**National Essential Medicine List**
**Paediatric Hospital Level Medication Review Process**
**Component: Endocrine**

## MEDICINE MOTIVATION:

### 1. Executive Summary

**Date: November 2021**
**Medicine (INN):** Insulin detemir, insulin glargine, insulin degludec
**Medicine (ATC):** A10AE05; A10AE54; A10AE56
**Indication (ICD10 code):** E10.69
**Patient population**: Type 1 Diabetes Mellitus (T1DM) under 18 years with severe hypoglycaemias, nocturnal hypoglycaemia or hypoglycaemia unawareness
**Prevalence of condition**: T1DM: estimate (African region) 0-14y: 9.4 per 1000; 0-19y: 25.8 per 1000[1]; Proportion with hypoglycaemia: 85.7 episodes per 100 patient years[2]
**Level of Care:** Secondary
**Prescriber Level:** Specialist
**Current standard of Care:** Neutral protamine Hagedorn (NPH) insulin
**Efficacy estimates: (preferably NNT)** very few statistically significant estimates, see Table 2 for risk ratio and NNT estimates.
**Motivator/reviewer name(s):** Tanya Dennis
**PTC affiliation:** None

### 2. Name of author(s)/motivator(s)

Tanya Dennis

### 3. Author affiliation and conflict of interest details

Lecturer, University of the Witwatersrand, Division of Community Paediatrics
Declarations of Interest: Astra Zeneca, Eli Lily– Husband AD Board. Astra Zeneca, Boeringer Ingelheim, Pfizer, Merck – Husband given talks.

### 4. Introduction/ Background

Children with Type 1 Diabetes Mellitus (T1DM) are at greater risk of complications related to insulin therapy than their adult counterparts, due largely to their dependence on a caregiver to administer and regulate their treatment. Strict glycaemic control early in the course of the disease is recommended to prevent long term microvascular complications and death[3] however this increases the risk of hypoglycaemic episodes. However, improved glycaemic control has to be weighed against the risk of hypoglycaemia.

Insulin analogues have been developed to better mimic the physiological response to glycaemic load in patients who are insulin dependent. The long acting analogues have a lower peak effect with more stable delivery.[4,5]

Reported benefits of insulin analogue therapy include:

- Improved basal bolus regimen application
- Reduced nocturnal hypoglycaemia[5]
- Improved perceived quality of life[6]

Children diagnosed with type 1 diabetes in early life (before 5-6 years of age) have been shown to have their neuropsychological profiles adversely affected. While hypoglycaemic events have not been directly related, severe recurrent hypoglycaemic episodes to a developing brain should be avoided for the potential risk.[7]

Complications of hypoglycaemia:

- Emotional morbidity for child and caregivers
- Treatment adherence negatively affected to avoid repeat episodes of hypoglycaemia[8]

The recent inclusion of long-acting insulin analogues on the World Health Organization's Model Essential Medicines List for Children was rationalised as follows: "the available evidence showed that the magnitude of clinical benefit of long-acting insulin analogues over human insulin for most clinical outcomes was small, making the large price differential between insulin analogues and human insulin difficult to justify. However, the Committee considered that the observed benefits of insulin analogues over human insulin with regard to lower incidence of symptomatic and nocturnal hypoglycaemia were consistent and clinically important, particularly for the subset of patients at high risk of hypoglycaemia, justifying the decision to recommend inclusion."[9]

A longitudinal cohort study from Japan[10] describes three cohorts of children with T1DM over time (1995, 2000 and 2008). The progression from the use of two insulin analogues went from 0 to 94.7%. They demonstrated a statistically significant improvement in glycaemic control (HbA1c % 9.33 $\pm$ 2.05 in 1995 cohort to 7.75 $\pm$ 1.19 in the 2008 cohort; p <.0001). The percentage of patients with optimal control improved from 18.5% to 43.9%. There was a general increase in body mass index, with increasing rates of overweight (12.2% to 18%) and obesity (2.3% to 5%). The total daily insulin dose per body weight (U/kg/d) remained similar (1.01 $\pm$0.32 to 1.08 $\pm$0.34). The incidence rate from the 2000 cohort to the 2008 cohort is mentioned to be lower, p= .02. There was a significant change in the regimen utilised over the cohorts, from predominant twice a day regimen to a multiple daily insulin regimen. The authors attribute the improvements in glycaemic control and decrease in incidence rate of severe hypoglycaemias to the basal-bolus regimens and the switch to analogue insulins. However, they also mention that their patients have access to monthly follow up visits and get face-to-face advice when struggling with control, particularly during puberty. In addition, there is no mention of calculating total daily insulin dose by ideal body weight. Given the progressively increasing BMI in the cohorts, their insulin dose by kilogram of ideal body weight had probably increased. While the use of insulin analogues may have contributed to their improved outcomes, many clinical factors had changed over time.

