoints quoted in trial registers[a]**

(Continued)

	Source: NT
	Endpoints quoted in publication(s)[a,b]
	Primary outcome measure(s): HbA1c **Secondary outcome measure(s)**: 9-point blood glucose profiles, hypoglycaemia, FPG, adverse events **Other outcome measure(s)**: weight
	Endpoints quoted in abstract of publication(s)[a,b]
	Primary outcome measure(s): HbA1c **Secondary outcome measure(s)**: 9-point blood glucose profiles, hypoglycaemia, FPG, adverse events **Other outcome measure(s)**: weight
SWITCH 1	**Endpoints quoted in trial registers[a]**
	Source: NCT02034513 **Primary outcome measure(s)**: severe or blood glucose confirmed symptomatic hypoglycaemic episodes (maintenance period) **Secondary outcome measure(s):** severe or blood glucose confirmed symptomatic nocturnal hypoglycaemic episodes (maintenance period), proportion of participants with one or more severe hypoglycaemic episodes (maintenance period), incidence of adverse events (32 weeks for each treatment period), change from baseline in HbA1c, FPG **Other outcome measure(s)**: (according to appendix to main publication: Treatment Related Impact Measure for minor HYPOglycaemic events (TRIM-HYPO) and SF-36 v2) **Trial results available in trials register**: yes
	Endpoints quoted in publication(s)[a,b]
	Primary outcome measure(s): hypoglycaemia **Secondary outcome measure(s)**: glycaemic variables **Other outcome measure(s)**: insulin dose, (co-publication: cost, HbA1c/severe hypoglycaemia)
	Endpoints quoted in abstract of publication(s)[a,b]
	Primary outcome measure(s): hypoglycaemia **Secondary outcome measure(s)**: **Other outcome measure(s)**: (co-publication: cost, HbA1c/severe hypoglycaemia)
Thalange 2013	**Endpoints quoted in trial registers[a]**
	Source: NCT00435019 (main study); NCT00623194 (extension study) **Primary outcome measure(s)**: Main study: HbA1c (after 52 weeks of treatment) Extension: insulin antibodies

(Continued)

	Secondary outcome measure(s): Main study: adverse events, insulin antibodies; extension study: insulin antibodies, HbA1c, FPG, hypoglycaemia, BMI, body weight, ketoacidosis, insulin dose, laboratory values, fundoscopy, blood pressure, pulse **Other outcome measure(s)**: — **Trial results available in trials register**: yes
	Endpoints quoted in publication(s)[a,b]
	Primary outcome measure(s): HbA1c **Secondary outcome measure(s)**: adverse events **Other outcome measure(s)**: weight, insulin dose, hypoglycaemia
	Endpoints quoted in abstract of publication(s)[a,b]
	Primary outcome measure(s): HbA1c **Secondary outcome measure(s)**: hypoglycaemia **Other outcome measure(s)**: weight, insulin dose, glucose
Urakami 2017	**Endpoints quoted in trial registers[a]**
	Source: NT
	Endpoints quoted in publication(s)[a,b]
	Primary outcome measure(s): — **Secondary outcome measure(s)**: — **Other outcome measure(s)**:
	Endpoints quoted in abstract of publication(s)[a,b]
	Primary outcome measure(s): — **Secondary outcome measure(s)**: — **Other outcome measure(s)**:
Vague 2003	**Endpoints quoted in trial registers[a]**
	Source: NT
	Endpoints quoted in publication(s)[a,b]
	Primary outcome measure(s): HbA1c **Secondary outcome measure(s)**: hypoglycaemia, safety, glucose **Other outcome measure(s)**: weight, insulin dose
	Endpoints quoted in abstract of publication(s)[a,b]
	Primary outcome measure(s): HbA1c

(Continued)

Secondary outcome measure(s): hypoglycaemia, safety, glucose

Other outcome measure(s): weight, insulin dose

— denotes not reported
[a]Primary and secondary outcomes refer to verbatim specifications in publication/records. Unspecified outcome measures refer to all outcomes not described as primary or secondary outcome measures.

[b]Publication(s) refers to study information published in scientific journals (primary reference, duplicate publications, companion documents or multiple reports of a primary study).

AE: adverse event; **BMI:** body mass index; **CGM**: continuous glucose monitoring; **CSR**: clinical study report;**EMA**: European Medicines Agency; **FBG**: fasting blood glucose; **FDA**: Food and Drug Administration (US); **FPG**: fasting plasma glucose; **HbA1c**: glycosylated haemoglobin A1c; **ITR-QOLN**: insulin therapy related quality of life at night; **ITSQ-J**: insulin treatment satisfaction questionnaire - Japan; **NT**: no trial register document available; **QoL**: quality of life; **SAE**: serious adverse event; **SF-36**: short-form 36; **SMBG**: self-measured blood glucose; **SMPG**: self-measured plasma glucose.

Appendix 13. High risk of outcome reporting bias according to Outcome Reporting Bias In Trials (ORBIT) classification

Study 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]
Bartley 2008	ND				
BEGIN Basal-Bolus Type 1	ND				
BEGIN Flex T1	ND				
BEGIN Young	ND				
Bolli 2009	Severe hypoglycaemia	Yes			
	Moderate/mild/nocturnal hypoglycaemia	Yes			
Chase 2008	ND				
Davies 2014	ND				
Fulcher 2005	ND				
Heller 2009	ND				
Home 2005	ND				
Kobayashi 2007	Health-related quality of life	Yes			
Liu 2016	ND				
NCT00595374	Health-related quality of life	Yes			

(Continued)

	Diabetic ketoacidosis			Yes	
	Mild/moderate hypoglycaemia	Yes			
	Nocturnal hypoglycaemia	Yes			
	HbA1c	Yes			
NCT00605137	ND				
Pieber 2007	Severe hypoglycaemia combined with HbA1c	Yes			
Porcellati 2004	Adverse events (severe and non-severe)				Yes
PRESCHOOL	ND				
Ratner 2000	ND				
Robertson 2007	HbA1c combined with hypoglycaemia	Yes			
Russell-Jones 2004	Diabetic ketoacidosis			Yes	
	HbA1c combined with hypoglycaemia				
Schober 2002	All-cause mortality				Yes
Standl 2004	Diabetic ketoacidosis			Yes	
	Non-fatal myocardial infarction			Yes	
	Non-fatal stroke				Yes
SWITCH 1	Mortality, hypoglycaemia, safety			Yes (not reported at cross-over)	
Thalange 2013	ND				
Urakami 2017	ND				
Vague 2003	HbA1c combined with hypoglycaemia	Yes			

[a]Clear that outcome was measured and analysed; study report stated that outcome was analysed but reported only that the result was not significant
(Classification 'A', table 2, Kirkham 2010)
[b]Clear that outcome was measured and analysed;study report stated that outcome was analysed but reported no results
(Classification 'D', table 2, Kirkham 2010)
[c]Clear that outcome was measured but was not necessarily analysed; judgement suggests that likely to have been analysed but not reported due to non-significant results
(Classification 'E', table 2, Kirkham 2010)
[d]Unclear whether outcome was measured; not mentioned, but clinical judgement suggests likely to have been measured and analysed but not reported on the basis of non-significant results

(Continued)
(Classification 'G', table 2, Kirkham 2010)

CSR: clinical study report;**HbA1c:** glycosylated haemoglobin A1c; **ND**: none detected.

Appendix 14. Definition of endpoint measurement[a]

Study ID	Endpoints	Definition
Bartley 2008	All-cause mortality	ND (IO)
	Health-related quality of life	—
	Severe hypoglycaemia	Hypoglycaemia requiring third party assistance (IO)
	Cardiovascular mortality	One participant died due to cardiovascular disease (IO)
	Non-fatal myocardial infarction	Acute myocardial infarction[b] (IO)
	Non-fatal stroke	—
	End-stage renal disease	—
	Blindness	—
	Serious adverse events	A serious adverse event is an experience that at any dose results in any of the following: • death • a life-threatening experience • in-participant hospitalisation or prolongation of existing hospitalisation • a persistent or significant disability/incapacity • a congenital anomaly/birth defect • important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgement, they may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition[b] (IO)
	Diabetic ketoacidosis	Diabetic ketoacidosis[b] (IO)
	Non-serious adverse events	An adverse event is any undesirable medical event occurring to a participant in a clinical study, whether or not related to the study product(s). A non-serious adverse event is any adverse event which does not fulfil the definition of a serious adverse event[b] (SO)
	Noctural hypoglycaemia	Hypoglycaemia between 23:00 to 06:00 h (SO)
	Mild/moderate hypoglycaemia	All SMPG values < 3.1 mmol/L as well as signs and symptoms of hypoglycaemia minor if plasma glucose < 3.1 mmol/L and the individual dealt with

(Continued)

		the episode him/herself, and as symptoms only if episodes were not confirmed by a plasma glucose measurement and no assistance was required (SO)
	Socioeconomic effects	—
	HbA1c	ND (IO)
	Combined HbA1c and severe hypoglycaemia	Percentage of participants reaching HbA1c ≤ 7.0% at the end of the study without symptomatic hypoglycaemia with a plasma glucose < 4.0 mmol/L or any single plasma glucose value < 3.1 mmol/L during the last month of treatment" (IO)
BEGIN Basal-Bolus Type 1	All-cause mortality	All-cause mortality (IO, AO)
	Health-related quality of life	Short Form-36 v2 (SO)
	Severe hypoglycaemia	Hypoglycaemia requiring third party assistance (IO)
	Cardiovascular mortality	Cause of each death described separately (myocardial infarction event; sudden death; ventricular tachycardia event) (IO, AO)
	Non-fatal myocardial infarction	Myocardial infarction (IO, AO)
	Non-fatal stroke	—
	End-stage renal disease	—
	Blindness	—
	Serious adverse events	A serious adverse event is an experience that at any dose results in any of the following: • death • a life-threatening experience • in-participant hospitalisation or prolongation of existing hospitalisation • a persistent or significant disability/incapacity • a congenital anomaly/birth defect • important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgement, they may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition[b] (IO)
	Diabetic ketoacidosis	Ketoacidosis (IO)
	Non-serious adverse events	A non-serious adverse event is any adverse event which does not fulfil the definition of a serious adverse event[b] (SO)
	Noctural hypoglycaemia	Hypoglycaemic episodes occurring from 00:01 to 05:59 h (SO)

(Continued)

	Mild/moderate hypoglycaemia	Confirmed hypoglycaemic episodes included those with a plasma glucose value of < 3.1 mmol/L (SO)
	Socioeconomic effects	—
	HbA1c	ND
	Combined HbA1c and severe hypoglycaemia	HbA1c < 7% without severe hypoglycaemia[b] (IO)
BEGIN Flex T1	All-cause mortality	Fatal serious adverse events (one committed suicide) (IO, AO)
	Health-related quality of life	—
	Severe hypoglycaemia	Hypoglycaemia requiring third party assistance (IO, AO)
	Cardiovascular mortality	ND
	Non-fatal myocardial infarction	Acute coronary syndrome (IO, AO)
	Non-fatal stroke	Stroke (IO, AO)
	End-stage renal disease	—
	Blindness	—
	Serious adverse events	A serious adverse event is an experience that at any dose results in any of the following: • death • a life-threatening experience • in-participant hospitalisation or prolongation of existing hospitalisation • a persistent or significant disability/incapacity • a congenital anomaly/birth defect; • important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgement, they may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition[b] (IO)
	Diabetic ketoacidosis	—
	Non-serious adverse events	A non-serious adverse event is any adverse event that does not fulfil the definition of a serious adverse event[b] (SO)
	Nocturnal hypoglycaemia	Episodes occurring between 00:01 and 05:59 hours (inclusive) (SO)
	Mild/moderate hypoglycaemia	Minor hypoglycaemic episodes are defined as participants able to treat her/himself and plasma glucose below 3.1 mmol/L (OBS page 68 + 69 in CSR - different definitions) (SO)

(Continued)

	Socioeconomic effects	—
	HbA1c	ND (IO)
	Combined HbA1c and severe hypoglycaemia	Treatment targets at the end of study achieved without hypoglycaemic episodes in the last 12 weeks of treatment considering severe episodes only, and severe and minor episodes together[b] (IO)
BEGIN Young	All-cause mortality	ND (IO, AO)
	Health-related quality of life	—
	Severe hypoglycaemia	The child has altered mental status and cannot assist in their own care, is semiconscious or unconscious, or in a coma ± convulsions and may require parenteral therapy (glucagon or iv glucose) (IO)
	Cardiovascular mortality	ND (IO, AO)
	Non-fatal myocardial infarction	—
	Non-fatal stroke	—
	End-stage renal disease	—
	Blindness	—
	Serious adverse events	A serious adverse event is an experience that at any dose results in any of the following: • death • a life-threatening experience • in-participant hospitalisation or prolongation of existing hospitalisation • a persistent or significant disability/incapacity • a congenital anomaly/birth defect; • important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgement, they may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition[b] (IO)
	Diabetic ketoacidosis	Diabetic ketoacidosis (IO)
	Non-serious adverse events	A non-serious AE is any AE which does not fulfil the definition of an SAE[b] (IO)
	Nocturnal hypoglycaemia	Hypoglycaemic episodes occurring between 11 p.m. and 7 a.m. inclusive were classified as nocturnal (SO)
	Mild/moderate hypoglycaemia	Confirmed hypoglycaemia was defined as SMPG < 3.1 mmol/L[c] (SO)
	Socioeconomic effects	—

(Continued)

	HbA1c	ND (IO)
	Combined HbA1c and severe hypoglycaemia	—
Bolli 2009	All-cause mortality	—
	Health-related quality of life	Well-Being Enquiry for Diabetics questionnaire (SO)
	Severe hypoglycaemia	Serious hypoglycaemia was defined as an event with blood glucose < 2.3 mmol/L, severe hypoglycaemia an event with symptoms consistent with hypoglycaemia, during which the participant required the assistance of another person, or with prompt recovery after oral carbohydrate, iv glucose or glucagon administration (IO)
	Cardiovascular mortality	—
	Non-fatal myocardial infarction	—
	Non-fatal stroke	—
	End-stage renal disease	—
	Blindness	—
	Serious adverse events	Serious adverse events (IO)
	Diabetic ketoacidosis	—
	Non-serious adverse events	Adverse events (SO)
	Nocturnal hypoglycaemia	Serious nocturnal hypoglycaemia (blood glucose < 2.3 mmol/L[c]); hypoglycaemia which occurred between bedtime and before getting up in the morning (IO)
	Mild/moderate hypoglycaemia	Blood glucose ≤ 4.0 mmol/L[c] (SO)
	Socioeconomic effects	—
	HbA1c	ND (IO)
	Combined HbA1c and severe hypoglycaemia	—
Chase 2008	All-cause mortality	—
	Health-related quality of life	The Diabetes Quality of Life for Youth questionnaire and Parents' Diabetes Quality of Life[b] (SO)
	Severe hypoglycaemia	Severe hypoglycaemia was defined as an event requiring assistance from another person and associated with either BG < 2.0 mmol/L or prompt recovery after oral carbohydrate, iv glucose, or intramuscular or subcutaneous glucagon administration (IO)

(Continued)

	Cardiovascular mortality	—
	Non-fatal myocardial infarction	—
	Non-fatal stroke	—
	End-stage renal disease	—
	Blindness	—
	Serious adverse events	A serious adverse event is an experience that at any dose results in any of the following: • death • a life-threatening experience • in-participant hospitalisation or prolongation of existing hospitalisation • a persistent or significant disability/incapacity • a congenital anomaly/birth defect; • important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgement, they may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition[b] (IO)
	Diabetic ketoacidosis	Diabetic ketoacidosis (IO)
	Non-serious adverse events	The term adverse event covered any unfavourable and unintended sign, symptom, syndrome, or illness that developed or worsened during the period of observation in the clinical study[b] (SO)
	Nocturnal hypoglycaemia	Hypoglycaemia from midnight and 6 a.m. (SO)
	Mild/moderate hypoglycaemia	The rates of biochemical hypoglycaemia were ascertained by analysis of SMBG data and divided into 3 categories: < 3.9 mmol/L, < 2.8 mmol/L and < 2.0 mmol/L[c] (SO)
	Socioeconomic effects	—
	HbA1c	ND (IO)
	Combined HbA1c and severe hypoglycaemia	—
Davies 2014	All-cause mortality	All-cause mortality (IO, AO)
	Health-related quality of life	Short Form-36 v2[b] (SO)
	Severe hypoglycaemia	Hypoglycaemia requiring third party assistance (IO)
	Cardiovascular mortality	Cardiovascular mortality (IO, AO)

(Continued)

	Non-fatal myocardial infarction	Non-fatal myocardial infarction (IO, AO)
	Non-fatal stroke	Non-fatal stroke (IO, AO)
	End-stage renal disease	End-stage renal disease (IO)
	Blindness	Blindness (IO)
	Serious adverse events	Serious adverse events: adverse event that at any dose results in any of the following death, a life-threatening experience, in-participant hospitalisations/prolongation of existing hospitalisation, persistent/significant disability/incapacity/congenital anomaly/birth defect or important medical issues (IO)
	Diabetic ketoacidosis	Diabetic ketoacidosis (IO)
	Non-serious adverse events	Mild: no/transient symptoms, no interference with participant's daily activities. Moderate: marked symptoms, moderate interference with participant's daily activities (SO)
	Nocturnal hypoglycaemia	Hypoglycaemia between 00:01 and 05:59 hours (SO)
	Mild/moderate hypoglycaemia	Confirmed hypoglycaemia was defined as plasma glucose < 3.1 mmol/L regardless of symptoms (SO)
	Socioeconomic effects	—
	HbA1c	ND (IO)
	Combined HbA1c and severe hypoglycaemia	HbA1c < 7% without confirmed severe hypoglycaemia during the last 12 weeks of treatment[b] (IO)
Fulcher 2005	All-cause mortality	ND (IO)
	Health-related quality of life	—
	Severe hypoglycaemia	Symptoms consistent with hypoglycaemia required the assistance of another person and was associated with a blood glucose level < 2.8 mmol/L or prompt recovery after oral carbohydrate, iv glucose or sc glucagon administration (IO)
	Cardiovascular mortality	ND (IO)
	Non-fatal myocardial infarction	—
	Non-fatal stroke	—
	End-stage renal disease	—
	Blindness	—
	Serious adverse events	A serious adverse event is an experience that at any dose results in any of the following: • death

(Continued)

		• a life-threatening experience • in-participant hospitalisation or prolongation of existing hospitalisation • a persistent or significant disability/incapacity • a congenital anomaly/birth defect; • important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgement, they may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition[b] (IO)
	Diabetic ketoacidosis	Diabetic ketoacidosis (IO)
	Non-serious adverse events	Adverse event covers any sign, symptom, syndrome, or illness that appears or worsens in a patient during the period of observation in the clinical study and that may impair the well-being of the patient. The term also covers laboratory findings or results of other diagnostic procedures that are considered to be clinically relevant[b]. A non-serious adverse event is any adverse event not meeting the serious adverse event criteria[b] (SO)
	Nocturnal hypoglycaemia	Hypoglycaemia occurring after the evening insulin injection and before the morning insulin dose
	Mild/moderate hypoglycaemia	Symptomatic hypoglycaemia was defined as an event with symptoms consistent with hypoglycaemia that was mild (2.8–3.6 mmol/L) or moderate (< 2.8 mmol/L)
	Socioeconomic effects	Information in relation to whether participants had suffered any income loss because of diabetes during the study (SO, IO)
	HbA1c	ND (IO)
	Combined HbA1c and severe hypoglycaemia	—
Heller 2009	All-cause mortality	ND (IO)
	Health-related quality of life	—
	Severe hypoglycaemia	The patient could not treat the episode by himself/herself (IO)
	Cardiovascular mortality	One patient died from acute myocardial infarction (IO)
	Non-fatal myocardial infarction	Myocardial ischaemia (IO)
	Non-fatal stroke	Cerebrovascular accident (IO)
	End-stage renal disease	—
	Blindness	—
	Serious adverse events	A serious adverse event is an experience that at any dose results in any of the following:

(Continued)

		• death • a life-threatening experience • in-participant hospitalisation or prolongation of existing hospitalisation • a persistent or significant disability/incapacity • a congenital anomaly/birth defect; • important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgement, they may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition[b] (IO)
	Diabetic ketoacidosis	Diabetic ketoacidosis (IO)
	Non-serious adverse events	A non-serious adverse event is any adverse event which does not fulfil the definition of a serious adverse event[b] (SO)
	Nocturnal hypoglycaemia	Episodes of hypoglycaemia occurring from 11 p.m. up to but not including 6 a.m. (SO)
	Mild/moderate hypoglycaemia	Minor: the patient could treat himself/herself and the measured plasma glucose value was < 3.1 mmol/L; symptoms only: the patient could treat himself/herself and no plasma glucose measurement was taken or the measured plasma glucose value was ≥ 3.1 mmol/L (SO)
	Socioeconomic effects	—
	HbA1c	ND (IO)
	Combined HbA1c and severe hypoglycaemia	HbA1c ≤ 7% without major hypoglycaemia during the last month of treatment (IO)
Home 2005	All-cause mortality	ND (IO)
	Health-related quality of life	Well-being Questionnaire (W-BQ) (SO)
	Severe hypoglycaemia	Severe symptomatic hypoglycaemia was defined as an event consistent with symptomatic hypoglycaemia requiring the assistance of another person, with either a blood glucose level < 2.8 mmol/L or prompt recovery after administration of oral carbohydrate, iv glucose or glucagon (IO)
	Cardiovascular mortality	ND (IO)
	Non-fatal myocardial infarction	—
	Non-fatal stroke	—
	End-stage renal disease	—
	Blindness	—
	Serious adverse events	A serious adverse event is an experience that at any dose results in any of the following:

(Continued)

		• death • a life-threatening experience • in-participant hospitalisation or prolongation of existing hospitalisation • a persistent or significant disability/incapacity • a congenital anomaly/birth defect; • important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgement, they may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition[b] (IO)
	Diabetic ketoacidosis	Diabetic ketoacidosis
	Non-serious adverse events	A non-serious adverse event is any adverse event not meeting the serious adverse event criteria (SO)
	Nocturnal hypoglycaemia	Symptomatic hypoglycaemia occurring during sleep between bedtime and rising in the morning, or before the morning pre-breakfast self-blood glucose measurement and the morning insulin injection. Only participants with confirmed blood glucose < 2.0 mmol/L were considered clinically relevant (SO)
	Mild/moderate hypoglycaemia	Hypoglycaemia was categorised as symptomatic (clinical symptoms confirmed by blood glucose < 2.8 mmol/L) or asymptomatic (confirmed by blood glucose < 2.8 mmol/L without symptoms) (SO)
	Socioeconomic effects	Information about loss of income during the study (SO, IO)
	HbA1c	ND (IO)
	Combined HbA1c and severe hypoglycaemia	—
Kobayashi 2007	All-cause mortality	"No participants died" (IO)
	Health-related quality of life	Insulin Therapy Related Quality of Life at Night
	Severe hypoglycaemia	Any event requiring assistance of another person to recover from hypoglycaemic symptoms with or without measurement of blood glucose levels (IO)
	Cardiovascular mortality	"No participants died" (IO)
	Non-fatal myocardial infarction	—
	Non-fatal stroke	—
	End-stage renal disease	—
	Blindness	—
	Serious adverse events	Serious adverse events (IO)

(Continued)

	Diabetic ketoacidosis	—
	Non-serious adverse events	Adverse events (SO)
	Nocturnal hypoglycaemia	Hypoglycaemia occurring between 23:00 to 06:00 (SO)
	Mild/moderate hypoglycaemia	Any symptoms consistent with hypoglycaemia (SO)
	Socioeconomic effects	—
	HbA1c	ND (IO)
	Combined HbA1c and severe hypoglycaemia	—
Liu 2016	All-cause mortality	ND (IO)
	Health-related quality of life	—
	Severe hypoglycaemia	Hypoglycaemia requiring the assistance of a third party or involving a seizure, coma, unconsciousness or the use of glucagon (IO)
	Cardiovascular mortality	ND (IO)
	Non-fatal myocardial infarction	—
	Non-fatal stroke	—
	End-stage renal disease	—
	Blindness	—
	Serious adverse events	A serious adverse event is an experience that at any dose results in any of the following: • death • a life-threatening experience • in-participant hospitalisation or prolongation of existing hospitalisation • a persistent or significant disability/incapacity • a congenital anomaly/birth defect • important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgement, they may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition[b] (IO)
	Diabetic ketoacidosis	Diabetic ketoacidosis (IO)
	Non-serious adverse events	An adverse event is any untoward medical occurrence in a patient or clinical investigation where a patient administered a pharmaceutical product

(Continued)

		and which does not necessarily have to have a causal relationship with the treatment[b] (SO)
	Nocturnal hypoglycaemia	Hypoglycaemia occurring between 23:00–07:00 (SO)
	Mild/moderate hypoglycaemia	Hypoglycaemia was defined as asymptomatic (blood glucose values < 3.9 mmol/L without clinical symptoms), symptomatic (blood glucose < 3.9 mmol/L with associated clinical symptoms) (SO)
	Socioeconomic effects	—
	HbA1c	ND (IO)
	Combined HbA1c and severe hypoglycaemia	—
NCT00595374	All-cause mortality	Reported no one died (IO)
	Health-related quality of life	Quality of life (SO)
	Severe hypoglycaemia	—
	Cardiovascular mortality	Reported no one died (IO)
	Non-fatal myocardial infarction	—
	Non-fatal stroke	—
	End-stage renal disease	—
	Blindness	—
	Serious adverse events	Serious adverse event (IO)
	Diabetic ketoacidosis	—
	Non-serious adverse events	Any adverse event that started one day or more after the start of active medication (SO)
	Nocturnal hypoglycaemia	—
	Mild/moderate hypoglycaemia	—
	Socioeconomic effects	—
	HbA1c	—
	Combined HbA1c and severe hypoglycaemia	—
NCT00605137	All-cause mortality	No patients died (IO)
	Health-related quality of life	—

(Continued)

	Severe hypoglycaemia	Hypoglycaemia requiring third party assistance (IO)
	Cardiovascular mortality	No patients died (IO)
	Non-fatal myocardial infarction	—
	Non-fatal stroke	—
	End-stage renal disease	—
	Blindness	—
	Serious adverse events	A serious adverse event is an experience that at any dose results in any of the following: • death • a life-threatening experience • in-participant hospitalisation or prolongation of existing hospitalisation • a persistent or significant disability/incapacity • a congenital anomaly/birth defect • important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgement, they may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition(IO)
	Diabetic ketoacidosis	Diabetic ketoacidosis (IO)
	Non-serious adverse events	An adverse event is any untoward medical occurrence in a patient or clinical investigation where a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. A non-serious adverse event is any adverse event which does not fulfil the definition of a serious adverse event (SO)
	Nocturnal hypoglycaemia	Hypoglycaemia from 23:00 - 06:00, inclusive (SO)
	Mild/moderate hypoglycaemia	Minor hypoglycaemic episodes blood glucose < 3.1 mmol/L and able treat the period themselves), symptoms only (no blood glucose measurement or blood glucose > 3.1 mmol/L) and biochemical hypoglycaemia (defined as asymptomatic hypoglycaemic with blood glucose value < 3.1 mmol/L) (SO)
	Socioeconomic effects	—
	HbA1c	ND (IO)
	Combined HbA1c and severe hypoglycaemia	—
Pieber 2007	All-cause mortality	No patients died (IO)
	Health-related quality of life	—

(Continued)

	Severe hypoglycaemia	Hypoglycaemia requiring third party assistance (IO)
	Cardiovascular mortality	No patients died (IO)
	Non-fatal myocardial infarction	—
	Non-fatal stroke	—
	End-stage renal disease	—
	Blindness	—
	Serious adverse events	A serious adverse event is an experience that at any dose results in any of the following: • death • a life-threatening experience • in-participant hospitalisation or prolongation of existing hospitalisation • a persistent or significant disability/incapacity • a congenital anomaly/birth defect • important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgement, they may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition[b] (IO)
	Diabetic ketoacidosis	—
	Non-serious adverse events	From CSR: An adverse event (AE) is any undesirable medical event occurring to a participant in a clinical study, whether or not related to the study product(s). A non-serious adverse event is any AE that does not fulfil the definition of an SAE (SO)
	Nocturnal hypoglycaemia	Hypoglycaemia between 23:00 and 06:00 (SO)
	Mild/moderate hypoglycaemia	Confirmed hypoglycaemia if plasma glucose was < 3.1 mmol/L and the individuals dealt with the episode themselves (SO)
	Socioeconomic effects	—
	HbA1c	ND (IO)
	Combined HbA1c and severe hypoglycaemia	Risk of severe hypoglycaemia adjusted for HbA1c (IO)
Porcellati 2004	All-cause mortality	ND (IO)
	Health-related quality of life	—
	Severe hypoglycaemia	Hypoglycaemia requiring external help (IO)
	Cardiovascular mortality	ND (IO)

(Continued)

	Non-fatal myocardial infarction	—
	Non-fatal stroke	—
	End-stage renal disease	—
	Blindness	—
	Serious adverse events	—
	Diabetic ketoacidosis	—
	Non-serious adverse events	—
	Nocturnal hypoglycaemia	Nocturnal episodes of hypoglycaemia were calculated from values measured at 03.00 h or any time between 01.00 and 07.30 h when participants awoke with symptoms suggestive of hypoglycaemia (SO)
	Mild/moderate hypoglycaemia	Hypoglycaemia was defined as any episode associated with measurement of blood glucose ≤ 4.0 mmol/L irrespective of symptoms. Hypoglycaemia was considered mild when the episodes were self-treated by the patients (SO)
	Socioeconomic effects	—
	HbA1c	ND (IO)
	Combined HbA1c and severe hypoglycaemia	—
PRESCHOOL	All-cause mortality	All-cause mortality (IO)
	Health-related quality of life	—
	Severe hypoglycaemia	Severe hypoglycaemia was defined as an event requiring assistance from another person, as a result of altered consciousness, to administer carbohydrate, glucagon or to take other actions (IO)
	Cardiovascular mortality	ND (IO)
	Non-fatal myocardial infarction	—
	Non-fatal stroke	—
	End-stage renal disease	—
	Blindness	—
	Serious adverse events	A serious adverse event is an experience that at any dose results in any of the following: • death • a life-threatening experience

(Continued)

		• in-participant hospitalisation or prolongation of existing hospitalisation • a persistent or significant disability/incapacity • a congenital anomaly/birth defect; • important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgement, they may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition[b] (IO)
	Diabetic ketoacidosis	Diabetic ketoacidosis (IO)
	Non-serious adverse events	An adverse event is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment[b] (SO)
	Nocturnal hypoglycaemia	Hypoglycaemia between 23:00 hours and 07:00 hours (SO)
	Mild/moderate hypoglycaemia	Composite hypoglycaemia rate consisting of (i) symptomatic hypoglycaemia episodes, which were recorded in patient diaries, then validated by study investigators; (ii) low CGM glucose excursions (< 3.9 mmol/L), which were confirmed by finger stick blood glucose < 3.9mmol/L 10 min before to 10 min after the low CGM excursion (i.e. confirmed low CGM); (iii) FSBG < 3.9 mmol/L, which was recorded ≥ 1 h from the end of a confirmed low CGM excursion (SO)
	Socioeconomic effects	—
	HbA1c	ND (IO)
	Combined HbA1c and severe hypoglycaemia	—
Ratner 2000	All-cause mortality	ND (IO)
	Health-related quality of life	Well-being Questionnaire[b] (SO)
	Severe hypoglycaemia	Symptomatic hypoglycaemia requiring third party assistance (IO)
	Cardiovascular mortality	One died secondary to cardiopulmonary arrest (IO)
	Non-fatal myocardial infarction	—
	Non-fatal stroke	—
	End-stage renal disease	—
	Blindness	—

(Continued)

	Serious adverse events	Events causing death, life-threatening, hospitalisations, medical intervention to prevent impairment (IO)
	Diabetic ketoacidosis	—
	Non-serious adverse events	The term adverse event covers any sign, symptom, syndrome, or illness that appears or worsens in a participant during the period of observation in the clinical study and that may impair the well-being of the participant, but do not meet the criteria of severeness (SO)
	Nocturnal hypoglycaemia	Hypoglycaemia occurring while asleep after the bedtime insulin dose and before the morning insulin dose and before the morning blood glucose measurement (SO)
	Mild/moderate hypoglycaemia	Hypoglycaemia was divided into 3 subsets; all events, severe hypoglycaemia and nocturnal hypoglycaemia (SO)
	Socioeconomic effects	Pharmacoeconomics was assessed throughout the treatment phase in terms of direct costs (volumes of health care resource utilisation) and indirect costs (time lost from work and other usual activities, and time lost by informal caregivers)[b] (SO, IO)
	HbA1c	ND (IO)
	Combined HbA1c and severe hypoglycaemia	—
Robertson 2007	All-cause mortality	No patients died (IO)
	Health-related quality of life	—
	Severe hypoglycaemia	Episodes requiring assistance from another person due to severe central nervous system dysfunction (IO)
	Cardiovascular mortality	No patients died (IO)
	Non-fatal myocardial infarction	—
	Non-fatal stroke	—
	End-stage renal disease	—
	Blindness	—
	Serious adverse events	A serious adverse event is an experience that at any dose results in any of the following: • death • a life-threatening experience • in-participant hospitalisation or prolongation of existing hospitalisation • a persistent or significant disability/incapacity • a congenital anomaly/birth defect

(Continued)

		• important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgement, they may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition[b] (IO)
	Diabetic ketoacidosis	Diabetic ketoacidosis (IO)
	Non-serious adverse events	An adverse event is any undesirable medical event occurring to a participant in a clinical study, whether or not related to the study product(s). A non-serious adverse event is any adverse event which does not fulfil the definition of a serious adverse event[b] (SO)
	Nocturnal hypoglycaemia	Hypoglycaemic between 22.00 (included) − 07.00 h (excluded) (SO)
	Mild/moderate hypoglycaemia	Self-treated episodes of hypoglycaemia with plasma glucose measurements < 3.1 mmol/L whether symptomatic or not[b] (SO)
	Socioeconomic effects	—
	HbA1c	ND (IO)
	Combined HbA1c and severe hypoglycaemia	Quote: "HbA 1c as a covariate, since there is an association between HbA1c and hypoglycaemia" (IO)
Russell-Jones 2004	All-cause mortality	No participants died (IO)
	Health-related quality of life	—
	Severe hypoglycaemia	Requiring third party assistance (from CSR: an episode with severe central nervous system symptoms consistent with hypoglycaemia in which the participant is unable to treat himself/herself and which has one of the following characteristics: Blood glucose < 2.8 mmol/L or reversal of symptoms after either food intake or glucagon/iv glucose administration) (IO)
	Cardiovascular mortality	No participants died (IO)
	Non-fatal myocardial infarction	—
	Non-fatal stroke	—
	End-stage renal disease	—
	Blindness	—
	Serious adverse events	Serious adverse events A serious adverse event is an experience that at any dose results in any of the following: • death • a life-threatening experience • in-participant hospitalisation or prolongation of existing hospitalisation • a persistent or significant disability/incapacity

(Continued)

		• a congenital anomaly/birth defect; • important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgement, they may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition[b] (IO)
	Diabetic ketoacidosis	—
	Non-serious adverse events	An adverse event is any undesirable medical event occurring to a participant in a clinical study, whether or not considered related to the study product(s). A non-serious adverse event is any adverse event that does not fulfil the definition of a serious adverse event[b] (SO)
	Nocturnal hypoglycaemia	Hypoglycaemia between 11 p.m. to 6 a.m. (SO)
	Mild/moderate hypoglycaemia	Minor if the blood glucose value was < 2.8 mmol/L and the patient dealt with the episode alone; and as symptoms only if no assistance was required and the event was not confirmed by a blood glucose measurement (SO)
	Socioeconomic effects	—
	HbA1c	ND (IO)
	Combined HbA1c and severe hypoglycaemia	—
Schober 2002	All-cause mortality	No patients died (IO)
	Health-related quality of life	—
	Severe hypoglycaemia	An event with symptoms consistent with hypoglycaemia in which the participant required assistance from another person, and which was associated with a blood glucose level below 2.8 mmol/L or prompt recovery after oral carbohydrate or iv glucose or glucagon administration[b](IO)
	Cardiovascular mortality	No patients died (IO)
	Non-fatal myocardial infarction	—
	Non-fatal stroke	—
	End-stage renal disease	—
	Blindness	—
	Serious adverse events	Adverse events were considered 'serious' because they either required hospitalisations, were life-threatening or medically important (quote: "If a symptomatic hypoglycaemic event led to hospitalisation or was considered life-threatening or medically important, it had to be reported as a serious adverse event") (IO)
	Diabetic ketoacidosis	Ketoacidosis (IO)

(Continued)

	Non-serious adverse events	Quote from CSR: "The term adverse event covers any sign, symptom, syndrome, or illness that appears or worsens in a participant during the period of observation in the clinical study and that may impair the well-being of the participant." (SO)
	Nocturnal hypoglycaemia	Nocturnal hypoglycaemia was defined as hypoglycaemia while the participant was sleeping between bedtime and after the evening injection and before getting up in the morning (SO)
	Mild/moderate hypoglycaemia	Hypoglycaemia was categorised as either symptomatic, i.e. with clinical symptoms that could be confirmed by blood glucose levels below 2.8 mmol/L, or asymptomatic, i.e. any event with a confirmed blood glucose level below 2.8 mmol/L but without any symptoms (SO)
	Socioeconomic effects	—
	HbA1c	ND (IO)
	Combined HbA1c and severe hypoglycaemia	—
Standl 2004	All-cause mortality	One participant died (IO)
	Health-related quality of life	Diabetes Health Profile[b](SO)
	Severe hypoglycaemia	Requiring third party assistance (IO)
	Cardiovascular mortality	—
	Non-fatal myocardial infarction	—
	Non-fatal stroke	—
	End-stage renal disease	—
	Blindness	—
	Serious adverse events	A serious adverse event is an experience that at any dose results in any of the following: • death • a life-threatening experience • in-participant hospitalisation or prolongation of existing hospitalisation • a persistent or significant disability/incapacity • a congenital anomaly/birth defect • important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgement, they may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition[b] (IO)
	Diabetic ketoacidosis	ND

(Continued)

	Non-serious adverse events	Adverse events were considered treatment-emergent if reported during treatment and not present beforehand, or if they increased in severity during treatment (SO)
	Nocturnal hypoglycaemia	Hypoglycaemia between 23:00 to 06:00 h (SO)
	Mild/moderate hypoglycaemia	If blood glucose was below 2.8 mmol/L and the patient handled the episode him- or herself (footnote: the study had an additional definition 'symptoms only' if not confirmed by BG measurement) (SO)
	Socioeconomic effects	—
	HbA1c	ND (IO)
	Combined HbA1c and severe hypoglycaemia	ND
SWITCH 1	All-cause mortality	All-cause death (IO, AO)
	Health-related quality of life	SF-36 v2 (SO)
	Severe hypoglycaemia	Episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions, neurological recovery following the return of plasma glucose to normal, or both (IO, AO)
	Cardiovascular mortality	ND
	Non-fatal myocardial infarction	All types of myocardial infarction: • Spontaneous myocardial infarction (including re-infarction) • Myocardial infarction secondary to ischaemia due to imbalance between oxygen demand and supplies • Percutaneous coronary intervention-related myocardial infarction (including myocardial infarction associated with stent thrombosis) • Coronary artery bypass graft surgery-related myocardial infarction • Silent myocardial infarction • Hospitalisation for unstable angina pectoris • All events with symptoms of myocardial ischaemia requiring hospitalisation (IO, AO)
	Non-fatal stroke	Cerebrovascular event is defined: Any acute episode of focal or global neurological dysfunction caused by brain, spinal cord or retinal vascular injury as a result of haemorrhage or infarction (IO, AO)
	End-stage renal disease	—
	Blindness	—
	Serious adverse events	A serious adverse event is an experience that at any dose results in any of the following: • death • a life-threatening experience • in-participant hospitalisation or prolongation of existing hospitalisation

(Continued)

		• a persistent or significant disability/incapacity • a congenital anomaly/birth defect • important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgement, they may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition[b] (IO)
	Diabetic ketoacidosis	—
	Non-serious adverse events	Any untoward medical occurrence in a participant administered a product, and which does not necessarily have a causal relationship with this treatment. A non-serious adverse event is any adverse event which does not fulfil the definition of a serious adverse event (SO)
	Nocturnal hypoglycaemia	Episodes between 12:01 a.m. and 5:59 a.m. (SO)
	Mild/moderate hypoglycaemia	Blood glucose ≤ 3.9 mmol/L or > 3.9 mmol/L when they occur in conjunction with hypoglycaemic symptoms, able to treat themselves (SO)
	Socioeconomic effects	Cost-effectiveness analysis/quality-adjusted life years (IO)
	HbA1c	ND (IO)
	Combined HbA1c and severe hypoglycaemia	Association between the individual patient-level risk of hypoglycaemia and HbA1c was investigated (IO)
Thalange 2013	All-cause mortality	All-cause mortality (IO)
	Health-related quality of life	—
	Severe hypoglycaemia	Severe hypoglycaemia was defined as episodes where the persons were semi-conscious, unconscious or in a coma, with or without convulsions (IO)
	Cardiovascular mortality	ND (IO)
	Non-fatal myocardial infarction	—
	Non-fatal stroke	—
	End-stage renal disease	—
	Blindness	—
	Serious adverse events	Serious adverse events were defined as, amongst others, a life-threatening experience, inpatient hospitalisations or prolongation of existing hospitalisations, a persistent or significant disability/incapacity or death (IO)
	Diabetic ketoacidosis	Diabetic ketoacidosis (IO)
	Non-serious adverse events	Any undesirable medical event occurring to a participant in a clinical study, whether or not related to the study product(s) (SO)
	Nocturnal hypoglycaemia	Nocturnal if they occurred between 22:00 and 07:00 h (SO)

(Continued)

	Mild/moderate hypoglycaemia	Mild hypoglycaemia was defined as episodes where the participants were able to treat themselves. Moderate hypoglycaemia was categorised as episodes where participants required assistance, but responded to oral treatment (SO)
	Socioeconomic effects	—
	HbA1c	ND
	Combined HbA1c and severe hypoglycaemia	—
Urakami 2017	All-cause mortality	—
	Health-related quality of life	—
	Severe hypoglycaemia	Severe hypoglycaemia is defined as an event associated with impaired consciousness or seizure (IO)
	Cardiovascular mortality	Cardiovascular mortality (IO)
	Non-fatal myocardial infarction	Non-fatal myocardial infarction (IO)
	Non-fatal stroke	Non-fatal stroke (IO)
	End-stage renal disease	End-stage renal disease (IO)
	Blindness	Blindness (IO)
	Serious adverse events	Serious adverse events (IO)
	Non-serious adverse events	Non-serious adverse events (SO)
	Nocturnal hypoglycaemia	Hypoglycaemia occurring between 22:00 h – 06:59 h. Nocturnal hypoglycaemia was defined as when the person noted symptoms of hypoglycaemia with self-monitored plasma glucose levels < 70 mg/dL (SO)
	Mild/moderate hypoglycaemia	Hypoglycaemia was defined as a self-monitored plasma glucose level < 3.9 mmol/L (SO)
	Socioeconomic effects	—
	HbA1c	ND (IO)
	Combined HbA1c and severe hypoglycaemia	—
Vague 2003	All-cause mortality	No patients died (IO)
	Health-related quality of life	—
	Severe hypoglycaemia	Hypoglycaemic episode with severe central nervous system symptoms consistent with hypoglycaemia, in which the participant was unable to treat

(Continued)

	himself/herself and which had one of the following characteristics: blood glucose recorded as < 2.8 mmol/L or symptom reversal achieved with food, glucose or glucagon (IO)
Cardiovascular mortality	—
Non-fatal myocardial infarction	—
Non-fatal stroke	—
End-stage renal disease	—
Blindness	—
Serious adverse events	Serious adverse events if resulting in a fatal or life-threatening illness, prolonged significant disability, hospitalisations or prolongation of hospitalisations (IO)
Diabetic ketoacidosis	—
Non-serious adverse events	An adverse event was defined as an undesirable medical incident occurring during the study, irrespective of its relation to study products (SO)
Nocturnal hypoglycaemia	Hypoglycaemia between 23:00 to 06:00 (SO)
Mild/moderate hypoglycaemia	Minor if blood glucose was < 2.8 mmol/L and the patients dealt with the episode themselves (in addition according to CSR: any asymptomatic blood glucose measurement) (SO)
Socioeconomic effects	—
HbA1c	ND (IO)
Combined HbA1c and severe hypoglycaemia	HbA1c adjustment and risk of severe hypoglycaemia (IO)

—: denotes not reported
[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).
[b]Definition of outcome from clinical study report.
[c]Converted from mg/dL to mmol/L from https://www.diabetes.co.uk/blood-sugar-converter.html).