## 5. Purpose/Objective i.e.

- Reduced incidence of severe hypoglycaemia, nocturnal hypoglycaemia and hypoglycaemia unawareness in at risk population

## 6. PICO

**-P** *Children and adolescents with type 1 diabetes and recurrent severe hypoglycaemias, hypoglycaemia unawareness or nocturnal hypoglycaemias*

**-I** *Insulin analogue (long-acting) – insulin glargine, insulin detemir, insulin degludec*

**-C** *Standard insulin therapy (NPH insulin)*

**-O** *Reduced incidence of severe hypoglycaemia, secondary outcomes: improved quality of life, improved glycaemic control*

## 7. Methods:

### a. Data sources

- Cochrane library search
- Pubmed
- Medline

### b. Search strategy

Cochrane Library

Type 1 diabetes mellitus in Title Abstract Keyword AND insulin degludec in Title Abstract Keyword AND neutral protamine hagedorn in Title Abstract Keyword AND hypoglycaemia in Title Abstract Keyword AND randomised controlled trial in Title Abstract Keyword

- Type 1 diabetes mellitus in Title Abstract Keyword AND insulin detemir in Title Abstract Keyword AND neutral protamine hagedorn in Title Abstract Keyword AND hypoglycaemia in Title Abstract Keyword AND randomised controlled trial in Title Abstract Keyword
- Type 1 diabetes mellitus in Title Abstract Keyword AND insulin glargine in Title Abstract Keyword AND hypoglycaemia in Title Abstract Keyword AND "randomised controlled trial" in Title Abstract Keyword AND children in Title Abstract Keyword - (Word variations have been searched)

Pubmed

- (((((type 1 diabetes mellitus) AND (hypoglycaemia)) AND (children and adolescents)) AND (neutral protamine hagedorn insulin)) AND (insulin degludec)) AND (randomised controlled trial)
- (((((type 1 diabetes mellitus) AND (hypoglycaemia)) AND (children and adolescents)) AND (neutral protamine hagedorn insulin)) AND (insulin glargine)) AND (randomised controlled trial)
- (((((type 1 diabetes mellitus) AND (hypoglycaemia)) AND (children and adolescents)) AND (neutral protamine hagedorn insulin)) AND (insulin detemir)) AND (randomised controlled trial)

Medline

- type 1 diabetes mellitus AND hypoglycaemia AND ( children and adolescents ) AND neutral protamine hagedorn insulin AND insulin detemir AND randomized controlled trials
- type 1 diabetes mellitus AND hypoglycaemia AND ( children and adolescents ) AND neutral protamine hagedorn insulin AND insulin glargine AND randomized controlled trials
- type 1 diabetes mellitus AND hypoglycaemia AND ( children and adolescents ) AND neutral protamine hagedorn insulin AND insulin degludec AND randomized controlled trials

## c. Excluded studies:

**Table 1: Studies excluded from the review**

| | |
|---|---|
| Garg 2010[11] | Clinical experience, not RCT |
| Semlitsch et al, 2020[12] | Type 2 DM (T2DM) |
| Harris, 2021[13] | T2DM |
| Harris, 2020[14] | T2DM |
| Swinnen, 2011[15] | T2DM |
| Vardi, 2008[16] | Newer systematic review (SR) available |
| McCance, 2012[17] | Maternal/perinatal |
| Bartley, 2008[18] | Efficacy/safety study |
| Arutchelvam, 2009[19] | Comparison of basal insulins following exercise |
| Thalange, 2013[20] | Included in SR |
| Fajardo, 2008[21] | T2DM |
| Hermansen, 2007[22] | Weight gain |
| Ridderstrale, 2013[23] | T2DM |
| Saravanan, 2017[24] | T2DM |
| Hoogma, 2006[25] | Subcut infusion vs MDI |
| Dixon, 2007[26] | Cost-effectiveness of health technology |
| Thalange, 2011[27] | Included in SR |
| Pedersen-Bjergaard, 2014[28] | Adult study |
| Home, 2015[29] | T2DM |
| Fulcher, 2005[30] | Adult study |
| Rosenstock, 2009[31] | T2DM |
| Ling, 2020[32] | T2DM |
| Chatterjee, 2006[33] | Opinion |
| Mathiesen, 2011[34] | GDM |
| Witthaus, 2001 | Treatment satisfaction/psychological well being |
| Dunn, 2003[35] | Review |
| HOE 901/2004 study investigators group, 2003[36] | T2DM |
| Simpson, 2007[37] | Lispro review |
| Ji, 2020[38] | Diabetes in pregnancy |
| Robertson, 2007[39] | Included in SR |
| Monami, 2009[40] | Adult study |
| Chapman, 2005[41] | Not RCT |
| Petit-Bibal, 2015[42] | Aspart and detemir |
| Hassan, 2008[43] | Rapid acting insulins included |
| Schober, 2002[44] | Included in SR |
| Philoteou, 2011[45] | Rapid acting insulins included |
| Murphy, 2003[46] | Rapid acting insulins included |

## 8. Results

### Evidence synthesis: Hemmingsen, et al 2021[47]

Systematic review and meta-analysis
N=8780 (21% children < 18 years)
Population: Type 1 diabetes mellitus

Table 2 outlines the details of the Cochrane review of the different comparisons. Overall, there were very few statistically significant differences found for the outcomes of interest.

Primary Outcome – Severe hypoglycaemia

- All comparisons except for Insulin detemir vs NPH insulin were not statistically significant different for the primary outcome of interest.
- For insulin detemir compared to NPH insulin the result was only statistically significant for the combined population (adults and children) and not children alone (RR 0.69 [0.52, 0.92], P=0.01, NNT = 33 in favour of insulin detemir – *low risk of bias*).

Secondary Outcome – Hypoglycaemia as an adverse event

- No comparisons were found to be statistically significant different for hypoglycaemia as an adverse event.

Secondary Outcome – Nocturnal hypoglycaemia (any and severe)

- All the comparisons were found to be not significantly different for severe hypoglycaemia.
- Insulin glargine was found to be significantly different to NPH insulin for any nocturnal hypoglycaemia in children (RR 1.01 [0.95, 1.08], P=0.05, NNT = 10 in favour of insulin glargine – *low risk of bias*).
- Insulin detemir was found to be significantly different to NPH insulin for any nocturnal hypoglycaemia in children (RR 0.87 [0.81, 0.94], P=0.0003, NNT=10 in favour of insulin detemir – *low risk of bias*).

Secondary Outcome - Glycaemic control (HbA1c)

- All the comparisons were found to be not significantly different for glycaemic control except for Insulin degludec compared to insulin glargine.
- The comparison for insulin degludec and insulin glargine was only for the combined population and not children alone (MD 0.10 [0.00, 0.21], P=0.05 – *low risk of bias*).

Secondary Outcome – Quality of Life

- Estimates for quality of life could not be determine for two of the comparisons (Insulin detemir vs NPH insulin and Insulin detemir vs insulin glargine).
- Insulin degludec was found to be significantly different compared to insulin detemir for mental health in the combined population and not children alone (MD -3.0 [-4.44, -1.56], P<0.0001 – *moderate risk of bias*).
- Results for quality of life were found to be not statistically significant for insulin glargine vs NPH insulin and Insulin degludec vs insulin glargine.

Table 2: Details of Hemmingsen et al. 2021 Cochrane Review

| Interventions | Outcomes | | | | |
|---|---|---|---|---|---|
| | Severe hypoglycaemia | Hypoglycaemia as adverse event | Nocturnal hypoglycaemia | Glycaemic control (HbA1c) | Quality of life |
| **Insulin glargine vs NPH insulin** | | | | | |
| All individuals (adults and children) | Risk ratio 0.84 [0.67, 1.04]<br>Low risk of bias<br>P=0.11, in favour of insulin glargine ***(not stat. sig.)*** | RR 0.94 [0.64, 1.39]<br>P=0.76, in favour of insulin glargine ***(not stat. sig.)*** | RR 1.00 [0.96, 1.06]<br>P=0.96, in favour of insulin glargine ***(not stat. sig.)***<br>Severe:<br>RR 0.83 [0.62, 1.12]<br>P=0.23, in favour of insulin glargine ***(not stat. sig.)*** | Mean difference 0.02 [-0.06, 0.11]<br>Low risk of bias<br>P=0.59 | Mean difference 0.62 [-0.71, 1.96]<br>Moderate risk of bias<br>P=0.36 |
| Children only | RR 1.14 [0.59, 2.21]<br>Low risk of bias<br>P=0.70, in favour of insulin glargine ***(not stat. sig***.) | RR 0.95 [0.32; 2.87]<br>P=0.93, in favour of insulin glargine ***(not stat. sig.)*** | RR 1.01 [0.95, 1.08]<br>**P=0.05, NNT = 10 in favour of insulin glargine (statistically significant)**<br>Severe:<br>RR 0.77 [0.47, 1.25]<br>Low risk of bias<br>P= 0.23, in favour of insulin glargine ***(not stat. sig.)*** | MD 0.03 [-0.13, 0.20]<br>Low risk of bias<br>P=0.70 | No specific data |
| **Insulin detemir vs NPH insulin** | | | | | |
| All individuals (adults and children) | RR 0.69 [0.52, 0.92]<br>Low risk of bias<br>**P=0.01, NNT = 33 in favour of insulin detemir (statistically significant)** | RR 0.94 [0.48, 1.86]<br>P=0.82, in favour of insulin detemir ***(not stat. sig.)*** | RR 0.91 [0.87, 0.95]<br>**P<0.0001, NNT=18 in favour of insulin detemir (statistically significant)**<br>Severe:<br>RR 0.67 [0.39, 1.17], Low risk of bias<br>P=0.16, in favour of insulin detemir ***(not stat. sig.)*** | Mean difference 0.01 [-0.08, 0.10]<br>Low risk of bias<br>P=0.89 | No data |
| Children only | RR 0.61 [0.30, 1.23]<br>P=0.17, in favour of insulin detemir ***(not stat. sig.)*** | RR 0.95 [0.16, 5.57]<br>P=0.95, in favour of insulin detemir ***(not stat. sig.)*** | RR 0.87 [0.81, 0.94]<br>**P=0.0003, NNT=10 in favour of insulin detemir (statistically significant)**<br>Severe:<br>RR 0.64 [0.13, 3.17], Low risk of bias<br>P=0.09, in favour of NPH insulin ***(Not stat. sig.)*** | MD 0.13 [-0.04, 0.31]<br>Low risk of bias<br>P=0.13 | No data |