AE: adverse events; **a.m.:** ante meridiem; **BG**: blood glucose**; CGM:** continuous glucose monitoring;**CSR:** clinical study report; **FSBG**: finger stick blood glucose; **HbA1c:** glycosylated haemoglobin A1c; **iv**: intravenous; **ND**: not defined; **p.m.**: post meridiem; **SAE:** serious adverse events; **sc**: subcutaneous; **SF-36:** short-form 36; **SMPG**: self-monitored plasma glucose; **W-BQ:** well-being questionnaire.

Appendix 15. Adverse events (I)

Study ID	Intervention(s) and comparator(s)	Participants included in analysis (n)	Deaths (n)	Deaths (% of participants)	Participants with at least one adverse event (n)	Participants with at least one adverse event (%)	Participants with at least one severe/serious adverse event (n)	Participants with at least one severe/serious adverse event (%)
Bartley 2008	I: detemir	331	4	1.2	265[a]	80.1	50[a]	15.1
	C: NPH	164	0	0	135	82.3	27	16.5
BEGIN Basal-Bolus Type 1	I: degludec	472	2	0.2	397	84.1	49	10
	C: glargine	155	1	0.6	128	83.1	17	11
BEGIN Flex T1	I: degludec	165	1[b]	0.6	125	75.8	7	4.2
	C: glargine	161	0	0	161	72.0	8	5.0
BEGIN Young	I: degludec	174	0	0	161	92.5	18	10.3
	C: detemir	175	0	0	157	89.7	16	9.1
Bolli 2009	I: glargine	90	—	—	19	22.3	2	2.2
	C: NPH	85	—	—	13	15.1	0	0
Chase 2008	I: glargine	85	0	0	71[b]	83.5	18	21.2
	C: NPH/Lente	90	0	0	67	74.4	7	7.8
Davies 2014	I: degludec	301	0	0	216	71.2	23	7
	C: detemir	152	0	0	112	73.7	8	5
Fulcher 2005	I: glargine	62	0	0	57	91.9	5[b]	8.1
	C: NPH	63	0	0	56	88.9	3	4.8

(Continued)

Heller 2009	I: detemir	299	0[b]	0	277	92.6	35	11.7
	C: glargine	144	1	0.7	129	89.6	7	4.9
Home 2005	I: glargine	292	0[b]	0	192[b]	65.8	26[c]	9.0
	C: NPH	293	0	0	185	63.1	29	10.0
Kobayashi 2007	I: detemir	196	0[b]	0	173[b]	88.3	13	6.6
	C: NPH	98	0	0	87[b]	88.8	10[b]	10.2
Liu 2016	I: glargine	107	0	0	81	75.7	3	2.8
	C: NPH	54	0	0	44	81.5	6	11.1
NCT00595374 [b]	I: detemir	75	0	0	60	80.0	4	5.3
	C: NPH	38	0	0	29	76.3	1	2.6
NCT00605137 [b]	I: detemir	55	0	0	36	83.6	3	5.5
	C: NPH	27	0	0	23	85.2	1	3.7
Pieber 2007	I: detemir	161	0[b]	0	117[b]	72.7	14	8.7
	C: glargine	159	0	0	121	76.1	11	6.9
Porcellati 2004	I: glargine	61	0	0	—	—	—	—
	C: NPH	60	0	0	—	—	—	—
PRESCHOOL	I: glargine	62	0	0	30	48.4	8[b]	12.9
	C: NPH	63	0	0	33	52.4	2	3.2
Ratner 2000	I: glargine	264	0[b]	0	223	84.5	33[b]	12.5
	C: NPH	270	1	0.4	234	86.7	37	13.7
Robertson 2007	I: detemir	232	0[b]	0	202	87.0	24[b]	10

(Continued)

	C: NPH	115	0	0	104	90.0	10	9
Russell-Jones 2004	I: detemir	491	0[b]	0	361[b]	73.5	26[b]	5.3
	C: NPH	256	0	0	183	71.5	11	4.3
Schober 2002	I: glargine	174	0[b]	0	109	62.6	10	5.7
	C: NPH	175	0	0	105	60.0	24	13.7
Standl 2004	I: detemir	236	1[b]	0.4	164[b]	69.5	17[b]	7.2
	C: NPH	224	0	0	156	69.6	18	8.0
SWITCH 1 [d]	I: degludec	249	—	—	—	—	—	—
	C: glargine	251	—	—	—	—	—	—
Thalange 2013	I: detemir	177	0	0	132	74.6	14	7.9
	C: NPH	170	0	0	135	79.4	20	11.7
Urakami 2017	I: degludec	9	—	—	0	0	0	0
	C: glargine	9	—	—	0	0	0	0
Vague 2003	I: detemir	301	0[b]	0	219	72.7	14[b]	4.7
	C: NPH	146	0	0	112	76.8	4	2.7

—: denotes not reported

[a]Data from CSR. In publication, exact number was no stated. For adverse events, it was stated that adverse events were about 80% in both groups; in publication, it was reported that serious adverse events were reported for about 15%–17%.
[b]Data from CSR/synopsis.
[c]Data from CSR. The publication stated that 53 participants in total experienced serious adverse events - this number does not completely apply when calculating the percentage.
[d]No data for this adverse events table was reported before cross-over.

C: comparator; **CSR**; clinical study report; **I**: intervention; **N**: number of participants; **NPH**: neutral protamine Hagedorn.

Appendix 16. Adverse events (II)

Study ID	Intervention(s) and comparator(s)	Participants included in analysis (n)	Participants discontinuing study due to an adverse event (n)	Participants discontinuing study due to an adverse event (%)	Participants with at least one hospitalisation (n)	Participants with at least one hospitalisation (%)	Participants with at least one outpatient treatment (n)	Participants with at least one outpatient treatment (%)
Bartley 2008	I: detemir	331	13[a]	3.9	—	—	—	—
	C: NPH	164	1	0.6	—	—	—	—
BEGIN Basal-Bolus Type 1	I: degludec	472	12	2.5	—	—	—	—
	C: glargine	157	2	1.3	—	—	—	—
BEGIN Flex T1	I: degludec	165	4	2.4	—	—	—	—
	C: glargine	161	1	0.6	—	—	—	—
BEGIN Young	I: degludec	174	2	1.1	—	—	—	—
	C: detemir	175	0	0	—	—	—	—
Bolli 2009	I: glargine	90	0	0	—	—	—	—
	C: NPH	85	0	0	—	—	—	—
Chase 2008	I: glargine	85	1	1.2	—	—	—	—
	C: NPH/Lente	90	2	2.2	—	—	—	—
Davies 2014	I: degludec	301	3	1.0	—	—	—	—
	C: detemir	152	1	0.7	—	—	—	—
Fulcher 2005	I: glargine	62	0[b]	0	6[b]	9.7	37[b]	59.7
	C: NPH	63	1	1.6	4	6.3	31	49.2
Heller 2009	I: detemir	299	6	2.0	—	—	—	—

(Continued)

	C: glargine	144	4	2.8	—	—	—	—
Home 2005	I: glargine	292	2	0.7	3[b]	1.0	131[b]	45.6
	C: NPH	293	2	0.7	3	1.0	118	41.7
Kobayashi 2007	I: detemir	197	3	1.5	—	—	—	—
	C: NPH	99	1	1.0	—	—	—	—
Liu 2016	I: glargine	107	0	0	—	—	—	—
	C: NPH	55	1	1.8	—	—	—	—
NCT00595374	I: detemir	75	—	—	—	—	—	—
	C: NPH	38	—	—	—	—	—	—
NCT00605137	I: detemir	55	0	0	—	—	—	—
	C: NPH	27	0	0	—	—	—	—
Pieber 2007	I: detemir	161	3	1.9	—	—	—	—
	C: glargine	159	1	0.6	—	—	—	—
Porcellati 2004	I: glargine	61	0	0	—	—	—	—
	C: NPH	60	0	0	—	—	—	—
PRESCHOOL	I: glargine	61	0	0	—	—	—	—
	C: NPH	64	2	3.1	—	—	—	—
Ratner 2000	I: glargine	264	8	3.0	7[b]	2.7	28[c]	10.6
	C: NPH	270	1	0.4	11	4.1	28	10.4
Robertson 2007	I: detemir	232	1	0.4	—	—	—	—
	C: NPH	115	0	0	—	—	—	—

(Continued)

Russell-Jones 2004	I: detemir	491	5	1.0	—	—	—	—
	C: NPH	256	2	0.8	—	—	—	—
Schober 2002	I: glargine	174	0[b]	0	12[d]	7.2	75[d]	44.9
	C: NPH	175	0	0	25	14.7	81	47.7
Standl 2004	I: detemir	236	5[b]	2.1	—	—	—	—
	C: NPH	224	2	0.9	—	—	—	—
SWITCH 1	I: degludec	249	5[e]	2.0	—			
	C: glargine	251	5	2.0				
Thalange 2013	I: detemir	177	1	0.6	—	—	—	—
	C: NPH	171	0	0	—	—	—	—
Urakami 2017	I: degludec	9	—	—	—	—	—	—
	C: glargine	9	—	—	—	—	—	—
Vague 2003	I: detemir	301	2	0.7	—	—	—	—
	C: NPH	146	0	0	—	—	—	—

—: denotes not reported

[a]Reasons for withdrawals described in CSR.
[b]Data available from CSR/synopsis.
[c]From CSR: reported as medically important/required medical intervention.
[d]Data from CSR: in the glargine group, 167 participants were included, in the NPH group, 170 participants.
[e]Reported before cross-over.

C: comparator; **CSR**: clinical study report; **I**: intervention; **N**: number of participants; **NPH**: neutral protamine Hagedorn.

Appendix 17. Adverse events (III)

Study ID	Intervention(s) and comparator(s)	Participants included in analysis (n)	Participants with a specific adverse event (description)	Participants with at least one specific adverse event (n)	Participants with at least one specific adverse event (%)
Bartley 2008	I: detemir	331	(1) Upper respiratory tract infection[a]	(1) 69	(1) 20.8
			(2) Nasopharyngitis	(2) 59	(2) 17.8
			(3) Influenza	(3) 46	(3) 13.9
			(4) Urinary tract infection	(4) 19	(4) 5.7
			(5) Pharyngitis	(5) 19	(5) 5.7
			(6) Gastroenteritis	(6) 17	(6) 5.1
			(7) Diabetic retinopathy	(7) 26	(7) 7.9
			(8) Diarrhoea	(8) 20	(8) 6.0
			(9) Headache	(9) 19	(9) 5.7
			(10) Pharyngolaryngeal pain	(10) 17	(10) 5.1
			(11) Application site disorder	(11) 19	(11) 5.7
	C: NPH	164	(1) Upper respiratory tract infection	(1) 28	(1) 17.1
			(2) Nasopharyngitis	(2) 37	(2) 22.6
			(3) Influenza	(3) 21	(3) 12.8
			(4) Urinary tract infection	(4) 9	(4) 5.5
			(5) Pharyngitis	(5) 10	(5) 6.1
			(6) Gastroenteritis	(6) 13	(6) 7.9
			(7) Diabetic retinopathy	(7) 16	(7) 9.8
			(8) Diarrhoea	(8) 9	(8) 5.5
			(9) Headache	(9) 13	(9) 7.9
			(10) Pharyngolaryngeal pain	(10) 8	(10) 4.9
			(11) Application site disorder	(11) 10	(11) 6.1
BEGIN Basal-Bolus Type 1	I: degludec	472	(1) Infections and infestations[b]	(1) 292	(1) 61.9
			(2) Gastrointestinal disorders	(2) 105	(2) 22.2
			(3) Nervous system disorders	(3) 94	(3) 19.9
			(4) Injury, poisoning and procedural complications	(4) 99	(4) 21.0
				(5) 90	(5) 19.1
			(5) Musculoskeletal and connective tissue disorders	(6) 80	(6) 16.9
				(7) 83	(7) 17.6

(Continued)

		(6) Respiratory, thoracic and mediastinal disorders (7) Metabolism and nutrition disorders (8) General disorders and administration site conditions (9) Skin and subcutaneous tissue disorders (10) Eye disorders (11) Cardiovascular disorders (12) Psychiatric disorders (13) Investigations (14) Immune system disorders (15) Renal and urinary disorders (16) Ear and labyrinth disorders (17) Reproductive system and breast disorders (18) Endocrine disorders (19) Blood and lymphatic system disorders (20) Neoplasms benign, malignant, and unspecified (including cysts and polyps) (21) Surgical and medical procedures (22) Hepatobiliary disorders (23) Congenital, familial and genetic disorders	(8) 57 (9) 43 (10) 38 (11) 24 (12) 25 (13) 20 (14) 11 (15) 12 (16) 10 (17) 10 (18) 6 (19) 5 (20) 3 (21) 2 (22) 1 (23) 0	(8) 12.1 (9) 9.1 (10) 6.1 (11) 5.1 (12) 5.3 (13) 4.2 (14) 2.3 (15) 2.5 (16) 2.1 (17) 2.1 (18) 1.3 (19) 1.1 (20) 0.6 (21) 0.4 (22) 0.4 (23) 0
C: glargine	154	(1) Infections and infestations (2) Gastrointesinal disorders (3) Nervous system disorders (4) Injury, poisoning and procedural complications (5) Musculoskeletal and connective tissue disorders (6) Respiratory, thoracic and mediastinal disorders (7) Metabolism and nutrition disorders (8) General disorders and administration site conditions (9) Skin and subcutaneous tissue disorders	(1) 97 (2) 33 (3) 39 (4) 31 (5) 31 (6) 29 (7) 20 (8) 23 (9) 16 (10) 10 (11) 7 (12) 6	(1) 63.0 (2) 21.4 (3) 25.3 (4) 20.1 (5) 20.1 (6) 18.8 (7) 13.0 (8) 14.9 (9) 10.4 (10) 6.5 (11) 4.5 (12) 3.9

(Continued)

			(10) Eye disorders	(13) 6	(13) 3.9
			(11) Cardiovascular disorders	(14) 11	(14) 7.1
			(12) Psychiatric disorders	(15) 4	(15) 2.6
			(13) Investigations	(16) 3	(16) 1.9
			(14) Immune system disorders	(17) 2	(17) 1.3
			(15) Renal and urinary disorders	(18) 1	(18) 0.6
			(16) Ear and labyrinth disorders	(19) 1	(19) 0.6
			(17) Reproductive system and breast disorders	(20) 3	(20) 1.9
			(18) Endocrine disorders	(21) 1	(21) 0.6
			(19) Blood and lymphatic system disorders	(22) 1	(22) 0.6
			(20) Neoplasms benign, malignant, and unspecified (inclusive cysts and polyps)	(23) 1	(23) 0.6
			(21) Surgical and medical procedures		
			(22) Hepatobiliary disorders		
			(23) Congenital, familial and genetic disorders		
BEGIN Flex T1	I: degludec	165	(1) Gastroenteritis[a]	(1) 9	(1) 5.5
			(2) Nasopharyngitis	(2) 43	(2) 26.1
			(3) Sinusitis	(3) 10	(3) 6.1
			(4) Upper respiratory tract infections	(4) 9	(4) 5.5
			(5) Headache	(5) 16	(5) 9.7
			(6) Diarrhoea	(6) 1	(6) 0.6
			(7) Nausea	(7) 7	(7) 4.2
			(8) Vomiting	(8) 9	(8) 5.5
			(9) Cough	(9) 4	(9) 2.4
			(10) Oropharyngeal pain	(10) 11	(10) 6.7
			(11) Wrong drug administered	(11) 9	(11) 5.5
			(12) Injection-site reactions	(12) 3	(12) 1.8
	C: glargine	161	(1) Gastroenteritis	(1) 5	(1) 3.1
			(2) Nasopharyngitis	(2) 29	(2) 18
			(3) Sinusitis	(3) 7	(3) 4.3
			(4) Upper respiratory tract infections	(4) 13	(4) 8.1
			(5) Headache	(5) 18	(5) 11.2
			(6) Diarrhoea	(6) 9	(6) 5.6

(Continued)

			(7) Nausea	(7) 8	(7) 5.0
			(8) Vomiting	(8) 5	(8) 3.1
			(9) Cough	(9) 10	(9) 6.2
			(10) Oropharyngeal pain	(10) 11	(10) 6.8
			(11) Wrong drug administered	(11) 7	(11) 4.3
			(12) Injection-site reactions	(12) 4	(12) 2.5
BEGIN Young	I: degludec	174	(1) Ear pain[a,b]	(1) 10	(1) 5.8
			(2) Abdominal pain	(2) 12	(2) 6.9
			(3) Abdominal upper pain	(3) 28	(3) 16.1
			(4) Diarrhoea	(4) 22	(4) 12.6
			(5) Nausea	(5) 13	(5) 7.5
			(6) Vomiting	(6) 26	(6) 14.9
			(7) Pyrexia	(7) 30	(7) 17.2
			(8) Bronchitis	(8) 9	(8) 5.2
			(9) Ear infection	(9) 9	(9) 5.2
			(10) Viral gastroenteritis	(10) 15	(10) 8.6
	C: detemir	175	(1) Ear pain	(1) 5	(1) 2.9
			(2) Abdominal pain	(2) 8	(2) 4.6
			(3) Abdominal upper pain	(3) 17	(3) 9.7
			(4) Diarrhoea	(4) 17	(4) 9.7
			(5) Nausea	(5) 9	(5) 5.1
			(6) Vomiting	(6) 22	(6) 12.6
			(7) Pyrexia	(7) 28	(7) 16.0
			(8) Bronchitis	(8) 8	(8) 4.6
			(9) Ear infection	(9) 11	(9) 6.3
			(10) Viral gastroenteritis	(10) 22	(10) 12.6
Bolli 2009	I: glargine	90	—	—	—
	C: NPH	85	—	—	—
Chase 2008	I: glargine	85	—	—	—
	C: NPH/Lente	90	—	—	—
Davies 2014	I: degludec	301	(1) Eye disorder[a,b]	(1) 20	(1) 6.6
			(2) Gastrointestinal disorders	(2) 20	(2) 6.6
			(3) Nasopharyngitis	(3) 94	(3) 31.2

(Continued)