| Interventions | Outcomes | | | | |
|---|---|---|---|---|---|
| | Severe hypoglycaemia | Hypoglycaemia as adverse event | Nocturnal hypoglycaemia | Glycaemic control (HbA1c) | Quality of life |
| **Insulin detemir vs insulin glargine** | | | | | |
| All individuals (adults and children) | RR 0.59 [0.13, 2.63]<br>Low risk of bias<br>P=0.49, in favour of insulin glargine ***(not stat. sig.)*** | RR 1.16 [0.14, 9.48]<br>P=0.89, in favour of insulin glargine ***(not stat. sig.)*** | RR 1.01 [0.93, 1.09]<br>P=0.84, in favour of insulin glargine ***(not stat. sig.)***<br><u>Severe:</u><br>RR 0.55 [0.06, 5.12], P=0.60, in favour of insulin glargine ***(not stat. sig.)*** | MD -0.01 [-0.13, 0.12]<br>P=0.89 | No data |
| **Insulin degludec vs insulin detemir** | | | | | |
| All individuals (adults and children) | RR 1.17 [0.81, 1.69]<br>Low risk of bias<br>P=0.42, in favour of insulin detemir ***(not stat. sig.)*** | RR 0.69 [0.29, 1.69]<br>P=0.86, in favour of insulin detemir ***(not stat. sig.)*** | RR 1.04 [0.94, 1.15]<br>P=0.40, in favour of insulin degludec ***(not stat. sig.)***<br><u>Severe:</u><br>RR 1.12 [0.51, 2.46]<br>Low risk of bias. P=0.29, in favour of insulin detemir ***(not stat. sig.)*** | MD 0.05 [-0.08, 0.18]<br>Low risk of bias<br>P=0.44 | <u>Physical health:</u> MD -0.60 [-1.83, 0.63]<br>P=0.34<br><u>Mental health:</u><br>MD -3.0 [-4.44, -1.56]<br>Moderate risk of bias<br>**P<0.0001** |
| Children only | RR 1.3 [0.81, 2.12]<br>Low risk of bias<br>P=0.30, in favour of insulin detemir ***(not stat. sig.)*** | RR 2.01 [0.37, 10.84], P=0.42<br>in favour of insulin detemir ***(not stat. sig.)*** | RR 1.07, 0.94, 1.12],<br>P=0.29, in favour of insulin detemir ***(not stat. sig.)***<br><u>Severe:</u><br>RR 1.01 [0.30, 3.41], Low risk of bias<br>P=0.99, in favour of insulin detemir ***(not stat. sig.)*** | MD 0.11 [-0.08, 0.30]<br>Low risk of bias<br>P=0.26 | No data |
| **Insulin degludec vs insulin glargine** | | | | | |
| All individuals (adults and children) | RR 1.22, [0,82, 1.82]<br>Low risk of bias<br>P=0.32, in favour of insulin glargine ***(not stat. sig.)*** | RR 0.81 [0.40, 1.66]<br>P=0.57, in favour of insulin degludec **(not stat. sig.)** | RR 0.99 [0.91, 1.07], P= 0.76, in favour of insulin degludec ***(not stat. sig.)***<br><u>Severe:</u><br>RR 1.39 [0.59, 3.27], P=0.46, in favour of insulin glargine ***(not stat. sig.)*** | MD 0.10 [0.00, 0.21]<br>Low risk of bias<br>**P=0.05** | <u>Physical health:</u><br>MD -0.04 [-1.12, 1.13]<br>Low risk of bias. P=0.94<br><u>Mental health:</u><br>MD -0.09 [-1.03, 0.85]<br>Low risk of bias. P=0.85 |
| | Not estimable, moderate to high risk of bias | Not estimable | Not estimable | MD 0.00, [-.055, 0.55]<br>Moderate – high risk of bias. P=1.00 | Not estimable |

## 8. Evidence quality:

Level 1 evidence including a child cohort.

## 9. Alternative agents:

Continue management with current standard of care.

## 10. Costs

| Product | Product Price* | Price per ml |
|---|---|---|
| Insulin, Analogue, Human, Long Acting; 100IU/ml; pen, prefilled; 3 ml | R51.02 | R17.01 |
| Insulin, Biosynthetic, Human, Isophane; 100IU/ml; injection; 10 ml | R34.14 | R3.41 |
| Insulin, Biosynthetic, Human, Isophane; 100IU/ml; pen, prefilled; 3 ml | R32.06 | R10.69 |

**Master Health Product List (MHPL) December 2021*

Current contract prices for long acting show that there a 1.5 to almost 5 fold difference in price compared to the isophane insulin.

## 11. Conclusion

Existing level 1 evidence does not provide compelling reasons for the introduction of long-acting insulin analogues onto the EML. As such, the PERC **does not** recommend the procurement of long-acting insulin analogues for use at paediatric hospital level at this time.

A review of this decision would be indicated with a substantial decrease in the cost of insulin analogues or if evidence of a marked improvement of glycaemic control, decrease in risk of complications or improved quality of life emerges.

**EVIDENCE TO DECISION FRAMEWORK**

| | JUDGEMENT | SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS |
|---|---|---|
| QUALITY OF EVIDENCE | **What is the overall confidence in the evidence of effectiveness?**<br>Confident: ☐ Not confident: x Uncertain: ☐ | No clear evidence of benefit, wide confidence intervals for hypoglycaemia outcomes, minimal data on quality of life outcomes, no clear effect on glycaemic control |

| | | |
|---|---|---|
| **BENEFITS & HARMS** | **Do the desirable effects outweigh the undesirable effects?**<br><br>Benefits outweigh harms [ ] Harms outweigh benefits [ ] Benefits = harms or Uncertain [x] | No clear benefit or harm |
| **THERAPEUTIC INTERCHANGE** | Therapeutic alternatives available:<br>Yes [x] No [ ]<br><br>List the members of the group.<br><br>NPH insulin<br><br>List specific exclusion from the group: | Rationale for therapeutic alternatives included:<br>Current standard of care: Human insulin, intermediate acting NPH insulin (as presented in systematic review)<br><br>References:<br>Hemmingsen 2021[47]<br><br>Rationale for exclusion from the group:<br><br>References: |
| **VALUES & PREFERENCES / ACCEPTABILITY** | **Is there important uncertainty or variability about how much people value the options?**<br>Minor [ ] Major [x] Uncertain [ ]<br><br>**Is the option acceptable to key stakeholders?**<br>Yes [x] No [ ] Uncertain [ ] | There is a theoretical consideration for improved adherence, and a perceived improvement in quality of life (not clearly confirmed by evidence as reviewed in the systematic review).<br><br>Type 1 diabetics and clinicians who treat this condition feel strongly about the benefit of this treatment is safer and beneficial to the population at risk (anecdotal). |
| **RESOURCE USE** | **How large are the resource requirements?**<br><br>More intensive [x] Less intensive [ ] Uncertain [ ] | *See Costing section*<br>Current contract prices for long acting show that there a 1.5 to almost 5 fold difference in price compared to the isophane insulin.<br><br>No cost-effectiveness assessment was done with this medicines review. However, TQ review of insulin analogues in 2016 showed major price differential from current standard of care.<br>**Additional resources:** |
| **EQUITY** | **Would there be an impact on health inequity?**<br><br>Yes [x] No [ ] Uncertain [ ] | Major cost implication for unclear benefit of the new insulins.<br>Cost-effectiveness analysis in Japan indicates that pharmaceutical costs can be offset by savings decreased need for other medical |

| | | |
|---|---|---|
| | | resources.[48] Limitations in study and limited ability to generalise to South African context. |
| **FEASIBILITY** | **Is the implementation of this recommendation feasible?**<br>Yes [x] No [ ] Uncertain [ ] | Simple adjustment of regimen to patients at risk. Commonly practiced in high income countries where human insulins are phased out.[10] |

| **Type of recommendation** | We recommend against the option and for the alternative | We suggest not to use the option or to use the alternative | We suggest using either the option or the alternative | We suggest using the option | We recommend the option |
|---|---|---|---|---|---|
| | **X** | ☐ | ☐ | ☐ | ☐ |

**Recommendation**
Continue management with current protocols. Long acting insulin analogues should not be added to the Essential Medicines List at current pricing.

**Rationale:**
No compelling evidence in systematic review for benefit, large cost implication likely

**Level of Evidence:**
Level 1

**Review indicator:**

| Evidence of efficacy | Evidence of harm | Price reduction |
|---|---|---|
| x | | X |

**VEN status:**

| Vital | Essential | Necessary |
|---|---|---|
| | | |

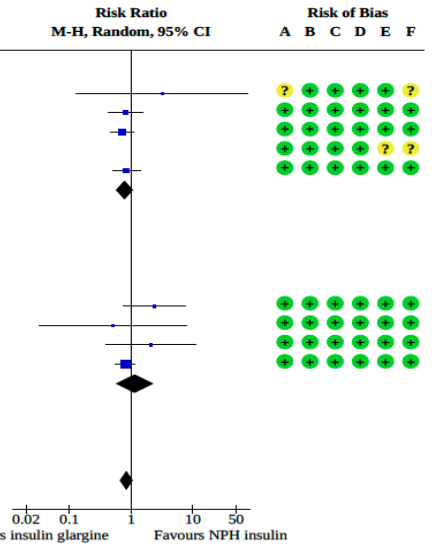
**Monitoring and evaluation considerations** n/a

**Research priorities**
Quality of life studies with use of insulin analogues in the paediatric population

# Appendices – Forest Plots

## Insulin glargine vs NPH insulin

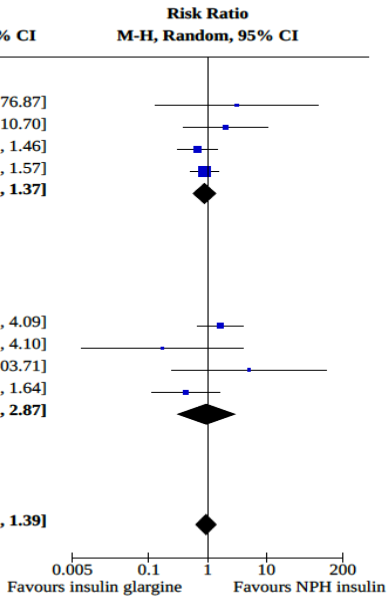
**Analysis 2.3. Comparison 2: Insulin glargine versus NPH insulin, Outcome 3: Severe hypoglycaemia**




| 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

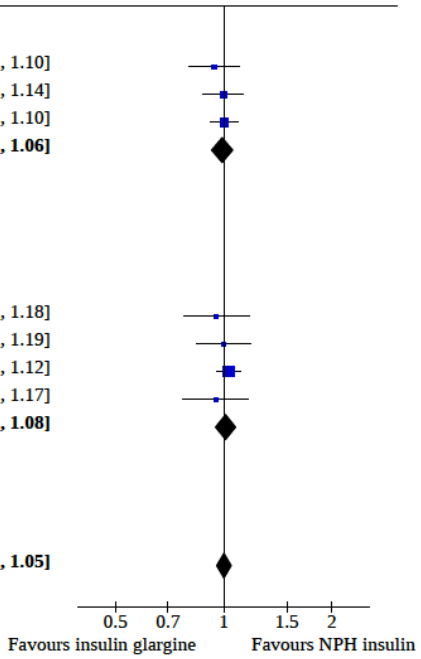
**Analysis 2.5. Comparison 2: Insulin glargine versus NPH insulin, Outcome 5: Hypoglycaemia reported as a serious adverse event**