			(4) Metabolism and nutrition disorders	(4) 15	(4) 5.0
			(5) Nervous system disorders	(5) 21	(5) 7.0
			(6) Musculoskeletal disorders	(6) 42	(6) 14.0
			(7) Respiratory disorders	(7) 21	(7) 7.0
	C: detemir	152	(1) Eye disorder	(1) 7	(1) 4.6
			(2) Gastrointestinal disorders	(2) 9	(2) 5.9
			(3) Infections	(3) 49	(3) 32.2
			(4) Metabolism and nutrition disorders	(4) 11	(4) 7.2
			(5) Nervous system disorders	(5) 5	(5) 3.3
			(6) Musculoskeletal disorders	(6) 12	(6) 7.9
			(7) Respiratory disorders	(7) 8	(7) 5.3
Fulcher 2005	I: glargine	62	(1) Upper respiratory tract infections[a, c]	(1) 4	(1) 7.2
			(2) Infections	(2) 4	(2) 7.2
			(3) Rhinitis	(3) 7	(3) 7.2
			(4) Headache	(4) 6	(4) 9.8
			(5) Diarrhoea	(5) 3	(5) 4.3
			(6) Injection site pain/reactions	(6) 5	(6) 8.1
			(7) Ecchomysis	(7) 5	(7) 8.1
			(8) Sore throat	(8) 4	(8) 6.5
			(9) Flu syndrome	(9) 7	(9) 11.3
			(10) Nausea	(10) 6	(10) 9.7
	C: NPH	63	(1) Upper respiratory tract infections	(1) 7	(1) 11.2
			(2) Infections	(2) 4	(2) 6.2
			(3) Rhinitis	(3) 3	(3) 5.4
			(4) Headache	(4) 3	(4) 4.2
			(5) Diarrhoea	(5) 1	(5) 0.8
			(6) Injection site pain/reactions	(6) 7	(6) 11.1
			(7) Ecchomysis	(7) 8	(7) 12.7
			(8) Sore throat	(8) 7	(8) 11.1
			(9) Flu syndrome	(9) 7	(9) 11.1
			(10) Nausea	(10) 6	(10) 9.5
Heller 2009	I: detemir	299	(1) Injection site reaction[a]	(1) 24	(1) 8
			(2) Headache	(2) 66	(2) 22.1

(Continued)

			(3) Pharyngolaryngeal pain	(3) 159	(3) 53.2
			(4) Arthralgia	(4) 16	(4) 5.4
	C: glargine	144	(1) Injection site reaction	(1) 2	(1) 1.4
			(2) Headache	(2) 27	(2) 18.8
			(3) Pharyngolaryngeal pain	(3) 70	(3) 48.6
			(4) Arthralgia	(4) 0	(4) 0
Home 2005	I: glargine	292	(1) Injection site mass[a]	(1) 8	(1) 3
			(2) Injection site reaction	(2) 3	(2) 1
			(3) Respiratory system	(3) 77	(3) 35.2
	C: NPH	293	(1) Injection site mass	(1) 9	(1) 3
			(2) Injection site reaction	(2) 6	(2) 2
			(3) Respiratory system	(3) 79	(3) 27.0
Kobayashi 2007	I: detemir	197	(1) Metabolism and nutrition disorder[a]	(1) 8	(1) 4.1
			(2) Infections and infestations	(2) 4	(2) 2.0
			(3) Respiratory, thoracic and mediastinal disorders	(3) 2	(3) 1.0
				(4) 1	(4) 0.5
			(4) Injury, poisoning, procedural disorders	(5) 1	(5) 0.5
			(5) Nervous system disorder		
	C: NPH	99	(1) Metabolism and nutrition disorder	(1) 1	(1) 1.0
			(2) Infections and infestations	(2) 1	(2) 1.0
			(3) Respiratory, thoracic and mediastinal disorders	(3) 0	(3) 0.0
				(4) 4	(4) 4.1
			(4) Injury, poisoning, procedural disorders	(5) 2	(5) 2.0
			(5) Nervous system disorder		
Liu 2016	I: glargine	107	(1) Respiratory, thoracic and mediastinal disorders[a]	(1) 3	(1) 2.8
				(2) 74	(2) 69.2
			(2) Hypoglycaemia	(3) 28	(3) 26.2
			(3) Nasopharyngitis	(4) 18	(4) 16.8
			(4) Upper respiratory tract infection		
	C: NPH	54	(1) Respiratory, thoracic and mediastinal disorders	(1) 3	(1) 5.6
				(2) 41	(2) 75.9
			(2) Hypoglycaemia	(3) 17	(3) 31.5
			(3) Nasopharyngitis	(4) 11	(4) 20.4

(Continued)

			(4) Upper respiratory tract infection		
NCT00595374	I: detemir	75	—	—	—
	C: NPH	38	—	—	—
NCT00605137	I: detemir	55	(1) Infections and infestations	(1) 29	(1) 52.7
			(2) Increased albumin/creatinine ratio	(2) 3	(2) 5.5
	C: NPH	27	(1) Infections and infestations	(1) 14	(1) 51.9
			(2) Increased albumin/creatinine ratio	(2) 1	(2) 3.7
Pieber 2007	I: detemir	161	(1) Respiratory system disorder[a]	(1) 53	(1) 36
			(2) Gastrointestinal system disorder	(2) 33	(2) 20.5
			(3) Headache	(3) 23	(3) 14.3
			(4) Skin and appendages disorder	(4) 6	(4) 3.7
	C: glargine	159	(1) Respiratory system disorder	(1) 67	(1) 42.1
			(2) Gastrointestinal system disorder	(2) 30	(2) 18.9
			(3) Headache	(3) 31	(3) 19.5
			(4) Skin and appendages disorder	(4) 9	(4) 5.7
Porcellati 2004	I: glargine	61	—	—	—
	C: NPH	60	—	—	—
PRESCHOOL	I: glargine	62	(1) Vomiting[b,c]	(1) 5	(1) 8.1
			(2) Device lead damage	(2) 5	(2) 8.1
			(3) Pyrexia	(3) 3	(3) 4.8
			(4) Gastroenteritis	(4) 6	(4) 9.7
			(5) Nasopharyngitis	(5) 6	(5) 9.7
			(6) Pharyngitis	(6) 6	(6) 9.7
			(7) Upper respiratory tract infection	(7) 4	(7) 6.5
			(8) Bronchitis	(8) 3	(8) 4.8
			(9) Otitis media	(9) 1	(9) 1.6
			(10) Tonsilitis	(10) 1	(10) 2.6
			(11) Cough	(11) 2	(11) 3.2
	C: NPH	63	(1) Vomiting	(1) 4	(1) 6.4
			(2) Device lead damage	(2) 2	(2) 3.2
			(3) Pyrexia	(3) 7	(3) 11.1
			(4) Gastroenteritis	(4) 6	(4) 9.5

(Continued)

			(5) Nasopharyngitis	(5) 5	(5) 7.9
			(6) Pharyngitis	(6) 2	(6) 3.2
			(7) Upper respiratory tract infection	(7) 6	(7) 9.5
			(8) Bronchitis	(8) 5	(8) 7.9
			(9) Otitis media	(9) 4	(9) 6.4
			(10) Tonsilitis	(10) 4	(10) 6.4
			(11) Cough	(11) 4	(11) 6.4
Ratner 2000	I: glargine	264	(1) Injection site reaction[a]	(1) 40	(1) 15.2
			(2) Respiratory system	(2) 123	(2) 46.6
			(3) Body as whole	(3) 90	(3) 34.1
			(4) Digestive system	(4) 60	(4) 22.7
			(5) Nervous system	(5) 43	(5) 16.3
			(6) Metabolic and nutritional disorder	(6) 33	(6) 12.5
			(7) Cardiovascular system	(7) 32	(7) 12.1
			(8) Muscoskeletal system	(8) 28	(8) 10.6
			(9) Special senses	(9) 27	(9) 10.2
			(10) Urogenital systems	(10) 19	(10) 7.2
			(11) Lymphatic systems	(11) 6	(11) 2.3
			(12) Endocrine system	(12) 4	(12) 1.5
	C: NPH	270	(1) Injection site reaction	(1) 28	(1) 10.4
			(2) Respiratory system	(2) 139	(2) 51.5
			(3) Body as whole	(3) 112	(3) 41.5
			(4) Digestive system	(4) 71	(4) 26.3
			(5) Nervous system	(5) 50	(5) 18.5
			(6) Metabolic and nutritional disorder	(6) 41	(6) 15.2
			(7) Cardiovascular system	(7) 41	(7) 15.2
			(8) Muscoskeletal system	(8) 45	(8) 16.7
			(9) Special senses	(9) 26	(9) 9.6
			(10) Urogenital systems	(10) 32	(10) 11.9
			(11) Lymphatic systems	(11) 8	(11) 3.0
			(12) Endocrine system	(12) 4	(12) 1.5
Robertson 2007	I: detemir	232	(1) Injection site reaction[a]	(1) 8	(1) 2.4
			(2) Respiratory system disorder	(2) 134	(2) 57.8
			(3) Gastrointestinal system disorder	(3) 91	(3) 39.2

(Continued)

			(4) Headache	(4) 72	(4) 31.2
			(5) Influenza-like symptoms	(5) 32	(5) 13.8
	C: NPH	115	(1) Injection site reaction	(1) 2	(1) 1.7
			(2) Respiratory system disorder	(2) 64	(2) 55.7
			(3) Gastrointestinal system disorder	(3) 43	(3) 37.4
			(4) Headache	(4) 37	(4) 32.2
			(5) Influenza-like symptoms	(5) 24	(5) 20.9
Russell-Jones 2004	I: detemir	491	(1) Respiratory system disorder[a]	(1) 179	(1) 36.5
			(2) Headache	(2) 108	(2) 22
			(3) Gastrointestinal system disorder	(3) 107	(3) 21.8
			(4) Influenza-like symptoms	(4) 37	(4) 7.5
	C: NPH	256	(1) Respiratory system disorder	(1) 77	(1) 30.1
			(2) Headache	(2) 58	(2) 22.7
			(3) Gastrointestinal system disorder	(3) 56	(3) 21.9
			(4) Influenza-like symptoms	(4) 15	(4) 5.9
Schober 2002	I: glargine	174	(1) Injection site reaction[a]	16	9.2
	C: NPH	175	(1) Injection site reaction	15	8.6
Standl 2004	I: detemir	236	(1) Respiratory tract disorder[a]	(1) 89	(1) 37.7
			(2) Headache	(2) 60	(2) 25.4
			(3) Diarrhoea	(3) 16	(3) 6.9
			(4) Accidental injury	(4) 6	(4) 2.5
			(5) Skin and appendages disorder	(5) 5	(5) 2.1
	C: NPH	224	(1) Respiratory tract disorder	(1) 73	(1) 32.6
			(2) Headache	(2) 48	(2) 21.4
			(3) Diarrhoea	(3) 15	(3) 6.7
			(4) Accidental injury	(4) 12	(4) 5.4
			(5) Skin and appendages disorder	(5) 17	(5) 7.6
SWITCH 1 [d]	I: degludec	—	—	—	—
	C: glargine	—	—	—	—
Thalange 2013	I: detemir	177	(1) Nasopharyngitis (2) Pharyngitis (3) Upper respiratory tract infection (4) Headache (5) Gastroenteritis	(1) 75 (2) 19 (3) 18	(1) 42.4 (2) 10.7 (3) 10.2

(Continued)

			(6) Influenza	(4) 26	(4) 14.7
				(5) 18	(5) 10.2
				(6) 10	(6) 5.6
	C: NPH	170	(1) Nasopharyngitis (2) Pharyngitis (3) Upper respiratory tract infection (4) Headache (5) Gastroenteritis (6) Influenza	(1) 81 (2) 15 (3) 16 (4) 23 (5) 14 (6) 18	(1) 47.6 (2) 8.8 (3) 9.4 (4) 13.5 (5) 8.2 (6) 10.6
Urakami 2017	I: degludec	9	—	—	—
	C: glargine	9	—	—	—
Vague 2003	I: detemir	301	(1) Respiratory system disorders[a] (2) Central and peripheral nervous system disorder (3) Gastrointestinal system disorder (4) Back pain (5) Skin and appendages disorder	(1) 97 (2) 69 (3) 62 (4) 17 (5) 21	(1) 32.2 (2) 22.9 (3) 20.6 (4) 5.6 (5) 7.0
	C: NPH	146	(1) Respiratory system disorders (2) Central and peripheral nervous system disorder (3) Gastrointestinal system disorder (4) Back pain (5) Skin and appendages disorder	(1) 51 (2) 36 (3) 31 (4) 6 (5) 2	(1) 34.9 (2) 24.7 (3) 21.2 (4) 4.1 (5) 1.4

—: denotes not reported

[a]From CSR (a very detailed description available from CSR).
[b]Detailed description available at ClinicalTrials.gov.
[c]Number varies from publication and CSR. Quote: "The most frequently reported AEs were upper respiratory tract infections (glargine: 7.2%; NPH: 11.2%), infections (glargine: 7.2%; NPH: 6.2%) and rhinitis (glargine: 7.2%; NPH: 5.4%)." Quote from CSR: " Most patients in both treatment groups suffered from upper respiratory tract infections (glargine: 24%, NPH: 32%)".
[d]None of the information for this adverse events table was reported before cross-over.

C: comparator; **CSR**: clinical study report; **I**: intervention; **N**: number of participants; **NPH**: neutral protamine Hagedorn.

Appendix 18. Adverse events (IV)

Study ID	Intervention(s) and comparator(s)	Participants included in analysis (n)	Participants with at least one hypoglycaemic episode (n)	Participants with at least one hypoglycaemic episode (%)	Participants with at least one nocturnal hypoglycaemic episode (n)	Participants with at least one nocturnal hypoglycaemic episode (% participants)	Participants with at least one severe/serious hypoglycaemic episode (n)	Participants with at least one severe/serious hypoglycaemic episode (%)
Bartley 2008	I: detemir	331	309	93.4	237	71.6	49	14.8
	C: NPH	164	159	97.0	124	75.6	42	25.6
BEGIN Basal-Bolus Type 1	I: degludec	472	451	96	341	72	58[a]	12
	C: glargine	154	147	95	114	74	16	10
BEGIN Flex T1	I: degludec	165	164	99.4	121	73.3	21	12.7
	C: glargine	161	156	96.9	117	72.6	16	9.9
BEGIN Young	I: degludec	174	171	98.3	133	76.4	31	17.8
	C: detemir	175	168	96.0	125	71.4	24	13.8
Bolli 2009	I: glargine	90	—	—	—	—	—	—
	C: NPH	85	—	—	—	—	—	—
Chase 2008	I: glargine	85	85	100	55[a]	64.7	9	10.6
	C: NPH/Lente	90	88	97.8	61	67.8	4	4.4
Davies 2014	I: degludec	301	280	93.0	176	58.5	32	10.6
	C: detemir	152	139	91.4	89	58.6	16	10.5
Fulcher 2005	I: glargine	62	62[a]	100	50	81	13[a]	21
	C: NPH	63	59	93.7	54	86	16	25.4

(Continued)

Heller 2009	I: detemir	299	291[a]	97.3	256[a]	97.3	54[a]	18.1
	C: glargine	144	140	97.2	121	84.0	23	16.0
Home 2005	I: glargine	292	260	89.0	178	61.0	31	10.6
	C: NPH	293	248	84.6	179	61.1	44	15.0
Kobayashi 2007	I: detemir	196	178	92.7	133	69.3	2	1.0
	C: NPH	98	95	95.6	78	79.6	3	3.0
Liu 2016	I: glargine	107	99	92.5	83	77.6	1	0.9
	C: NPH	54	51	94.4	42	77.8	1	1.9
NCT00595374	I: detemir	75	—	—	—	—	—	—
	C: NPH	38	—	—	—	—	—	—
NCT00605137	I: detemir	55	53[a]	96.4	—	—	5	9.1
	C: NPH	27	27	100	—	—	3	11.1
Pieber 2007	I: detemir	161	120	75.9	47	29.3	3	1.9
	C: glargine	159	108	70.1	50	31.4	12	7.8
Porcellati 2004	I: glargine	61	—	—	—	—	0	0
	C: NPH	60	—	—	—	—	0	0
PRESCHOOL	I: glargine	61	61	100	59	96.7	4	6.6
	C: NPH	60	63	98.4	60	93.8	2	3.1
Ratner 2000	I: glargine	264	251[a]	95.1	204[a]	77.3	23[a]	8.7
	C: NPH	270	254	94.1	208	77.0	28	10.4
Robertson 2007	I: detemir	232	223	96.1	174	75.0	37	15.9

(Continued)

	C: NPH	115	113	98.3	101	87.8	23	20.0
Russell-Jones 2004	I: detemir	491	448	93.3	339	70.6	31	6.5
	C: NPH	256	229	92.7	180	72.9	22	8.9
Schober 2002	I: glargine	174	138	79.3	85	48.3	40	25.0
	C: NPH	175	138	78.9	89	50.9	50	28.8
Standl 2004	I: detemir	236	184	80.3	134[a]	58.5	20[a]	8.7
	C: NPH	224	169	76.8	137	62.3	12	5.5
SWITCH 1 [b]	I: degludec	—	—	—	—	—	—	—
	C: glargine	—	—	—	—	—	—	—
Thalange 2013	I: detemir	177	146	82.5	100	56.5	3	1.7
	C: NPH	170	150	88.2	111	65.3	12	7.0
Urakami 2017	I: degludec	9	9	100	2	22.2	0	0
	C: glargine	9	9	100	4	44.4	0	0
Vague 2003	I: Detemir	301	271	90.0	198	65.8	24	8.0
	C: NPH	146	138	94.5	110	75.3	21	14.4

—: denotes not reported

[a]Data from CSR.
[b]None of the information for this table was reported before cross-over.

C: comparator; **CSR:** clinical study report; **I**: intervention; **N**: number of participants; **NPH**: neutral protamine Hagedorn.

Appendix 19. Survey of study investigators providing information on included studies

Included studies	Date study author contacted	Date study author replied	Type of additional information	Type of additional data
Bartley 2008	11 December 2019	No reply		
BEGIN Basal-Bolus Type 1	15 January 2020	19 January 2020: Dr Heller replied that he would like to try to help with the request	Additional data	No reply with additional data
BEGIN Flex T1	21 January 2020	No reply		
BEGIN Young	6 February 2020	No reply		
Bolli 2009	11 December 2019	11 December 2019: would like to help, but did no longer have access to study data	Study protocol, 'Risk of bias' items, data on safety, additional data	Replied 13 December 2019: no additional data provided
Chase 2008	19 February 2020	No reply		
Davies 2014	9 December 2019	30 December 2019: Novo Nordisk received the request from Dr. Davies and assured assistance	Study protocol, 'Risk of bias' items, data on safety, additional data	20 January 2020: Novo Nordisk provided additional data
Fulcher 2005	8 December 2019	Corresponding author was initially contacted. Due to lack of response, Sanofi was contacted on 29 January 2020 (replied same day that they would look further into the request)	Study protocol, 'Risk of bias' items, data on safety, additional data	31 January 2020: CSR was provided
Heller 2009	12 December 2019	Replied 19 January 2020 that he would try to help. As no further action, Novo Nordisk was contacted	Study protocol, 'Risk of bias' items, data on safety, additional data	Novo Nordisk provided CSR
Home 2005	12 December 2019	12 December 2019: would try to help, although data were old	Study protocol, 'Risk of bias' items, data on safety, additional data	Comments on data and suggestions
Kobayashi 2007	No contact information retrieved	21 March 2020: Novo Nordisk was contacted	Study protocol, 'Risk of bias' items, data on safety, additional data	26 May 2020: translated pages from CSRs provided
Liu 2016	17 February 2020	No reply from study authors. Sanofi was contacted 23/3-20.	Asked for study protocol, 'Risk of	26 March 2020: Sanofi provided CSR

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			bias' items and outcomes	
NCT00595374	27 January 2020: Novo Nordisk was asked if the study was published	28 January 2020: Novo Nordisk replied they would look into the request	Asked for additional information	No CSR or additional information could be provided
NCT00605137	28 February 2020: Novo Nordisk was asked if the study was published	2 March 2020: Novo Nordisk replied they would look further into the request. Replied 9 March 2020 that CSR was only available in Japanese, but they were willing to provide some translated pages.	Asked for study protocol, 'Risk of bias' items and outcomes	24 May 2020: pages from CSR provided, study protocol provided
Pieber 2007	25 January 2020	No reply by the investigators, Novo Nordisk was contacted	Study protocol, 'Risk of bias' items, data on safety, additional data	Novo Nordisk provided CSR
Porcellati 2004	12 December 2019	11 December 2019: would like to help, but did no longer have access to study data	NA	NA
PRESCHOOL	19 February 2020	No reply from investigators. Sanofi was contacted.	'Risk of bias' items, outcomes	Sanofi provided CSR
Ratner 2000	13 January 2020: no reply 12 February 2020: Sanofi contacted	12 February 2020: Sanofi replied they were willing to assist	Study protocol, 'Risk of bias' items, data on safety, additional data	14 February 2020: Sanofi provided CSR
Robertson 2007	12 February 2020	12 February 2020: investigator did not have access to the data (retired). Novo Nordisk was contacted	'Risk of bias' items, additional data	12 February 2020: Novo Nordisk provided CSR
Russell-Jones 2004	16 January 2020	19 January 2020: authors would like to help, but never replied. Novo Nordisk was contacted.	Study protocol, 'Risk of bias' items, data on safety, additional data	Novo Nordisk provided CSR
Schober 2002	17 February 2020	No reply from authors. Sanofi was contacted	'Risk of bias' items, additional data	Sanofi provided CSR
Standl 2004	28 November 2019: no reply; 29 January 2020: Novo Nordisk was contacted	No reply from investigator, Novo Nordisk was contacted	'Risk of bias' items, additional data	Novo Nordisk provided CSR
SWITCH 1	28 January 2020	1 February 2020: corresponding author replied that they would like to help. As investigator did	Data before crossover	24 March 2020: Novo Nordisk replied that

(Continued)

			not have access to data, Novo Nordisk was contacted		the requested analyses for data before cross-over were not performed
Thalange 2013		21 February 2020	No reply		
Urakami 2017		12 February 2020	14 February 2020: corresponding author replied they would like to help	Study protocol, 'Risk of bias' items, data before cross-over	No study protocol provided, but provided data on outcomes
Vague 2003		23 January 2020: no valid contact information available for the first author; Novo Nordisk was contacted	25 January 2020: Novo Nordisk replied that they would assist	Study protocol, 'Risk of bias' items, data on safety, additional data	Novo Nordisk provided CSR

Studies awaiting assessment	**Study completion date**	**Date study author contacted**	**Date study author replied**	**Type of additional information**	**Type of additional data**
Basal Analog Study	RT/CA	11 February 2020: asked for full-text publication of study	11 February 2020: study never published. A new request if data could be provided.	11 February 2020: no additional data provided	NA
EudraCT 2007-004144-74	RT	11 February 2020: asked if full-text publication was available and duration of the intervention	12/2-20 - investigator replied that no full-text article was currently available, but might be in the future. No reply on duration of intervention	NA	NA
IRC-T201203079224N1	RT	11 February 2020: asked for status of study	No reply		
J-Collection	RT	11 February 2020: asked for status of study	No reply		
Mianowska 2007	PM	17 February 2020: asked for data before cross-over	No reply		
NCT00564018	RT	11 February 2020: asked for status of study	No reply		
NCT01854723	RT	12 February 2020: investigator asked for full-text publication or data on study	No reply		

(Continued)

UMIN000001562	RT	12 February 2020: asked for study duration and full-text	No reply		
UMIN000020521	RT	11 February 2020: asked for status of study	No reply		
UMIN000021046	RT	11 February 2020: asked for status of study	No reply		

Excluded studies	Study completion date	Date study author contacted	Date study author replied	Date study author was asked for additional information (short summary)	Date study author provided data (short summary)
Orchard 2014	CA	11 February 2020: asked for full-text publication of study	26 February 2020: investigator replied that no full-text publication was planned. On the same day, the author was asked if additional information could be provided - study protocol and power point presentation provided by the authors	Information about study design and data, publications of study	Based on information from investigator, the study could be excluded

—: denotes not reported

CA: conference abstract; **CSR**: clinical study report; **NA**: not applicable; **PM**: published manuscript; **RT**: registered trial.