| 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% | | | | | | |

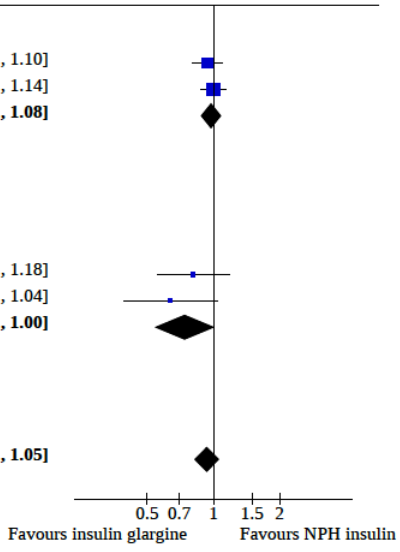
## Analysis 2.16. Comparison 2: Insulin glargine versus NPH insulin, Outcome 16: Nocturnal hypoglycaemia

| 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% | | | | | | |



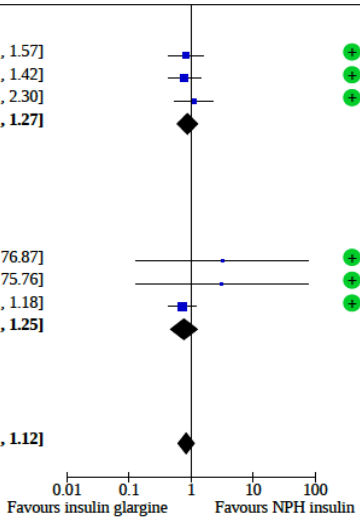

## Analysis 2.18. Comparison 2: Insulin glargine versus NPH insulin, Outcome 18: Nocturnal hypoglycaemia (symptoms)

| 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

| Study or Subgroup | Insulin glargine Events | Total | NPH insulin Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **2.19.1 Adults** | | | | | | |
| Fulcher 2005 | 13 | 62 | 16 | 63 | 21.6% | 0.83 [0.43 , 1.57] |
| Home 2005 | 18 | 292 | 23 | 293 | 25.2% | 0.79 [0.43 , 1.42] |
| Ratner 2000 | 14 | 264 | 13 | 270 | 16.5% | 1.10 [0.53 , 2.30] |
| **Subtotal (95% CI)** | | **618** | | **626** | **63.2%** | **0.87 [0.60 , 1.27]** |
| Total events: | 45 | | 52 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.53, df = 2 (P = 0.77); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.71 (P = 0.48) | | | | | | |
| **2.19.2 Children** | | | | | | |
| Chase 2008 | 1 | 85 | 0 | 90 | 0.9% | 3.17 [0.13 , 76.87] |
| PRESCHOOL | 1 | 61 | 0 | 64 | 0.9% | 3.15 [0.13 , 75.76] |
| Schober 2002 | 22 | 174 | 31 | 175 | 35.0% | 0.71 [0.43 , 1.18] |
| **Subtotal (95% CI)** | | **320** | | **329** | **36.8%** | **0.77 [0.47 , 1.25]** |
| Total events: | 24 | | 31 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 1.61, df = 2 (P = 0.45); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.06 (P = 0.29) | | | | | | |
| **Total (95% CI)** | | **938** | | **955** | **100.0%** | **0.83 [0.62 , 1.12]** |
| Total events: | 69 | | 83 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 2.31, df = 5 (P = 0.81); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.21 (P = 0.23) | | | | | | |
| Test for subgroup differences: Chi² = 0.17, df = 1 (P = 0.68), I² = 0% | | | | | | |



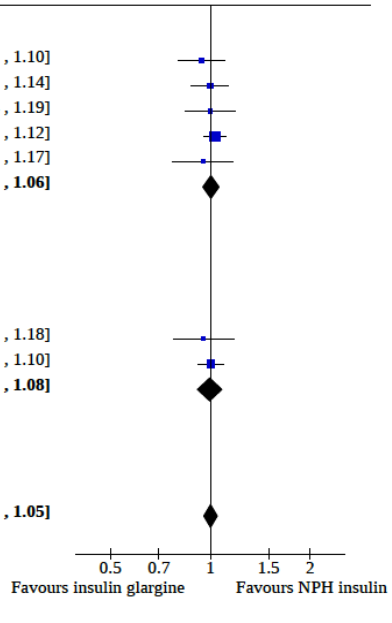


**Risk of bias legend**

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: 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

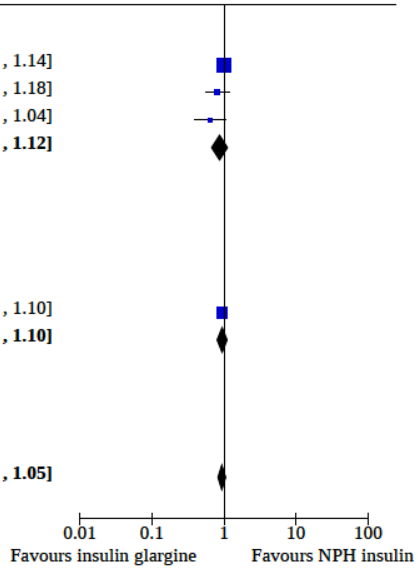
## Analysis 2.20. Comparison 2: Insulin glargine versus NPH insulin, Outcome 20: Nocturnal hypoglycaemia (published vs. unpublished data)

| 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% | | | | | | |



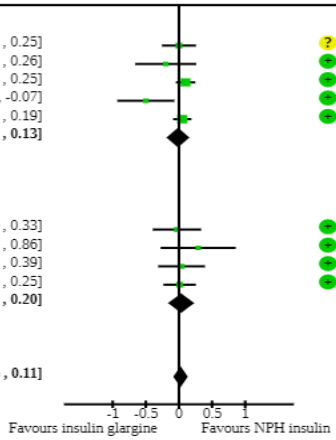
## Analysis 2.21. Comparison 2: Insulin glargine versus NPH insulin, Outcome 21: Symptomatic nocturnal hypoglycaemia (published vs. unpublished data)

| 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 2.24. 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 | Risk of Bias A B C D E F |
|---|---|---|---|---|---|---|---|---|---|
| **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% | | | | | | | | | |

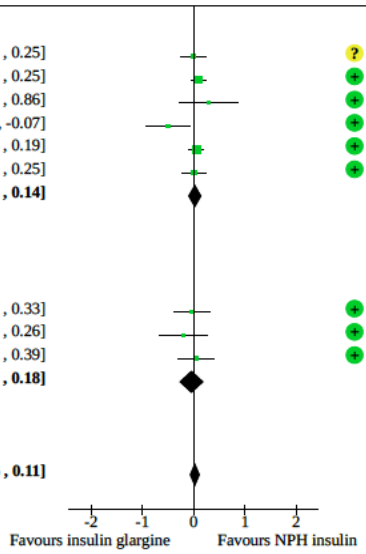



**Footnotes**
(1) SD calculated from SE

**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 |
|---|---|---|---|---|---|---|---|---|---|
| **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**

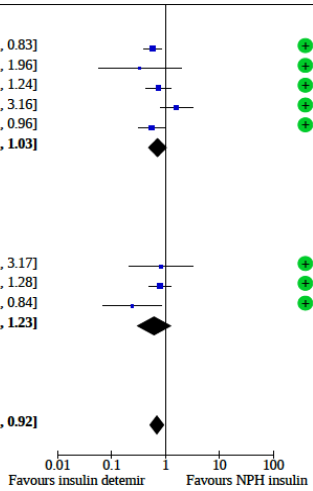
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: HbA1c (published vs unpublished data)
(C) Bias due to missing outcome data: HbA1c (published vs unpublished data)
(D) Bias in measurement of the outcome: HbA1c (published vs unpublished data)
(E) Bias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

## Insulin detemir vs NPH insulin

**Severe hypoglycaemia**

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

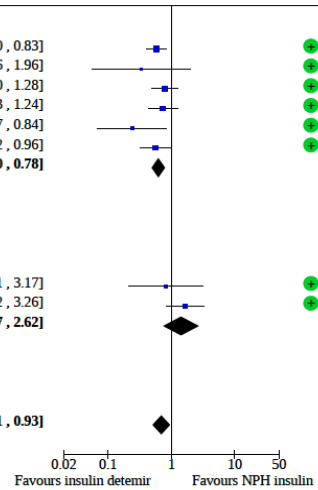
| Study or Subgroup | Insulin detemir Events | Total | NPH insulin Events | Total | Weight | Risk Ratio M-H, Random, 95% CI | Risk of Bias A B C D E F |
|---|---|---|---|---|---|---|---|
| **1.3.1 Adults** | | | | | | | |
| Bartley 2008 | 49 | 331 | 42 | 164 | 23.9% | 0.58 [0.40 , 0.83] | + + + + + + |
| Kobayashi 2007 | 2 | 196 | 3 | 98 | 2.5% | 0.33 [0.06 , 1.96] | + + + + + + |
| Russell-Jones 2004 | 31 | 491 | 22 | 256 | 17.1% | 0.73 [0.43 , 1.24] | + + + + + + |
| Standl 2004 | 20 | 236 | 12 | 224 | 12.1% | 1.58 [0.79 , 3.16] | + + + + + + |
| Vague 2003 | 24 | 301 | 21 | 146 | 16.2% | 0.55 [0.32 , 0.96] | + + + + + + |
| **Subtotal (95% CI)** | | **1555** | | **888** | **71.9%** | **0.71 [0.49 , 1.03]** | |
| Total events: | 126 | | 100 | | | | |
| Heterogeneity: Tau² = 0.08; Chi² = 7.75, df = 4 (P = 0.10); I² = 48% | | | | | | | |
| Test for overall effect: Z = 1.79 (P = 0.07) | | | | | | | |
| **1.3.2 Children** | | | | | | | |
| NCT00605137 | 5 | 55 | 3 | 27 | 4.1% | 0.82 [0.21 , 3.17] | + + + + + + |
| Robertson 2007 | 37 | 232 | 23 | 115 | 19.2% | 0.80 [0.50 , 1.28] | + + + + + + |
| Thalange 2013 | 3 | 177 | 12 | 170 | 4.8% | 0.24 [0.07 , 0.84] | + + + + + + |
| **Subtotal (95% CI)** | | **464** | | **312** | **28.1%** | **0.61 [0.30 , 1.23]** | |
| Total events: | 45 | | 38 | | | | |
| Heterogeneity: Tau² = 0.16; Chi² = 3.27, df = 2 (P = 0.20); I² = 39% | | | | | | | |
| Test for overall effect: Z = 1.37 (P = 0.17) | | | | | | | |
| **Total (95% CI)** | | **2019** | | **1200** | **100.0%** | **0.69 [0.52 , 0.92]** | |
| Total events: | 171 | | 138 | | | | |
| Heterogeneity: Tau² = 0.06; Chi² = 10.89, df = 7 (P = 0.14); I² = 36% | | | | | | | |
| Test for overall effect: Z = 2.50 (P = 0.01) | | | | | | | |
| Test for subgroup differences: Chi² = 0.13, df = 1 (P = 0.72), I² = 0% | | | | | | | |