Appendix 20. Subgroup and sensitivity analyses

Comparison/outcome	Outcome	Published versus unpublished	Adults versus children	Blinding	NPH once daily versus multiple doses	Duration of intervention	Income	Setting
Insulin detemir versus NPH insulin	All-cause mortality	P = 0.85	—	—	—	—	—	—
	Cardiovascular mortality, non-fatal myocardial infarction/stroke, blindness, end-stage renal disease, socioeconomic effects, HbA1c/severe hypoglycaemia combined	—	—	—	—	—	—	—
	Severe hypoglycaemia	P = 0.01	P = 0.72	—	—	—	—	—
	Serious adverse events	P = 0.11	P = 0.77	—	—	—	—	—
	Diabetic ketoacidosis	P = 0.93	P = 0.91	—	—	—	—	—
	Adverse events	P = 0.25	P = 0.40	—	—	—	—	—
	Any nocturnal hypoglycaemia	P = 0.90	P = 0.36	—	—	—	—	—
	Mild/moderate hypoglycaemia	P = 0.89	P = 0.82	—	—	—	—	—
	HbA1c	P = 0.30	P = 0.11	—	—	—	—	—
Insulin glargine versus NPH insulin	All-cause mortality, health-related quality of life, cardiovascular mortality, non-fatal myocardial infarction/stroke, blindness, end-stage renal disease, diabetic ketoacidosis, socioeconomic effects, HbA1c/severe hypoglycaemia combined	—	—	—	—	—	—	—
	Severe hypoglycaemia	P = 0.87	P = 0.29	—	—	—	—	—
	Serious adverse events	P = 0.99	P = 0.96	—	—	—	—	—
	Diabetic ketoacidosis	P = 0.48	P = 0.69	—	—	—	—	—
	Non-serious adverse events	P = 0.88	P = 0.64	—	—	—	—	—

(Continued)

	Nocturnal hypoglycaemia	P = 0.99	P = 0.57	—	—	—	—	—
	Mild/moderate hypoglycaemia	P = 0.80	P = 0.65	—	—	—	—	—
	HbA1c	P = 0.47	P = 0.36	—	—	—	—	—
Insulin detemir versus insulin glargine	All-cause mortality, health-related quality of life, cardiovascular mortality, non-fatal myocardial infarction/stroke, blindness, end-stage renal disease, serious adverse events, diabetic ketoacidosis, socioeconomic effects, HbA1c, HbA1c/severe hypoglycaemia combined	—	—	—	—	—	—	—
	Severe hypoglycaemia	P = 0.02	—	—	—	—	—	—
	Adverse events	P = 0.28	—	—	—	—	—	—
	Nocturnal hypoglycaemia	Not significant for multiple comparisons	—	—	—	—	—	—
	Mild/moderate hypoglycaemia	P = 0.29	—	—	—	—	—	—
Insulin degludec versus insulin detemir	All-cause mortality, health-related quality of life, cardiovascular mortality, non-fatal myocardial infarction/stroke, blindness, end-stage renal disease, HbA1c/severe hypoglycaemia combined	—	—	—	—	—	—	—
	Severe hypoglycaemia	—	P = 0.51	—	—	—	—	—
	Serious adverse events	—	P = 0.63	—	—	—	—	—
	Non-serious adverse events	P = 0.53	P = 0.53	—	—	—	—	—
	Nocturnal hypoglycaemia	—	P = 0.51	—	—	—	—	—
	Mild/moderate hypoglycaemia	—	P = 0.85	—	—	—	—	—
	HbA1c	—	P = 0.42	—	—	—	—	—

(Continued)

Insulin degludec versus insulin glargine	All-cause mortality	P = 0.46	—	—	—	—	—	—
	Health-related quality of life	P = 0.27 / 0.51	—	—	—	—	—	—
	Severe hypoglycaemia	-	—	—	—	—	—	—
	Non-fatal myocardial infarction/stroke, blindness, end-stage renal disease, serious adverse events, non-serious adverse events, nocturnal hypoglycaemia, socioeconomic effects	—	—	—	—	—	—	—
	Diabetic ketoacidosis	P = 0.16	—	—	—	—	—	—
	HbA1c	P = 0.26	P = 0.71	—	—	—	—	—

—: denotes not possible to perform subgroup analysis
HbA1c: glycosylated haemoglobin A1c; **NPH:** neutral protamine Hagedorn insulin.

Appendix 21. 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
Diabetes Health Profile employed in Standl 2004	Three dimensions: barriers to activity, psychological distress, and disinhibited eating. Only the dimension barriers to activity was included	Yes	—	—	—	—	—	—
ITR-QOLN (Fujimoto 2018) employed in Kobayashi 2007	21 questions divided into 4 domains (1) Anxiety before sleep (2) Disturbances during sleep (3) Glycaemic control before breakfast (4) Overall well-being	Yes	Seven-point scale (0–6)	.	Maximum 126 points	—	The higher score the better well-being	—
W-BQ employed in Home 2005; Ratner 2000	22-item incorporating four subscales to measure depression (6 items), anxiety (6 items), energy (4 items) and positive well-being (6 items)	Yes	Of the 22 items, then 8 of which are negatively phrased and 14 positively phrased	Each item is scored from 0 to 3, where 0 = not at all, and 3 = all the time	Depression: 0-18; Anxiety: 0-28; Energy: 0-12; Positive Well-being 0-18 General Well-being (total score): 0-66	—	The higher score the better well-being (higher scores for negatively-phrased statements indicate worse well-being while higher scores for positively-phrased statements indicate better well-being. In calculating the subscale scores for the Depression and Anxiety subscales of the W-BQ, the scores on the positively-worded items have to be reversed while for the Energy subscale the negatively-word-	Effect size of 0.20 or more is considered clinically meaningful for psychological outcomes

(Continued)

							ed item scores have to be reversed. The Positive Wellbeing subscale of the W-BQ (6 items) is simply added, as all the items are positively worded)	
Well-Being Enquiry for Diabetics (WED) questionnaire employed in Bolli 2009	50-item questionnaire providing an evaluation of four aspects of quality of life: symptoms (10), discomfort (10), serenity (10) and impact (20)	Yes	4-point Likert scale ('always/usually' to 'never/very infrequently')	Total score is the sum of the subscale scores	—	—	Sums of item scores, with higher scores indicating better quality of life	—
Diabetes Quality of Life for Youth employed in Chase 2008	(1) Life satisfaction (2) Disease impact (3) Diabetes related worries	Yes	(1) Very satisfied, moderately satisfied, neither satisfied nor dissatisfied, moderately dissatisfied, very dissatisfied (2) Never, seldom, sometimes, often, all the time (3) Does not apply, never, seldom, sometimes, often, all the time	Total score is the sum of the subscale scores	—	—	Higher score indicates better quality of life, except for one item (in subscale 2 - question B -7); here lower scores represent higher quality of life	—
Parents' Diabetes Quality of Life employed in Chase 2008	(1) Emotional burden of disease (2) Child-related worries (3) Satisfaction	Yes	(1) Very satisfied, moderately satisfied, neither satisfied nor dissatisfied, moderately dissatisfied, very dissatisfied (2) Never, seldom, sometimes, often, all the time	Total score is the sum of the subscale scores	—	—	Higher score indicates better quality of life	—

(Continued)

			(3) Does not apply, never, seldom, sometimes, often, all the time					
SF-36 v2 employed in BEGIN Basal-Bolus Type 1; Davies 2014; SWITCH 1	Physical functioning (10) Role-physical (4) Bodily pain (2) General health (5) Vitality (4) Social functioning (2) Role-emotional (3) Mental health (5) Reported health transition (1)	Yes	3, 5 and 6-point Likert scale	Scores for dimensions Physical component summary (PCS) Mental component summary (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	PCS: 2-3 points MCS: 3 points Dimensions: physical functioning/bodily pain/vitality: 2 points, if score < 40 3 points, if score ≥ 40 Role physical: 2 points Social functioning/mental health: 3 points Role emotional: 4 points

ITR-QOLN: insulin therapy related quality of life at night; **MCS:** mental health component summary score; **PCS:** physical component summary score; **SF -36**: short-form 36; **W-BQ**: well-being questionnaire; **WED:** well-being enquiry for diabetics.

Appendix 22. Source of information for outcome data: all-cause mortality

Study ID	Publication	Study author request	Trials register	Clinical study report	Clinical study synopsis	EMA report	FDA report
Bartley 2008	Yes	—	No	Yes	Yes	—	—
BEGIN Basal-Bolus Type 1	Yes	—	No	Yes	Yes	No	No
BEGIN Flex T1	No	—	No	Yes	Yes	No	No
BEGIN Young	Yes	—	No	Yes	No	Yes	No
Bolli 2009	No	—	—	—	—	—	—
Chase 2008	No	—	No	Yes	No	—	—
Davies 2014	Yes	Yes	No	Yes	No	No	No
Fulcher 2005	No	—	—	Yes	—	—	—
Heller 2009	No	—	No	Yes	Yes	—	—
Home 2005	No	Yes	—	Yes	—	No	Yes
Kobayashi 2007	No	—	No	Yes	Yes	—	—
Liu 2016	No	—	No	Yes	Yes	Yes	—
NCT00595374	—	—	No	—	Yes	—	—
NCT00605137	—	—	No	No	Yes	—	—
Pieber 2007	No	—	No	Yes	Yes	—	Yes
Porcellati 2004	Yes	—	—	—	—	—	—
PRESCHOOL	No	—	Yes	Yes	—	Yes	—
Ratner 2000	No	—	—	Yes	—	No	Yes
Robertson 2007	No	No	No	Yes	Yes	—	Yes

(Continued)

Russell-Jones 2004	No	No	No	Yes	Yes	No	Yes
Schober 2002	No	—	—	Yes	—	—	No
Standl 2004	No	—	—	Yes	Yes	No	Yes
SWITCH 1	No	No	No	No	No	—	No
Thalange 2013	Yes	—	No	Yes	Yes	Yes	—
Urakami 2017	No	No	—	—	—	—	—
Vague 2003	No	—	—	Yes	Yes	No	Yes

—: indicates source not available

EMA: European Medicines Agency; **FDA**: Food and Drug Administration.

Appendix 23. Source of information for outcome data: health-related quality of life

Study ID	Publication	Study author request	Trials register	Clinical study report	Clinical study synopsis	EMA report	FDA report
Bartley 2008	No	—	No	No	No	—	—
BEGIN Basal-Bolus Type 1	Yes	—	No	Yes	No	No	No
BEGIN Flex T1	No	—	No	No	No	No	No
BEGIN Young	No	—	No	No	No	No	No
Bolli 2009	Yes	—	—	—	—	—	—
Chase 2008	No	—	No	Yes	Yes	—	—
Davies 2014	No	Yes	No	Yes	No	No	No
Fulcher 2005	No	—	—	—	—	—	—
Heller 2009	No	—	No	Yes	No	—	—
Home 2005	No	No	—	Yes	—	No	No
Kobayashi 2007	No	—	No	—	Yes	—	—
Liu 2016	No	—	No	No	No	No	—
NCT00595374	—	—	No	—	Yes	—	—
NCT00605137	—	—	No	No	No	—	—
Pieber 2007	No	—	No	Yes	No	—	No
Porcellati 2004	No	—	—	—	—	—	—
PRESCHOOL	No	—	No	No	—	No	—
Ratner 2000	No	—	—	Yes	—	No	No
Robertson 2007	No	No	No	No	No	—	No

(Continued)

Russell-Jones 2004	No	No	No	No	No	No	No
Schober 2002	No	—	—	No	—	—	No
Standl 2004	Yes	—	—	Yes	No	No	No
SWITCH 1	No	No	No	Yes	No	—	No
Thalange 2013	Yes	—	No	No	No	—	No
Urakami 2017	No	No	—	—	—	—	—
Vague 2003	No	—	—	No	No	No	No

—: indicates source not available

EMA: European Medicines Agency; **FDA**: Food and Drug Administration.

Appendix 24. Source of information for outcome data: severe hypoglycaemia

Study ID	Publication	Study author request	Trials register	Clinical study report	Clinical study synopsis	EMA report	FDA report
Bartley 2008	Yes	—	No	Yes	No	—	—
BEGIN Basal-Bolus Type 1	Yes	—	No	Yes	No	Yes	Yes
BEGIN Flex T1	Yes	—	No	Yes	Yes	Yes	Yes
BEGIN Young	Yes	—	No	Yes	No	Yes	No
Bolli 2009	No	—	—	—	—	—	—
Chase 2008	Yes	—	No	Yes	Yes	—	—
Davies 2014	Yes	Yes	No	Yes	No	Yes	Yes
Fulcher 2005	No	—	—	Yes	—	—	—
Heller 2009	No	—	No	No	Yes	—	—
Home 2005	Yes	No	—	Yes	—	No	No
Kobayashi 2007	Yes	—	No	Yes	No	—	—
Liu 2016	Yes	—	Yes	Yes	No	Yes	—
NCT00595374	—	—	No	—	No	—	—
NCT00605137	—	—	No	No	Yes	—	—
Pieber 2007	Yes	—	No	Yes	Yes	—	Yes
Porcellati 2004	Yes	—	—	—	—	—	—
PRESCHOOL	Yes	—	Yes	Yes	—	No	—
Ratner 2000	No	—	—	Yes	—	No	No
Robertson 2007	Yes	No	No	Yes	Yes	—	Yes

(Continued)

Russell-Jones 2004	Yes	No	No	Yes	Yes	No	Yes
Schober 2002	Yes	—	—	Yes	—	—	Yes
Standl 2004	No	—	—	Yes	No	No	Yes
SWITCH 1	No	No	No	No	No	—	No
Thalange 2013	Yes	—	No	Yes	No	Yes	—
Urakami 2017	Yes	Yes	—	—	—	—	—
Vague 2003	Yes	—	—	Yes	No	No	Yes

—: indicates source not available

EMA: European Medicines Agency; **FDA**: Food and Drug Administration.

Appendix 25. Definition/type of outcome data: severe hypoglycaemia

Study ID	Publication	Study author request	Trials register	Clinical study report	Clinical study synopsis	EMA report	FDA report
Bartley 2008	Hypoglycaemia requiring third party assistance	—	ND	Major hypoglycaemic episode: person not able to treat episode him/herself	Mentioned under serious adverse events	—	—
BEGIN Basal-Bolus Type 1	Hypoglycaemia requiring third party assistance	—	Severe hypoglycaemic episodes are defined as requiring assistance to administer carbohydrate, glucagon, or other resuscitative actions	Severe hypoglycaemic episodes are defined as requiring assistance	Severe hypoglycaemia	Severe hypoglycaemic episodes, where the patient is not able to treat himself	Defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions
BEGIN Flex T1	Hypoglycaemia requiring third party assistance	—	Severe hypoglycaemic episodes are defined as requiring assistance to administer carbohydrate, glucagon, or other resuscitative actions	Severe hypoglycaemia: an episode requiring assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions	Severe hypoglycaemia	Severe hypoglycaemic episodes, where the patient is not able to treat himself	An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or resuscitative measures
BEGIN Young	The child has altered mental status and cannot assist in his/her own care, is semiconscious or unconscious, or in a coma ± convulsions and may require parenteral therapy (glucagon or iv glucose)	—	"Severe episodes or episodes with plasma glucose (PG) below or equal to 3.9 mmol/L (70 mg/dL) with or without symp-	"Severe hypoglycaemia: The child has altered mental status and cannot assist in his own care, is semiconscious or unconscious, or in coma ± convulsions and may require parenteral therapy (glucagon or iv glucose)"	Severe hypoglycaemia	Children and adolescents - severe hypoglycaemia: the child has altered mental status and cannot assist in his own care, is semiconscious or un-	"The child has altered mental status and cannot assist in his own care, is semiconscious or unconscious, or in coma ± convulsions and may re-

(Continued)

			toms of hypoglycaemia"			conscious, or in coma ± convulsions and may require parenteral therapy (glucagon or iv glucose)	quire parenteral therapy (glucagon or iv glucose)"
Bolli 2009	Serious hypoglycaemia was defined as an event with blood glucose < 2.3 mmol/L, severe hypoglycaemia as an event with symptoms consistent with hypoglycaemia, during which the participant required the assistance of another person, or with prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration	—	—	—	—	—	—
Chase 2008	Severe hypoglycaemia was defined as an event requiring assistance from another person and associated with either BG < 2.0 mmol/L or prompt recovery after oral carbohydrate, intravenous glucose, or intramuscular or subcutaneous glucagon administration	—	ND	"Severe hypoglycemia was defined, as an event with clinical symptoms that was considered to result from hypoglycemia in which the participant required the assistance of another person and one of the following was true: • The event was associated with a blood glucose level < 36 mg/dL (2.0 mmol/L), • Or the event was associated with prompt recovery after oral carbohydrate, IV glucose, or glucagon administration For further clarification, the definition of severe hypoglycaemia included all episodes in which neurological impairment was severe enough to prevent self-treatment and because of which	ND	—	—

(Continued)

				the participant was thought to be at risk for injury to themselves or others. Required assistance indicated that the participant could not help her/himself."			
Davies 2014	Hypoglycaemia requiring third party assistance	Hypoglycaemia requiring third party assistance	Severe hypoglycaemic episodes: episodes requiring active assistance of another person to administer carbohydrate, glucagon, or other resuscitative actions	"An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions"	Severe hypoglycaemia	Severe hypoglycaemic episodes, where the patient is not able to treat himself	Defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions
Fulcher 2005	Symptoms consistent with hypoglycaemia required the assistance of another person and was associated with a blood glucose level < 2.8 mmol/L or prompt recovery after oral carbohydrate, iv glucose or sc glucagon administration	—	—	"Was defined as an event with symptoms consistent with hypoglycaemia in which the participant required the assistance of another person and which was associated with a blood glucose level below 2.8 mmol/L or with prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration"	—	—	—
Heller 2009	The patient could not treat the episode by himself/herself	—	ND	The patient could not treat the episode by himself/herself	Major hypoglycaemia	—	—
Home 2005	Severe symptomatic hypoglycaemia was defined as an event consistent with symptomatic hypoglycaemia requiring the assistance of another person, with either a	ND	—	Severe hypoglycaemia was as an event with symptoms consistent with hypoglycaemia in which the participants required the assistance of another person and which was associated with a blood glucose level < 2.8 mmol/L (50 mg/dL) or prompt recovery after oral	—	ND	Severe hypoglycaemia was as an event with symptoms consistent with hypoglycaemia in

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	blood glucose level < 2.8 mmol/L or prompt recovery after administration of oral carbohydrate, iv glucose or glucagon			carbohydrate, intravenous glucose or glucagon administration			which the participants required the assistance of another person and with blood glucose level < 2.8 mmol/L (50 mg/dL) or prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration
Kobayashi 2007	Any event requiring assistance of another person to recover from hypoglycaemic symptoms with or without measurement of blood glucose levels	—	Major hypoglycaemia	Major hypoglycaemia	Major hypoglycaemia	—	—
Liu 2016	Hypoglycaemia requiring the assistance of a third party or involving a seizure, coma, unconsciousness or the use of glucagon	—	"Severe symptomatic hypoglycemia: Any event with clinical symptoms considered to result from a hypoglycemic episode for which the participants required the assistance of a third party (other than the participant or a par-	"Any event with clinical symptoms considered to result from a hypoglycemic episode for which the participants required the assistance of a third party (i.e. other than the patient or a parent/usual caregiver, e.g. from emergency personnel) because the participants/parents could not treat the event, with acute neurological impairment directly resulting from the hypoglycemic event. If a patient was assisted when necessary and not due to generosity, it would qualify as "require assistance". The occurrence of seizure, coma, unconsciousness, or the use of glucagon, would also qualify a hypoglycemic episode as severe."	Severe hypoglycaemia	"Severe symptomatic hypoglycaemia: Any event with clinical symptoms considered to result from a hypoglycaemic episode for which the participants required the assistance of a third party (i.e. other than the patient or a parent/usual caregiver, e.g. from emergency	—

(Continued)

			ent/usual caregiver), with acute neurological impairment directly resulting from the hypoglycemic event."			personnel) because the participants/parents could not treat the event, with acute neurological impairment directly resulting from the hypoglycaemic event"	
NCT00595374	—	—	ND	—	Major hypoglycaemia	—	—
NCT00605137	—	—	ND	Major hypoglycaemia	Hypoglycaemia requiring third party assistance	—	—
Pieber 2007	Hypoglycaemia requiring third party assistance	—	ND	The patient could not treat the episode by himself/herself	Major hypoglycaemia	—	ND
Porcellati 2004	Hypoglycaemia requiring external help	—	—	—	—	—	—
PRESCHOOL	Severe hypoglycaemia was defined as an event requiring assistance from another person, as a result of altered consciousness, to administer carbohydrate, glucagon or to take other actions	—	"Severe symptomatic hypoglycemia: any event with clinical symptoms considered to result from a hypoglycemic episode for which the patients required the assistance of a third par-	"Severe symptomatic hypoglycemia: any event with clinical symptoms considered to result from a hypoglycemic episode for which the patients required the assistance of a third party (i.e. other than the patient, or a parent/usual caregiver; e.g. from emergency personnel), because the patients/parents could not treat the event with acute neurological impairment directly resulting from the hypoglycemic event. The occurrence of seizure, coma, unconsciousness, or the use of glucagon, were also to qualify a hypoglycemic episode as severe"	—	Severe hypoglycaemia	—

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				ty (i.e. other than the patient, or a parent/usual caregiver; e.g. from emergency personnel), because the patients/parents could not treat the event with acute neurological impairment directly resulting from the hypoglycemic event. The occurrence of seizure, coma, unconsciousness, or the use of glucagon, were also to qualify a hypoglycemic episode as severe."			
Ratner 2000	Symptomatic hypoglycaemia requiring third party assistance	—	—	"Severe hypoglycemia was defined as an event with symptoms consistent with hypoglycemia in which the participant required the assistance of another person and which was associated with a blood glucose level below 2.8 mmol/L (50 mg/dL) or prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration"	—	ND	Severe hypoglycaemia was as an event with symptoms consistent with hypoglycaemia in which the participants required the assistance of another person and with

(Continued)

							blood glucose level < 2.8 mmol/L (50 mg/dL) or prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration
Robertson 2007	Episodes requiring assistance from another person due to severe central nervous system dysfunction	ND	ND	Hypoglycaemic episode requiring assistance from another person	Major hypoglycaemia	—	Severe CNS symptoms consistent with hypoglycaemia in which the patients required assistance with glucose < 3.1 mmol/L or reversal by food or glucagon
Russell-Jones 2004	Requiring third party assistance	ND	Major hypoglycaemia	An episode with severe central nervous system symptoms consistent with hypoglycaemia in which the participant is unable to treat himself/herself and which has one of the following characteristics: blood glucose < 2.8 mmol/L or reversal of symptoms after either food intake or glucagon/iv glucose administration	Major hypoglycaemia	Hypoglycaemic episodes were classified in the trials as: • Major - an episode with severe CNS symptoms consistent with hypoglycaemia in which the patient was unable to treat himself/herself and which had one of the follow-	

(Continued)

						ing characteristics: blood glucose < 2.8 mmol/L • Reversal of symptoms after either food intake or glucagon/iv glucose administration	
Schober 2002	An event with symptoms consistent with hypoglycaemia in which the participant required assistance from another person, and which was associated with a blood glucose level < 2.8 mmol/L or prompt recovery after oral carbohydrate or intravenous glucose or glucagon administration	—	—	An event with symptoms consistent with hypoglycaemia in which the participant required assistance from another person, and which was associated with a blood glucose level < 2.8 mmol/L or prompt recovery after oral carbohydrate or intravenous glucose or glucagon administration	—	—	Hypoglycaemia in which the participant required assistance from another person and with a blood glucose level below 2.8 mmol/L or prompt recovery administration of glucose or glucagon
Standl 2004	Hypoglycaemia requiring third party assistance	—	—	An episode with severe CNS symptoms consistent with hypoglycaemia in which the participant is unable to treat himself/herself and which has one of the following characteristics: • Blood glucose < 2.8 mmol/L • Reversal of symptoms after either food intake or glucagon/iv glucose administration	Hypoglycaemic episodes were classified in the trials as: • Major - an episode with severe CNS symptoms consistent with hypoglycaemia in which	Major hypoglycaemia was defined as severe CNS symptoms consistent with hyperglycaemia in which patients requires assistance, with blood glucose < 2.8 mmol/L or reversal by food or glucagon	

(Continued)

				the patient was unable to treat himself/herself and which had one of the following characteristics: blood glucose < 2.8 mmol/L • Reversal of symptoms after either food intake or glucagon/iv glucose administration			
SWITCH 1	Episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions, neurological recovery following the return of plasma glucose to normal, or both	ND	A hypoglycaemic episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose values may not be available during an event, but neurological recovery following the return of plas-	Severe hypoglycaemia was defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration	An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions	—	ND

(Continued)

			ma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration				
Thalange 2013	Severe hypoglycaemia was defined as episodes where the persons were semi-conscious, unconscious or in a coma, with or without convulsions	—	ND	"participant is semiconscious/ unconscious/in coma ± convulsion and may require parenteral treatment (glucagon or iv glucose)"	Severe hypoglycaemia	Severe hypoglycaemia may lead to unconsciousness and/ or convulsions and may result in temporary or permanent impairment of brain function or even death	—
Urakami 2017	Severe hypoglycaemia is defined as an event associated with impaired consciousness or seizure	"Severe hypoglycemia is defined as an event associated with impaired consciousness or seizure"	—	—	—	—	—
Vague 2003	Hypoglycaemic episode with severe central nervous system symptoms consistent with hypoglycaemia, in which the participant was unable to treat himself/herself and which had one of the following characteristics: blood glucose recorded as <	—	—	An episode with severe CNS symptoms consistent with hypoglycaemia in which the participant is unable to treat himself/herself and which has one of the following characteristics: • Blood glucose < 2.8 mmol/L or symptom reversal achieved with food, intravenous glucose or glucagon	Major hypoglycaemia	Hypoglycaemic episodes were classified in the trials as: • Major - an episode with severe CNS symptoms consistent with hypoglycaemia in	Major hypoglycaemia was defined as severe CNS symptoms consistent with hypoglycaemia in which patient requires assistance, with blood glucose

(Continued)

	2.8 mmol/L or symptom reversal achieved with food, glucose or glucagon		which the patient was unable to treat himself/herself and which had one of the following characteristics: blood glucose < 2.8 mmol/L • Reversal of symptoms after either food intake or glucagon/iv glucose administration	< 2.8 mmol/L or reversal by food or glucagon

—: indicates source not available

CNS: central nervous system; **EMA**: European Medicines Agency; **FDA**: Food and Drug Administration; **iv**:**intravenous; ND**: not defined; **NR**: not reported; **PG**: plasma glucose; **sc:** subcutaneous.

Appendix 26. Source of information for outcome data: cardiovascular mortality

Study ID	Publication	Study author request	Trials register	Clinical study report	Clinical study synopsis	EMA report	FDA report
Bartley 2008	Yes	—	No	Yes	Yes	—	—
BEGIN Basal-Bolus Type 1	Yes	—	No	Yes	Yes	No	No
BEGIN Flex T1	No	—	No	Yes	Yes	No	No
BEGIN Young	Yes	—	No	Yes	Yes	Yes	No
Bolli 2009	No	—	—	—	—	—	—
Chase 2008	No	—	No	Yes	No	—	—
Davies 2014	Yes	—	No	Yes	No	No	No
Fulcher 2005	No	—	—	Yes	—	—	—
Heller 2009	No	—	No	Yes	Yes	—	—
Home 2005	No	Yes	—	Yes	—	No	No
Kobayashi 2007	No	—	No	Yes	Yes	—	—
Liu 2016	No	—	No	Yes	Yes	Yes	—
NCT00595374	—	—	No	—	Yes	—	—
NCT00605137	—	—	No	No	Yes	—	—
Pieber 2007	No	—	No	Yes	Yes	—	No
Porcellati 2004	Yes	—	—	—	—	—	—
PRESCHOOL	No	—	Yes	Yes	—	Yes	—
Ratner 2000	No	—	—	Yes	No	No	No
Robertson 2007	No	No	No	Yes	Yes	—	Yes

(Continued)

Russell-Jones 2004	No	No	No	Yes	Yes	No	Yes
Schober 2002	No	—	—	Yes	—	—	No
Standl 2004	No	—	—	Yes	Yes	No	Yes
SWITCH 1	No	No	No	No	No	—	No
Thalange 2013	Yes	—	No	Yes	Yes	Yes	—
Urakami 2017	No	Yes	—	—	—	—	—
Vague 2003	No	—	—	Yes	Yes	No	Yes

—: indicates source not available

EMA: European Medicines Agency; **FDA**: Food and Drug Administration.

Appendix 27. Source of information for outcome data: non-fatal myocardial infarction

Study ID	Publication	Study author request	Trials register	Clinical study report	Clinical study synopsis	EMA report	FDA report
Bartley 2008	No	—	No	Yes	No	—	—
BEGIN Basal-Bolus Type 1	No	—	Yes	Yes	No	No	No
BEGIN Flex T1	No	—	No	Yes	No	No	No
BEGIN Young	No	—	No	No	No	No	No
Bolli 2009	No	—	—	—	—	—	—
Chase 2008	No	—	No	No	No	—	—
Davies 2014	No	Yes	No	No	No	No	No
Fulcher 2005	No	No	No	No	No	—	—
Heller 2009	No	—	No	Yes	No	—	—
Home 2005	No	No	—	Yes	—	No	No
Kobayashi 2007	No	—	No	No	No	—	—
Liu 2016	No	—	No	No	No	No	—
NCT00595374	—	—	No	—	No	—	—
NCT00605137	—	—	No	No	No	—	—
Pieber 2007	No	No	No	No	No	—	No
Porcellati 2004	No	—	—	—	—	—	—
PRESCHOOL	No	—	No	No	—	No	—
Ratner 2000	No	—	—	No	—	No	No
Robertson 2007	No	No	No	No	No	—	No

(Continued)

Russell-Jones 2004	No	No	No	No	No	No	No
Schober 2002	No	—	—	No	—	—	No
Standl 2004	No	—	—	No	No	No	No
SWITCH 1	No	No	No	No	No	—	No
Thalange 2013	No	—	No	No	No	No	—
Urakami 2017	No	Yes	—	—	—	—	—
Vague 2003	No	—	—	No	No	No	No

—: indicates source not available

EMA: European Medicines Agency; **FDA**: Food and Drug Administration.

Appendix 28. Source of information for outcome data: non-fatal stroke

Study ID	Publication	Study author request	Trials register	Clinical study report	Clinical study synopsis	EMA report	FDA report
Bartley 2008	No	—	No	No	No	—	—
BEGIN Basal-Bolus Type 1	No	—	No	Yes	No	No	No
BEGIN Flex T1	No	—	No	Yes	No	No	No
BEGIN Young	No	—	No	No	No	No	No
Bolli 2009	No	—	—	—	—	—	—
Chase 2008	No	—	No	No	No	—	—
Davies 2014	No	Yes	No	No	No	No	No
Fulcher 2005	No	—	—	No	—	—	—
Heller 2009	No	—	No	Yes	No	—	—
Home 2005	No	No	—	Yes	—	No	No
Kobayashi 2007	No	—	No	No	No	—	—
Liu 2016	No	—	No	No	No	No	—
NCT00595374	—	—	No	—	No	—	—
NCT00605137	—	—	No	No	No	—	—
Pieber 2007	No	No	No	No	No	—	No
Porcellati 2004	No	—	—	—	—	—	—
PRESCHOOL	No	—	No	No	—	No	—
Ratner 2000	No	—	—	No	—	No	No
Robertson 2007	No	No	No	No	No	—	No

(Continued)

Russell-Jones 2004	No	No	No	No	No	No	No
Schober 2002	No	—	—	No	—	—	No
Standl 2004	No	—	—	No	No	No	No
SWITCH 1	No	No	No	No	No	—	No
Thalange 2013	No	—	No	No	No	No	—
Urakami 2017	No	Yes	—	—	—	—	—
Vague 2003	No	—	—	No	No	No	No

—: indicates source not available

EMA: European Medicines Agency; **FDA**: Food and Drug Administration.

Appendix 29. Source of information for outcome data: end-stage renal disease

Study ID	Publication	Study author request	Trials register	Clinical study report	Clinical study synopsis	EMA report	FDA report
Bartley 2008	No	—	No	No	No	—	—
BEGIN Basal-Bolus Type 1	No	—	No	No	No	No	No
BEGIN Flex T1	No	—	No	No	No	No	No
BEGIN Young	No	—	No	No	No	No	No
Bolli 2009	No	—	—	—	—	—	—
Chase 2008	No	—	No	No	No	—	—
Davies 2014	No	Yes	No	No	No	No	No
Fulcher 2005	No	—	—	No	—	—	—
Heller 2009	No	—	No	No	No	—	—
Home 2005	No	No	—	No	—	No	No
Kobayashi 2007	No	—	No	No	No	—	—
Liu 2016	No	—	No	No	No	No	—
NCT00595374	—	—	No	—	No	—	—
NCT00605137	—	—	No	No	No	—	—
Pieber 2007	No	—	No	No	No	—	No
Porcellati 2004	No	—	—	—	—	—	—
PRESCHOOL	No	—	No	No	—	No	—
Ratner 2000	No	—	—	No	—	No	No
Robertson 2007	No	No	No	No	No	—	No

(Continued)

Russell-Jones 2004	No	No	No	No	No	No	No
Schober 2002	No	—	—	No	—	—	No
Standl 2004	No	—	—	No	No	No	No
SWITCH 1	No	No	No	No	No	—	No
Thalange 2013	No	—	No	No	No	No	—
Urakami 2017	No	Yes	—	—	—	—	—
Vague 2003	No	—	—	No	No	No	No

—: indicates source not available

EMA: European Medicines Agency; **FDA**: Food and Drug Administration.

Appendix 30. Source of information for outcome data: blindness

Study ID	Publication	Study author request	Trials register	Clinical study report	Clinical study synopsis	EMA report	FDA report
Bartley 2008	No	—	No	No	No	—	—
BEGIN Basal-Bolus Type 1	No	—	No	No	No	No	No
BEGIN Flex T1	No	—	No	No	No	No	No
BEGIN Young	No	—	No	No	No	No	No
Bolli 2009	No	—	—	—	—	—	—
Chase 2008	No	No	No	No	No	—	—
Davies 2014	No	Yes	No	No	No	No	No
Fulcher 2005	No	—	—	No	—	—	—
Heller 2009	No	—	No	No	No	—	—
Home 2005	No	No	—	No	—	No	No
Kobayashi 2007	No	—	No	No	No	—	—
Liu 2016	No	—	No	No	No	No	—
NCT00595374	—	—	No	—	No	—	—
NCT00605137	—	—	No	No	No	—	—
Pieber 2007	No	—	No	No	No	—	No
Porcellati 2004	No	—	—	—	—	—	—
PRESCHOOL	No	—	No	No	—	No	—
Ratner 2000	No	—	—	No	—	No	No
Robertson 2007	No	No	No	No	No	—	No

(Continued)

Russell-Jones 2004	No	No	No	No	No	No	No
Schober 2002	No	—	—	No	—	—	No
Standl 2004	No	—	—	No	No	No	No
SWITCH 1	No	No	No	No	No	—	No
Thalange 2013	No	—	No	No	No	No	—
Urakami 2017	No	Yes	—	—	—	—	—
Vague 2003	No	—	—	No	No	No	No

—: indicates source not available

EMA: European Medicines Agency; **FDA**: Food and Drug Administration.

Appendix 31. Source of information for outcome data: serious adverse events

Study ID	Publication	Study author request	Trials register	Clinical study report	Clinical study synopsis	EMA report	FDA report
Bartley 2008	Yes	—	No	Yes	Yes	—	—
BEGIN Basal-Bolus Type 1	Yes	—	Yes	Yes	Yes	No	No
BEGIN Flex T1	Yes	—	Yes	Yes	Yes	No	No
BEGIN Young	Yes	—	Yes	Yes	Yes	Yes	No
Bolli 2009	Yes	—	—	—	—	—	—
Chase 2008	Yes	—	No	Yes	No	—	—
Davies 2014	Yes	Yes	Yes	Yes	No	No	No
Fulcher 2005	No	—	—	Yes	—	—	—
Heller 2009	Yes	—	No	Yes	Yes	—	—
Home 2005	Yes	No	—	Yes	—	No	No
Kobayashi 2007	Yes	—	No	Yes	Yes	—	—
Liu 2016	No	—	Yes	Yes	Yes	Yes	—
NCT00595374	—	—	No	—	Yes	—	—
NCT00605137	—	—	No	No	Yes	—	—
Pieber 2007	Yes	—	No	Yes	Yes	—	No
Porcellati 2004	No	—	—	—	—	—	—
PRESCHOOL	No	—	Yes	Yes	—	Yes	—
Ratner 2000	No	—	—	Yes	—	No	No
Robertson 2007	No	No	No	Yes	Yes	—	Yes

(Continued)

Russell-Jones 2004	No	No	No	Yes	No	No	No
Schober 2002	Yes	—	—	Yes	—	—	No
Standl 2004	No	—	—	Yes	Yes	No	No
SWITCH 1	No	No	No	No	No	—	No
Thalange 2013	Yes	—	Yes	Yes	No	No	—
Urakami 2017	No	Yes	—	—	—	—	—
Vague 2003	No	—	—	Yes	Yes	No	No

—: indicates source not available

EMA: European Medicines Agency; **FDA**: Food and Drug Administration.

Appendix 32. Source of information for outcome data: diabetic ketoacidosis

Study ID	Publication	Study author request	Trials register	Clinical study report	Clinical study synopsis	EMA report	FDA report
Bartley 2008	No	—	No	Yes	Yes	—	—
BEGIN Basal-Bolus Type 1	Yes	—	Yes	Yes	No	No	No
BEGIN Flex T1	No	—	Yes	Yes	No	No	No
BEGIN Young	No	—	No	Yes	No	No	No
Bolli 2009	No	—	—	—	—	—	—
Chase 2008	Yes	—	No	Yes	No	—	—
Davies 2014	No	Yes	Yes	Yes	No	No	No
Fulcher 2005	No	—	—	Yes	—	—	—
Heller 2009	No	—	No	Yes	No	—	—
Home 2005	No	No	—	Yes	—	No	No
Kobayashi 2007	No	—	No	Yes	No	—	—
Liu 2016	Yes	—	No	Yes	No	Yes	—
NCT00595374	—	—	No	—	No	—	—
NCT00605137	—	—	No	No	Yes	—	—
Pieber 2007	No	—	No	No	No	—	No
Porcellati 2004	No	—	—	—	—	—	—
PRESCHOOL	No	—	Yes	Yes	—	Yes	—
Ratner 2000	No	—	—	Yes	—	No	No
Robertson 2007	Yes	No	No	Yes	Yes	—	Yes

(Continued)

Russell-Jones 2004	No	No	No	No	No	No	No
Schober 2002	Yes	—	—	Yes	—	—	No
Standl 2004	No	—	—	No	No	No	No
SWITCH 1	No	No	No	No	No	—	No
Thalange 2013	Yes	—	Yes	Yes	No	No	—
Urakami 2017	No	Yes	—	—	—	—	—
Vague 2003	No	—	—	Yes	No	No	No

—: indicates source not available

EMA: European Medicines Agency; **FDA**: Food and Drug Administration.

Appendix 33. Source of information for outcome data: non-serious adverse events

Study ID	Publication	Study author request	Trials register	Clinical study report	Clinical study synopsis	EMA report	FDA report
Bartley 2008	No	—	No	Yes	Yes	—	—
BEGIN Basal-Bolus Type 1	Yes	—	Yes	Yes	Yes	No	No
BEGIN Flex T1	Yes	—	Yes	Yes	Yes	No	No
BEGIN Young	Yes	—	Yes	Yes	Yes	Yes	No
Bolli 2009	Yes	—	—	—	—	—	—
Chase 2008	Yes	—	No	Yes	No	—	—
Davies 2014	No	Yes	Yes	Yes	No	No	No
Fulcher 2005	Yes	—	—	Yes	—	—	—
Heller 2009	Yes	—	No	Yes	Yes	—	—
Home 2005	No	No	—	Yes	—	No	No
Kobayashi 2007	No	—	No	Yes	Yes	—	—
Liu 2016	No	—	Yes	Yes	Yes	Yes	—
NCT00595374	—	—	No	—	Yes	—	—
NCT00605137	—	—	No	Yes	No	—	—
Pieber 2007	No	—	No	Yes	Yes	—	No
Porcellati 2004	No	—	—	—	—	—	—
PRESCHOOL	Yes	—	Yes	Yes	—	No	—
Ratner 2000	Yes	—	—	Yes	—	No	No
Robertson 2007	Yes	No	No	Yes	No	—	No

(Continued)

Russell-Jones 2004	No	No	No	Yes	No	No	No
Schober 2002	Yes	—	—	Yes	—	—	No
Standl 2004	No	—	—	Yes	No	No	No
SWITCH 1	No	No	No	No	No	—	No
Thalange 2013	Yes	—	Yes	Yes	No	No	—
Urakami 2017	No	Yes	—	—	—	—	—
Vague 2003	Yes	—	—	Yes	No	No	No

—: indicates source not available

EMA: European Medicines Agency; **FDA**: Food and Drug Administration.

Appendix 34. Source of information for outcome data: nocturnal hypoglycaemia

Study ID	Publication	Study author request	Trials register	Clinical study report	Clinical study synopsis	EMA report	FDA report
Bartley 2008	Yes	—	No	Yes	No	—	—
BEGIN Basal-Bolus Type 1	Yes	—	No	Yes	No	Yes	No
BEGIN Flex T1	Yes	—	Yes	Yes	Yes	Yes	No
BEGIN Young	Yes	—	No	Yes	No	Yes	No
Bolli 2009	No	—	—	—	—	—	—
Chase 2008	No	—	No	Yes	No	—	—
Davies 2014	Yes	Yes	No	Yes	No	Yes	No
Fulcher 2005	Yes	—	—	Yes	—	—	—
Heller 2009	Yes	—	No	Yes	Yes	—	—
Home 2005	Yes	No	—	Yes	—	No	No
Kobayashi 2007	Yes	—	No	No	Yes	—	—
Liu 2016	Yes	—	Yes	Yes	No	Yes	—
NCT00595374	—	—	No	—	No	—	—
NCT00605137	—	—	No	No	Yes	—	—
Pieber 2007	Yes	—	No	Yes	No	—	No
Porcellati 2004	No	—	—	—	—	—	—
PRESCHOOL	Yes	—	Yes	Yes	—	No	—
Ratner 2000	No	—	—	Yes	—	No	No
Robertson 2007	Yes	No	No	Yes	No	—	No

(Continued)

Russell-Jones 2004	Yes	No	No	Yes	No	No	No
Schober 2002	Yes	—	—	Yes	—	—	No
Standl 2004	No	—	—	Yes	No	No	—
SWITCH 1	No	No	No	No	No	—	No
Thalange 2013	Yes	—	No	Yes	No	Yes	—
Urakami 2017	No	Yes	—	—	—	—	—
Vague 2003	Yes	—	—	Yes	No	No	—

—: indicates source not available

EMA: European Medicines Agency; **FDA**: Food and Drug Administration.

Appendix 35. Definition/type of outcome data: nocturnal hypoglycaemia

Study ID	Publication	Study author request	Trials register	Clinical study report	Clinical study synopsis	EMA report	FDA report
Bartley 2008	Hypoglycaemia between 23:00 to 06:00	—	ND	Hypoglycaemia between 23:00 to 06:00	Hypoglycaemia between 23:00 to 06:00	—	—
BEGIN Basal-Bolus Type 1	Hypoglycaemic episodes occurring from 00:01 to 05:59	—	Nocturnal hypoglycaemic episodes are defined as occurring between 00:01 and 05:59 a.m.	Nocturnal hypoglycaemic episodes are defined as occurring between 00:01 and 05:59 a.m.	Nocturnal hypoglycaemic episodes are defined as occurring between 00:01 and 05:59 a.m.	Hypoglycaemic episodes occurring from 00:01 to 05:59	Nocturnal hypoglycaemic episodes are defined as occurring between 00:01 and 05:59 a.m.
BEGIN Flex T1	Episodes occurring between 00:01 and 05:59 (inclusive)	—	Nocturnal hypoglycaemic episodes are defined as occurring between 00:01 and 05:59 a.m.	Hypoglycaemia between 00:01 to 05:50 a.m.	"A hypoglycaemic episode with time of onset between 00:01 and 05:59 (both included) was considered nocturnal"	Hypoglycaemic episodes occurring from 00:01 to 05:59	Hypoglycaemic episodes in the timeframe 00:00 to 06:00
BEGIN Young	Hypoglycaemic episodes occurring between 11 p.m. and 7 a.m. inclusive were classified as nocturnal	—	Hypoglycaemia from 11 p.m. - 7 a.m./23:00 - 07:00	"Hypoglycaemic episodes were defined as nocturnal if the time of onset was between 11 p.m.-7 a.m./23:00-7:00"	"Nocturnal (11 p.m. - 7 a.m.]"	Hypoglycaemia from 11 p.m. - 7 a.m.	Hypoglycaemia from 11 p.m. - 7 a.m.
Bolli 2009	Hypoglycaemia which occurred between bedtime and before getting up in the morning	—	—	—	—	—	—
Chase 2008	Hypoglycaemia from midnight and 6 a.m.	—	ND	Hypoglycaemia from midnight and 6 a.m.	ND	—	—

(Continued)

Davies 2014	Hypoglycaemia between 00:01 and 05:59 hours	Hypoglycaemia between 00:01 and 05:59 hours	Nocturnal hypoglycaemic episodes are defined as occurring between 00:01 and 05:59 a.m.	"The nocturnal period was considered as the period between 00:01 and 05:59 a.m."	Nocturnal hypoglycaemia (00:01-05:59 a.m.)	Hypoglycaemic episodes occurring from 00:01 to 05:59 h	Nocturnal hypoglycaemic episodes are defined as occurring between 00:01 and 05:59 a.m.
Fulcher 2005	Hypoglycaemia occurring after the evening insulin injection and before the morning insulin dose	—	—	"Nocturnal hypoglycaemia was defined as hypoglycaemia occurring between bedtime after the evening injection and before getting up in the morning (i.e. before the morning determination of fasting blood glucose and before any morning insulin dose)"	—	—	—
Heller 2009	Hypoglycaemia between 23:00 and 06:00	—	ND	Hypoglycaemia between 23:00 and 06:00	Hypoglycaemia between 23:00 and 06:00	—	—
Home 2005	Symptomatic hypoglycaemia occurring during sleep between bedtime and rising in the morning, or before the morning pre-breakfast self-blood glucose measurement and the morning insulin injection. Only participants with confirmed blood glucose < 2.0 mmol/L were considered clinically relevant			"Nocturnal hypoglycemia was defined as hypoglycemia occurring while the participant was asleep, between bedtime after the evening injection and before getting up in the morning, i.e. before the morning determination of FBG and before the morning injection"		ND	ND
Kobayashi 2007	Hypoglycaemia between 00:01 and 05:59	—	ND	Nocturnal hypoglycaemia	Hypoglycaemia between 23:00 and 06:00	—	—
Liu 2016	Hypoglycaemia occurring between 23:00–07:00	—	"Any asymptomatic and/or symptomatic hy-	"Any asymptomatic and/or symptomatic hypoglycemic event that occurred between 23:00 to 07:00"	Nocturnal hypoglycaemia	Any asymptomatic and/or symptomatic hypo-	—

(Continued)

			poglycemic event that occurred between 23:00 to 07:00"			glycaemic event that occurred between 23:00 to 07:00	
NCT00595374	—	—	ND	—	Nocturnal hypoglycaemia	—	—
NCT00605137	—	—	ND	Nocturnal hypoglycaemia	Hypoglycaemia from 23:00 - 06:00, inclusive	—	—
Pieber 2007	Hypoglycaemia between 23:00 and 06:00	—	ND	Hypoglycaemia between 23:00 and 06:00	Hypoglycaemia between 23:00 and 06:00	—	ND
Porcellati 2004	Nocturnal episodes of hypoglycaemia were calculated from values measured at 03.00 or any time between 01.00 and 07.30 when participants awoke with symptoms suggestive of hypoglycaemia	—	—	—	—	—	—
PRESCHOOL	Hypoglycaemia between 23:00 hours and 07:00	—	"Nocturnal hypoglycemia: any event from the "all hypoglycemia" total that occurred between 23:00 and 07:00"	"Nocturnal hypoglycemia: any event from the “all hypoglycemia” total that occurred between 23:00 and 07:00"	—	ND	—
Ratner 2000	Hypoglycaemia occurring while asleep after the bedtime insulin dose and before the morning insulin dose and before the morn-	—	—	"Nocturnal hypoglycemia was defined as hypoglycemia which occurred while the participant was asleep between bedtime after the evening injection and before getting up in the morning (i.e. before	—	ND	ND

(Continued)

	ing blood glucose measurement			the morning determination of fasting blood glucose and before the morning injection)"			
Robertson 2007	Hypoglycaemic between 22.00 (included) − 07.00(excluded)	ND	ND	Hypoglycaemic between 22.00 (included) − 07.00(excluded)	Hypoglycaemia between (22:00 to 07:00)	—	ND
Russell-Jones 2004	Hypoglycaemia between 11 p.m. to 6 a.m.	ND	ND	Hypoglycaemia from 23:00 to 06:00	Hypoglycaemia from 23:00 to 06:00	Hypoglycaemia episodes occurring between 23:00 and 6:00	Hypoglycaemia episodes occurring between 23:00 and 06:00
Schober 2002	Nocturnal hypoglycaemia was defined as hypoglycaemia while the participants was sleeping between bedtime and after the evening injection and before getting up in the morning			"Nocturnal hypoglycemia was defined as hypoglycemia occurring while the participant was asleep, between bedtime after the evening injection and before getting up in the morning, i.e. before the morning determination of FBG and before the morning injection"		—	ND
Standl 2004	Hypoglycaemia between 23:00 to 06:00	—	—	Hypoglycaemia from 23:00 to 06:00	Hypoglycaemia from 23:00 to 06:00	Hypoglycaemia episodes occurring between 23:00 and 6:00	Hypoglycaemia episodes occurring between 23:00 and 6:00
SWITCH 1	Episodes between 12:01 a.m. and 5:59 a.m.	ND	Hypoglycaemia between 00:01 and 05.59 a.m.	Hypoglycaemia between 00:01 and 05.59 a.m.	Nocturnal hypoglycaemia	—	ND
Thalange 2013	Nocturnal if they occurred between 22:00 and 07:00	—	ND	"Episodes occurring between 22:00 (included) and 07:00 (excluded) were defined as nocturnal"	ND	ND	—
Urakami 2017	Hypoglycaemia occurring between 22:00 – 06:59	Hypoglycaemia occur-	—	—	—	—	—

(Continued)

		ring between 22:00 – 06:59					
Vague 2003	Hypoglycaemia between 23:00 to 06:00	—	—	Hypoglycaemia between 23:00 (included) and 06:00 (excluded)	Hypoglycaemia between 23:00 to 06:00	Hypoglycaemia episodes occurring between 23:00 and 6:00 hours	Hypoglycaemia episodes occurring between 23:00 and 6:00

—: indicates source not available

a.m.: ante meridiem; **EMA**: European Medicines Agency; **FBG**: fasting blood glucose; **FDA**: Food and Drug Administration; **ND**: not defined; **p.m.**: post meridiem.

Appendix 36. Source of information for outcome data: mild/moderate hypoglycaemia

Study ID	Publication	Study author request	Trials register	Clinical study report	Clinical study synopsis	EMA report	FDA report
Bartley 2008	Yes	—	No	Yes	Yes	—	—
BEGIN Basal-Bolus Type 1	Yes	—	No	Yes	No	Yes	No
BEGIN Flex T1	Yes	—	No	Yes	No	Yes	No
BEGIN Young	Yes	—	No	Yes	No	Yes	No
Bolli 2009	No	—	—	—	—	—	—
Chase 2008	Yes	—	No	Yes	—	—	—
Davies 2014	Yes	Yes	No	Yes	No	Yes	No
Fulcher 2005	No	—	—	Yes	—	—	—
Heller 2009	No	—	No	Yes	No	—	—
Home 2005	Yes	No	—	Yes	—	No	Yes
Kobayashi 2007	Yes	—	No	No	Yes	—	—
Liu 2016	Yes	—	Yes	Yes	No	Yes	—
NCT00595374	—	—	No	—	No	—	—
NCT00605137	—	—	No	Yes	Yes	—	—
Pieber 2007	Yes	—	No	Yes	No	—	No
Porcellati 2004	No	—	—	—	—	—	—
PRESCHOOL	Yes	—	Yes	Yes	—	No	—
Ratner 2000	No	—	—	Yes	—	No	Yes
Robertson 2007	Yes	No	No	Yes	No	—	Yes

(Continued)

Russell-Jones 2004	Yes	No	No	Yes	No	No	No
Schober 2002	Yes	—	—	Yes	—	—	No
Standl 2004	No	—	—	Yes	No	—	—
SWITCH 1	No	No	No	No	No	—	No
Thalange 2013	Yes	—	No	Yes	No	Yes	—
Urakami 2017	No	Yes	—	—	—	—	—
Vague 2003	Yes	—	—	Yes	No	No	No

—: indicates source not available

EMA: European Medicines Agency; **FDA**: Food and Drug Administration.

Appendix 37. Definition/type of outcome data: mild/moderate hypoglycaemia

Study ID	Publication	Study author request	Trials register	Clinical study report	Clinical study synopsis	EMA report	FDA report
Bartley 2008	All SMPG values < 3.1 mmol/L as well as signs and symptoms of hypoglycaemia minor if plasma glucose < 3.1 mmol/L and the individual dealt with the episode him/herself, and as symptoms only if episodes were not confirmed by a plasma glucose measurement and no assistance was required	—	ND	Plasma glucose < 3.1 mmol/L as well as signs and symptoms of hypoglycaemia minor if plasma glucose < 3.1 mmol/L and the individual dealt with the episode him/herself, and as symptoms only if episodes were not confirmed by a plasma glucose measurement and no assistance was required	ND	—	—
BEGIN Basal-Bolus Type 1	Confirmed hypoglycaemic episodes included those with a plasma glucose value of < 3.1 mmol/L	—	No	An episode with symptoms consistent with hypoglycaemia with confirmation by plasma glucose < 3.1 mmol/L or full blood glucose < 2.8 mmol/L and which is handled by the participant himself/herself	Confirmed hypoglycaemic episodes included those with a plasma glucose value of < 3.1 mmol/L	Mild hypoglycaemic episodes can be treated by oral administration of glucose or other products containing sugar	An episode not requiring third party assistance where a plasma glucose < 3.1 mmol/L or whole blood glucose < 2.8 mmol/L was recorded (with or without symptoms of hypoglycaemia)
BEGIN Flex T1	Minor hypoglycaemic episodes are defined as able to treat her/himself and plasma glucose below 3.1 mmol/L	—	Minor hypoglycaemic episodes are defined as able to treat her/himself and plasma glucose below 3.1 mmol/L.	Minor hypoglycaemic episode was defined as: an episode with symptoms consistent with hypoglycaemia with confirmation by PG < 3.1 mmol/L or full blood glucose < 2.8 mmol/L and which was handled by the participants themselves	Minor hypoglycaemia with a confirmed PG < 3.1 mmol/L	Mild hypoglycaemic episodes can be treated by oral administration of glucose or other products containing sugar	An episode not requiring third party assistance where a plasma glucose < 3.1 mmol/L or whole blood glucose < 2.8 mmol/L was recorded (with or with-

(Continued)

							out symptoms of hypoglycaemia)
BEGIN Young	Confirmed hypoglycaemia was defined as SMPG < 3.1 mmol/L	—	PG below or equal to 3.9 mmol/L (70 mg/dL) with or without symptoms of hypoglycaemia	"An episode with symptoms consistent with hypoglycaemia with confirmation by PG"	PG ≤ to 3.9 mmol/L (70 mg/dL) with or without symptoms of hypoglycaemia	An episode with symptoms consistent with hypoglycaemia with confirmation by plasma glucose < 3.1 mmol/L or full blood glucose < 2.8 mmol/L and which does not fulfil the requirements for being classified as a severe hypoglycaemic episode	Blood glucose < 3.1 mmol/L, self-treated
Bolli 2009	Blood glucose ≤ 4.0 mmol/L	—	—	—	—	—	—
Chase 2008	The rates of biochemical hypoglycaemia were ascertained by analysis of SMBG data and divided into 3 categories: < 3.9 mmol/L, < 2.8 mmol/L and < 2.0 mmol/L	—	ND	"The study co-ordinator also reviewed the participant's diary for any blood glucose values (< 70 mg/dL [3.9 mmol/L]) without symptoms and recorded these events in the CRF if, in the opinion of the investigator/study co-ordinator, they represented true hypoglycemia "	ND	—	—
Davies 2014	Confirmed hypoglycaemia was defined as plasma glucose < 3.1 mmol/L regardless of symptoms	Confirmed hypoglycaemia was defined as PG < 3.1mmol/L regardless of symptoms	Minor hypoglycaemic episodes: episodes where participant was able to treat her/himself	Able to treat him/herself and blood glucose ≤ 3.1 mmol/L	Mild hypoglycaemia with PG < 3.1 mmol/L	Mild hypoglycaemic episodes can be treated by oral administration of glucose or other	An episode not requiring third party assistance where a plasma glucose < 3.1 mmol/L or whole

(Continued)

			and plasma glucose < 3.1 mmol/L, with or without symptoms			products containing sugar	blood glucose < 2.8 mmol/L was recorded (with or without symptoms of hypoglycaemia)
Fulcher 2005	Symptomatic hypoglycaemia was defined as an event with symptoms consistent with hypoglycaemia that was mild (2.8–3.6 mmol/L) or moderate (< 2.8 mmol/L)	—	—	"It could be either mild (between 2.8 and 3.6 mmol/L), moderate (below 2.8 mmol/L but did not require the assistance of another person)"	—	—	—
Heller 2009	Minor: the patient could treat himself/herself and the measured plasma glucose value was < 3.1 mmol/L Symptoms only: the patient could treat himself/herself and no plasma glucose measurement was taken or the measured plasma glucose value was ≥ 3.1 mmol/L	—	ND	Minor: the patient could treat himself/herself and the measured plasma glucose value was < 3.1 mmol/L Symptoms only: the patient could treat himself/herself and no plasma glucose measurement was taken or the measured plasma glucose value was ≥ 3.1 mmol/L	Minor and moderate hypoglycaemia	—	—
Home 2005	Hypoglycaemia was categorised as symptomatic (clinical symptoms confirmed by blood glucose < 2.8 mmol/L) or asymptomatic (confirmed by blood glucose < 2.8 mmol/L without symptoms)	ND	—	"Hypoglycemia was either symptomatic, i.e. with clinical symptoms that could be confirmed by blood glucose below 2.8 mmol/L (50 mg/dL), or asymptomatic, i.e. any event with a confirmed blood glucose level below 2.8 mmol/L (50 mg/dL) but without any symptoms"	—	ND	Hypoglycaemia was either symptomatic, i.e. with clinical symptoms that could be confirmed by blood glucose below 2.8 mmol/L (50 mg/dL), or asymptomatic, i.e. any event with a confirmed

(Continued)

							blood glucose level below 2.8 mmol/L (50 mg/dL) but without any symptoms
Kobayashi 2007	Any symptoms consistent with hypoglycaemia	—	ND	Minor hypoglycaemia	Minor hypoglycaemia	—	—
Liu 2016	Hypoglycaemia was defined as asymptomatic (blood glucose values < 3.9 mmol/L without clinical symptoms), symptomatic (blood glucose < 3.9 mmol/L with associated clinical symptoms)	—	"Asymptomatic hypoglycemia: Blood glucose values < 70 mg/dL (3.9 mmol/L) without clinical symptoms and/or signs. Symptomatic hypoglycemia: Any event with clinical symptoms that were considered to result from a hypoglycemic episode with an accompanying blood glucose < 70 mg/dL (3.9 mmol/L)"	"Symptomatic hypoglycemia: Any event with clinical symptoms that were considered to result from a hypoglycemic episode with an accompanying blood glucose"	Asymptomatic and symptomatic hypoglycaemia	Any event with clinical symptoms that were considered to result from a hypoglycaemic episode with an accompanying blood glucose	—
NCT00595374	—	—	ND	—	Minor hypoglycaemia	—	—
NCT00605137	—	—	ND	Minor hypoglycaemia	Minor hypoglycaemic episodes: blood glucose	—	—

(Continued)

					< 3.1 mmol/L and able treat the period themselves) Symptoms only: no blood glucose measurement or blood glucose > 3.1 mmol/L Biochemical hypoglycaemia: defined as asymptomatic hypoglycaemic with blood glucose value < 3.1 mmol/L		
Pieber 2007	Confirmed hypoglycaemia if plasma glucose was < 3.1 mmol/L and the individuals dealt with the episode themselves	—	ND	Minor: the patient could treat himself/herself and the measured plasma glucose value was <3.1 mmol/L Symptoms only: the patient could treat himself/herself and no plasma glucose measurement was taken or the measured plasma glucose value was ≥ 3.1 mmol/L	Minor and moderate hypoglycaemia	—	ND
Porcellati 2004	Hypoglycaemia was defined as any episode associated with measurement of blood glucose ≤ 4.0 mmol/L irrespective of symptoms. Hypoglycaemia was considered mild when the episodes were self-treated by the patients	—	—	—	—	—	—
PRESCHOOL	Composite hypoglycaemia rate consisting of:	—	"Symptomatic hy-	"Symptomatic hypoglycemia: any event with clinical symptoms	—	ND	—

(Continued)

	(i) Symptomatic hypoglycaemia episodes, which were recorded in patient diaries, then validated by study investigators (ii) Low CGM glucose excursions (< 3.9 mmol/L), which were confirmed by finger stick blood glucose < 3.9 mmol/L 10 min before to 10 min after the low CGM excursion (i.e., confirmed low CGM) (iii) FSBG <3.9 mmol/L, which was recorded ≥1 h from the end of a confirmed low CGM excursion		poglycemia episodes validated by the study investigator based on entries in patients' diaries, - low continuous glucose monitoring system (CGMS) excursions (interstitial glucose < 70 mg/dL [3.9 mmol/L]) confirmed by fingerstick blood glucose (FSBG) < 70 mg/dL, - low FSBG readings (values < 70 mg/dL) performed at other times"	considered to result from hypoglycemia, validated by site based on data from patient diaries"			
Ratner 2000	Hypoglycaemia was divided into 3 subsets: all events, severe hypoglycaemia and nocturnal hypoglycaemia	—	—	"Hypoglycemia was either symptomatic (physical symptoms of hypoglycemia were present and was to be confirmed by blood glucose below 2.8 mmol/L [50 mg/dL]) or asymptomatic (no physical symptoms of hypoglycemia present but fasting blood glucose level from the SMBG measurements was below 2.8 mmol/L [50 mg/dL])"	—	ND	Hypoglycaemia was either symptomatic, i.e. with clinical symptoms that could be confirmed by blood glucose < 2.8 mmol/L (50 mg/dL), or asymptomatic, i.e. any event with a confirmed blood glucose level < 2.8 mmol/L (50 mg/dL) but

(Continued)

							without any symptoms
Robertson 2007	Confirmed episodes: all self-treated episodes of hypoglycaemia with plasma glucose measurements < 3.1 mmol/L whether symptomatic or not	ND	ND	Self-treated episodes of hypoglycaemia with plasma glucose measurements < 3.1 mmol/L whether symptomatic or not	Minor hypoglycaemia	—	Episode with blood glucose < 3.1 mmol/L handled by the patient or asymptomatic
Russell-Jones 2004	Minor, if the blood glucose value was < 2.8 mmol/L and the patient dealt with the episode alone Symptoms only, if no assistance was required and the event was not confirmed by a blood glucose measurement	ND	ND	An episode with symptoms consistent with hypoglycaemia with confirmation by a blood glucose measurement < 2.8 mmol/L and which was handled by the participant himself/herself or any asymptomatic blood glucose measurement	ND	Minor: • An episode with symptoms consistent with hypoglycaemia with confirmation by blood glucose measurement < 2.8 mmol/L and which was handled by the patient himself/herself • Any asymptomatic blood glucose measurement < 2.8 mmol/L	ND
Schober 2002	Hypoglycaemia was categorised as either symptomatic, i.e. with clinical symptoms that could be confirmed by blood glucose levels < 2.8 mmol/L,	—	—	"Hypoglycemia was either symptomatic, i.e. any event with clinical symptoms related to hypoglycemia regardless of whether it could be confirmed by blood glucose below 2.8 mmol/L (50 mg/dL), or asymp-	—	—	ND

(Continued)

	or asymptomatic, i.e. any event with a confirmed blood glucose level < 2.8 mmol/L but without any symptoms			tomatic, i.e. any event with a confirmed blood glucose level below 2.8 mmol/L (50 mg/dL) but without any symptoms"			
Standl 2004	If blood glucose was < 2.8 mmol/L and the patient handled the episode him- or herself	—	—	An episode with symptoms consistent with hypoglycaemia with confirmation by blood glucose measurement < 2.8 mmol/L and which was handled by the participant himself/herself, or any asymptomatic blood glucose measurement < 2.8 mmol/L	ND	Minor: • An episode with symptoms consistent with hypoglycaemia with confirmation by blood glucose measurement < 2.8 mmol/L and which was handled by the patient himself/herself • Any asymptomatic blood glucose measurement < 2.8 mmol/L	Hypoglycaemia with blood glucose < 2.8 mmol/L handled by the patient or asymptomatic
SWITCH 1	Blood glucose ≤ 3.9 mmol/L or > 3.9 mmol/L when they occur in conjunction with hypoglycaemic symptoms, able to treat themselves	ND	ND	Symptoms of hypoglycaemia and/or episode with low glucose measurement ≤ 3.9 mmol/L, able to self-treat	Asymptomatic hypoglycaemia: an episode not accompanied by typical symptoms of hypoglycaemia, but with a measured plasma glucose con-	—	ND

(Continued)

	centration ≤ 3.9 mmol/L
	Documented symptomatic hypoglycaemia: an episode during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration ≤ 3.9 mmol/L
	Pseudo-hypoglycaemia: an episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured plasma glucose concentration > 3.9 mmol/L but approaching that level
	Probable symptomatic hypoglycaemia: an episode during which symptoms

(Continued)

				typical of hypoglycaemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤ 3.9 mmol/L			
Thalange 2013	Mild hypoglycaemia was defined as episodes where the participants were able to treat themselves Moderate hypoglycaemia was categorised as episodes where participants required assistance, but responded to oral treatment	—	ND	Mild hypoglycaemia was defined as episodes where the participants were able to treat themselves Moderate hypoglycaemia was categorised as episodes where participants required assistance, but responded to oral treatment	ND	Able to self-treat and confirmed by capillary blood glucose < 2.8 mmol/L or 3.1 mmol/L if expressed as plasma glucose	—
Urakami 2017	Hypoglycaemia was defined as a self-monitored PG level < 70 mg/dL	Hypoglycaemia was defined as a self-monitored PG level < 70 mg/dL	—	—	—	—	—
Vague 2003	Minor if blood glucose was < 2.8 mmol/L and the patients dealt with the episode themselves	—	—	Minor if blood glucose was < 2.8 mmol/L and the patients dealt with the episode themselves and any asymptomatic blood glucose measurement < 2.8 mmol/L	ND	• Minor: An episode with symptoms consistent with hypoglycaemia with confirmation by blood glucose measurement <	Hypoglycaemia with blood glucose < 2.8 mmol/L handled by the patient or asymptomatic

(Continued)

						2.8 mmol/L and which was handled by the patient himself/herself. Any asymptomatic blood glucose measurement < 2.8 mmol/L

—: indicates source not available

CGM: continuous glucose monitoring;**CGMS:** continuous glucose monitoring system; **CRF**: case record form; **EMA**: European Medicines Agency; **FDA**: Food and Drug Administration; **FSBG:** fingerstick blood glucose; **ND**: not defined; **NR**: not reported; **PG**: plasma glucose; **SMBG:** self-measured blood glucose; **SMPG**: self-monitored plasma glucose.

Appendix 38. Source of information for outcome data: socioeconomic effects

Study ID	Publication	Study author request	Trials register	Clinical study report	Clinical study synopsis	EMA report	FDA report
Bartley 2008	Yes	—	No	No	No	—	—
BEGIN Basal-Bolus Type 1	Yes	—	No	No	No	No	No
BEGIN Flex T1	Yes	—	No	No	No	No	No
BEGIN Young	Yes	—	No	No	No	No	No
Bolli 2009	No	—	—	—	—	—	—
Chase 2008	No	—	No	No	No	—	—
Davies 2014	No	No	No	No	No	No	No
Fulcher 2005	No	—	—	Yes	—	—	—
Heller 2009	No	—	No	No	No	—	—
Home 2005	No	No	—	Yes	—	No	No
Kobayashi 2007	No	—	No	No	No	—	—
Liu 2016	No	—	No	No	No	No	—
NCT00595374	—	—	No	—	No	—	—
NCT00605137	—	—	No	No	No	—	—
Pieber 2007	Yes	—	No	No	No	—	No
Porcellati 2004	No	—	—	—	—	—	—
PRESCHOOL	No	—	No	No	—	No	—
Ratner 2000	No	No	No	No	No	No	No
Robertson 2007	No	No	No	No	No	—	No

(Continued)

Russell-Jones 2004	No	No	No	No	No	No	No
Schober 2002	No	—	—	Yes	—	—	No
Standl 2004	No	—	—	No	No	No	No
SWITCH 1	No	No	No	No	No	—	No
Thalange 2013	No	—	No	No	No	No	—
Urakami 2017	No	No	—	—	—	—	—
Vague 2003	No	—	—	No	No	No	No

—: indicates source not available

EMA: European Medicines Agency; **FDA**: Food and Drug Administration.

Appendix 39. Source of information for outcome data: HbA1c

Study ID	Publication	Study author request	Trials register	Clinical study report	Clinical study synopsis	EMA report	FDA report
Bartley 2008	Yes	—	No	Yes	No	—	—
BEGIN Basal-Bolus Type 1	No	—	Yes	Yes	Yes	Yes	No
BEGIN Flex T1	Yes	—	Yes	Yes	Yes	Yes	No
BEGIN Young	Yes	—	Yes	Yes	Yes	Yes	No
Bolli 2009	Yes	—	—	—	—	—	—
Chase 2008	No	—	No	Yes	No	—	—
Davies 2014	Yes	Yes	Yes	Yes	Yes	Yes	No
Fulcher 2005	No	—	—	Yes	—	—	—
Heller 2009	Yes	—	No	Yes	No	—	—
Home 2005	Yes	No	—	Yes	—	No	Yes
Kobayashi 2007	Yes	—	No	No	Yes	—	—
Liu 2016	Yes	—	Yes	Yes	Yes	Yes	—
NCT00595374	—	—	No	—	No	—	—
NCT00605137	—	—	No	No	Yes	—	—
Pieber 2007	Yes	—	No	Yes	No	—	Yes
Porcellati 2004	Yes	—	—	—	—	—	—
PRESCHOOL	No	—	No	Yes	—	No	—
Ratner 2000	Yes	—	—	Yes	—	No	No
Robertson 2007	Yes	No	No	Yes	Yes	—	Yes

(Continued)

Russell-Jones 2004	Yes	No	No	Yes	No	Yes	Yes
Schober 2002	Yes	—	—	Yes	—	—	No
Standl 2004	No	—	—	Yes	No	Yes	Yes
SWITCH 1	No	No	No	Yes	No	—	No
Thalange 2013	Yes	—	Yes	Yes	No	Yes	—
Urakami 2017	Yes	Yes	—	—	—	—	—
Vague 2003	Yes	—	—	Yes	No	Yes	Yes

—: indicates source not available

EMA: European Medicines Agency; **FDA**: Food and Drug Administration; **HbA1c**: glycosylated haemoglobin A1c.

Appendix 40. Source of information for outcome data: combined HbA1c + severe hypoglycaemia

Study ID	Publication	Study author request	Trials register	Clinical study report	Clinical study synopsis	EMA report	FDA report
Bartley 2008	No	—	No	No	No	—	—
BEGIN Basal-Bolus Type 1	No	—	No	Yes	Yes	No	No
BEGIN Flex T1	No	—	No	Yes	No	No	No
BEGIN Young	No	—	No	No	No	No	No
Bolli 2009	No	—	—	—	—	—	—
Chase 2008	No	—	No	No	No	—	—
Davies 2014	No	No	No	Yes	No	No	No
Fulcher 2005	No	—	—	No	—	—	—
Heller 2009	Yes	—	No	Yes	Yes	—	—
Home 2005	No	No	—	No	—	No	No
Kobayashi 2007	No	—	No	No	No	—	—
Liu 2016	No	—	No	No	No	No	—
NCT00595374	—	—	No	—	No	—	—
NCT00605137	—	—	No	No	No	—	—
Pieber 2007	No	—	No	No	No	—	No
Porcellati 2004	No	—	—	—	—	—	—
PRESCHOOL	No	—	No	No	—	No	—
Ratner 2000	No	—	—	—	—	No	No
Robertson 2007	No	No	No	No	No	—	No

(Continued)

Russell-Jones 2004	No	No	No	No	No	No	No
Schober 2002	No	—	—	No	—	—	No
Standl 2004	No	—	—	No	No	No	No
SWITCH 1	No	No	No	No	No	—	No
Thalange 2013	No	—	No	No	No	No	—
Urakami 2017	No	No	—	—	—	—	—
Vague 2003	No	—	—	No	No	No	No

—: indicates source not available

EMA: European Medicines Agency; **FDA**: Food and Drug Administration; ´**HbA1c**: glycosylated haemoglobin A1c.

Appendix 41. Overview of source of information for outcome data

Outcome measure	Publication[a]	Study author request[a]	Trials register with results[a]	Clinical study report[a]	Clinical study synopsis[a]	EMA report	FDA report
All-cause mortality	6/24	2/24	1/8	20/22	14/23	4	7
Cardiovascular mortality	6/24	2/24	1/8	20/22	15/23	4	4
Non-fatal myocardial infarction	1/24	2/24	1/8	5/22	0	0	0
Non-fatal stroke	1/24	2/24	0	4/22	0	0	0
End-stage renal disease	1/24	2/24	0	0	0	0	0
Blindness	1/24	2/24	0	0	0	0	0
Diabetic ketoacidosis	6/24	2/24	5/8	17/22	3/23	2	1
Serious adverse events	13/24	2/24	7/8	20/22	13/23	3	1
Non-serious adverse events	13/24	2/24	7/8	21/22	9/23	2	0
Severe hypoglycaemia	18/24	2/24	2/8	19/22	7/23	6	9
Nocturnal hypoglycaemia	17/24	2/24	3/8	19/22	4/23	6	0
Mild/moderate hypoglycaemia	16/24	2/24	2/8	20/22	3/23	6	3
Health-related quality of life	4/24	2/24	1/8	9/22	3/23	4	7
HbA1c	19/24	2/24	6/8	20 /22	8/23	9	6
HbA1c + severe hypoglycaemia	2/24	0	0	5/22	4/23	0	0
Socioeconomic effects	5/24	0	0	3/22	0	0	0

[a]Records with information / total number of available records

EMA: European Medicines Agency; **FDA**: Food and Drug Administration; **HbA1c**: glycosylated haemoglobin A1c.

Appendix 42. Overview of comparisons using various definitions of hypoglycaemia

Outcome measure	Detemir vs NPH	Glargine vs NPH	Detemir vs glargine	Degludec vs detemir	Degludec vs glargine
Severe hypoglycaemia	RR 0.69, 95% CI 0.52 to 0.92[a]	RR 0.84, 95% CI 0.67 to 1.04	RR 0.59, 95% CI 0.13 to 2.63	RR 1.17, 95% CI 0.81 to 1.69	RR 1.22, 95% CI 0.82 to 1.82
Hypoglycaemia reported as a serious adverse event	RR 0.93, 95% CI 0.51 to 1.71	RR 0.94, 95% CI 0.64 to 1.39	RR 1.16, 95% CI 0.14 to 9.48	RR 0.92, 95% CI 0.37 to 2.32	RR 0.81, 95% CI 0.40 to 1.66
Severe nocturnal hypoglycaemia	RR 0.67, 95% CI 0.39 to 1.17	RR 0.83, 95% CI 0.62 to 1.12	RR 0.55, 95% CI 0.06 to 5.12	RR 1.12, 95% CI 0.51 to 2.46	RR 1.39, 95% CI 0.59 to 3.27
Any nocturnal hypoglycaemia	RR 0.91, 95% CI 0.87 to 0.95[a]	RR 1.00, 95% CI 0.96 to 1.05	RR 1.01, 95% CI 0.93 to 1.09	No data	RR 0.99, 95% CI 0.91 to 1.07
Confirmed nocturnal hypoglycaemia	No data	No data	RR 1.01, 95% CI 0.92 to 1.10	RR 1.04, 95% CI 0.94 to 1.15	No data
Mild nocturnal hypoglycaemia	RR 0.90, 95% CI 0.85 to 0.96[a]	RR 0.84, 95% CI 0.66 to 1.07	No data	RR 0.97, 95% CI 0.86 to 1.10 (documented)	RR 0.98, 95% CI 0.90 to 1.07
Symptomatic nocturnal hypoglycaemia	RR 0.88, 95% CI 0.79 to 0.98[a]	RR 0.93, 95% CI 0.82 to 1.05	RR 1.02, 95% CI 0.81 to 1.29	RR 0.72, 95% CI 0.15 to 3.59	RR 1.22, 95% CI 0.72 to 2.07
Asymptomatic nocturnal hypoglycaemia	No evidence of a difference	Not reported	No data	RR 0.91, 95% CI 0.80 to 1.03	RR 0.84, 95% CI 0.71 to 1.00
Mild/moderate hypoglycaemia	RR 0.97, 95% CI 0.94 to 0.99[a]	RR 1.02, 95% CI 1.00 to 1.04	RR 1.04, 95% CI 0.94 to 1.14	RR 1.02, 95% CI 0.99 to 1.05	RR 1.02, 95% CI 0.99 to 1.04
HbA1c < 7.0% without major/severe hypoglycaemia	No data	No data	RR 1.11, 95% CI 0.81 to 1.51	RR 1.09, 95% CI 0.84 to 1.41	RR 0.92, 95% CI 0.78 to 1.10

[a]Favouring insulin detemir

CI: confidence interval; **HbA1c**: glycosylated haemoglobin A1c; **NPH:** neutral protamine Hagedorn; **RR**: risk ratio.

WHAT'S NEW

Date	Event	Description
27 April 2021	Amended	Analysis 2.15 corrected
27 April 2021	Amended	Analysis 2.15 corrected

HISTORY

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Review first published: Issue 3, 2021

CONTRIBUTIONS OF AUTHORS

All review authors read and approved the final review draft.

BH: protocol and review draft, data interpretation and review of drafts, contact with pharmaceutical companies and investigators, study selection, data extraction, data analysis, data interpretation, future review updates

MIM: search strategy development, performed electronic searches, searched regulatory agencies web pages, review of drafts

BR: protocol and review draft, study selection, data analysis, data interpretation and review of drafts, future review updates

DECLARATIONS OF INTEREST

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BR: none known.

MIM: none known.

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External sources

- Health Action International's ACCISS Study, Netherlands

  Health Action International's ACCISS Study was started in 2015 to identify and address the inequities and inefficiencies in the global insulin market. Health Action International is a not-for-profit foundation, based in Amsterdam The Netherlands, committed to advancing access to medicines globally.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In addition to the databases mentioned in the protocol, we searched the Health Technology Assessment (HTA) database, which became available in the meantime.

Because of scarce data, we changed the following outcome measures in the 'Summary of findings' tables.

- Instead of end-stage renal disease, we used severe nocturnal hypoglycaemia.
- Instead of combined glycosylated haemoglobin A1c (HbA1c) with severe hypoglycaemia, we used HbA1c only.

We renamed the outcome 'serious/severe hypoglycaemia' to 'severe hypoglycaemia' because this term was mainly used in the publications and clinical study reports. For the same reason, we renamed the outcome 'HbA1c combined with serious/severe hypoglycaemia' to 'HbA1c combined with severe hypoglycaemia'.

In addition to the outcome measure 'non-serious adverse events', we analysed 'withdrawals due to adverse events' because this outcome was detailed in the clinical study reports.

In addition to the outcome measure 'severe hypoglycaemia', we analysed 'hypoglycaemia reported as a serious adverse event' because this outcome was detailed in the clinical study reports and is the hardest clinical endpoint with regard to hypoglycaemic episodes.

We additionally evaluated the subgroup adults versus children because appropriate data were available and it appeared to be important to report this information for consumers and decision makers.

NOTES

We have based parts of the Methods, as well as Appendix 6 of this Cochrane Review, on a standard template established by the CMED Group.

INDEX TERMS

Medical Subject Headings (MeSH)

Bias; Confidence Intervals; Diabetes Mellitus, Type 1 [blood] [*drug therapy] [mortality]; Glycated Hemoglobin A [analysis]; Hypoglycemia [chemically induced] [mortality]; 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]; Myocardial Infarction [chemically induced] [mortality]; Quality of Life; Randomized Controlled Trials as Topic; Stroke [chemically induced] [mortality]

MeSH check words

Adolescent; Adult; Child; Child, Preschool; Female; Humans; Male; Young Adult