**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)

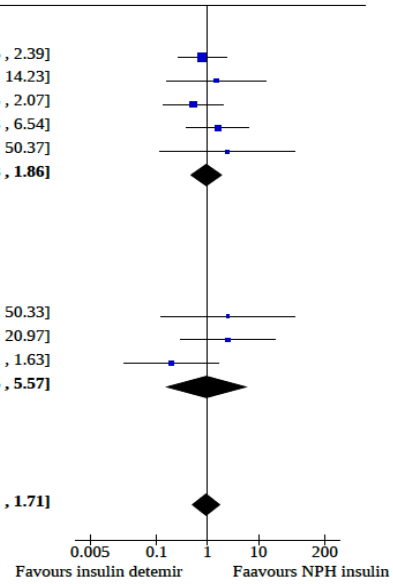
| Study or Subgroup | Insulin detemir Events | Total | NPH insulin Events | Total | Weight | Risk Ratio M-H, Random, 95% CI | Risk of Bias A B C D E F |
|---|---|---|---|---|---|---|---|
| **1.4.1 Published** | | | | | | | |
| Bartley 2008 | 49 | 331 | 42 | 164 | 23.4% | 0.58 [0.40 , 0.83] | + + + + + + |
| Kobayashi 2007 | 2 | 196 | 3 | 98 | 2.6% | 0.33 [0.06 , 1.96] | + + + + + + |
| Robertson 2007 | 37 | 232 | 23 | 115 | 19.1% | 0.80 [0.50 , 1.28] | + + + + + + |
| Russell-Jones 2004 | 31 | 491 | 22 | 256 | 17.1% | 0.73 [0.43 , 1.24] | + + + + + + |
| Thalange 2013 | 3 | 177 | 12 | 170 | 4.9% | 0.24 [0.07 , 0.84] | + + + + + + |
| Vague 2003 | 24 | 301 | 21 | 146 | 16.2% | 0.55 [0.32 , 0.96] | + + + + + + |
| **Subtotal (95% CI)** | | **1728** | | **949** | **83.4%** | **0.62 [0.50 , 0.78]** | |
| Total events: | 146 | | 123 | | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 4.51, df = 5 (P = 0.48); I² = 0% | | | | | | | |
| Test for overall effect: Z = 4.15 (P < 0.0001) | | | | | | | |
| **1.4.2 Unpublished** | | | | | | | |
| NCT00605137 | 5 | 55 | 3 | 27 | 4.3% | 0.82 [0.21 , 3.17] | + + + + + + |
| Standl 2004 | 20 | 210 | 12 | 206 | 12.4% | 1.63 [0.82 , 3.26] | + + + + + + |
| **Subtotal (95% CI)** | | **265** | | **233** | **16.6%** | **1.42 [0.77 , 2.62]** | |
| Total events: | 25 | | 15 | | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.80, df = 1 (P = 0.37); I² = 0% | | | | | | | |
| Test for overall effect: Z = 1.11 (P = 0.27) | | | | | | | |
| **Total (95% CI)** | | **1993** | | **1182** | **100.0%** | **0.69 [0.51 , 0.93]** | |
| Total events: | 171 | | 138 | | | | |
| Heterogeneity: Tau² = 0.06; Chi² = 11.39, df = 7 (P = 0.12); I² = 39% | | | | | | | |
| Test for overall effect: Z = 2.41 (P = 0.02) | | | | | | | |
| Test for subgroup differences: Chi² = 6.10, df = 1 (P = 0.01), I² = 83.6% | | | | | | | |




**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)

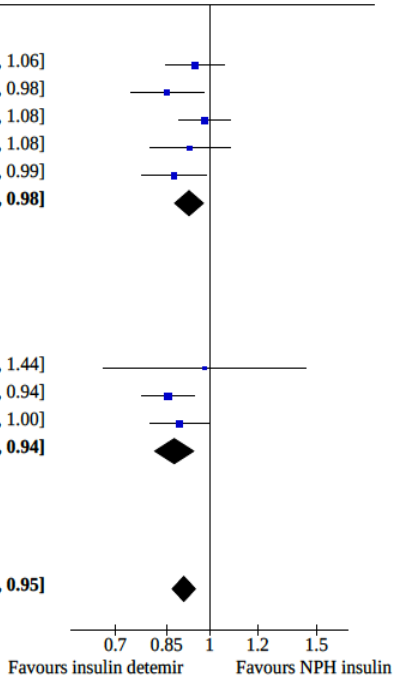
**Analysis 1.5. Comparison 1: Insulin detemir versus NPH insulin, Outcome 5: Hypoglycaemia reported as a serious adverse event**

| 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 1.15. 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% | | | | | | |

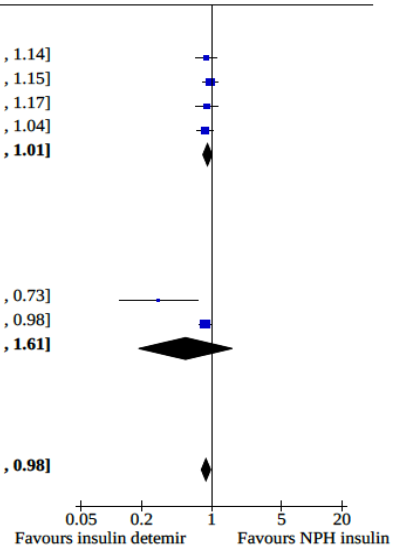



**Footnotes**

(1) Data from CSR after 6 months

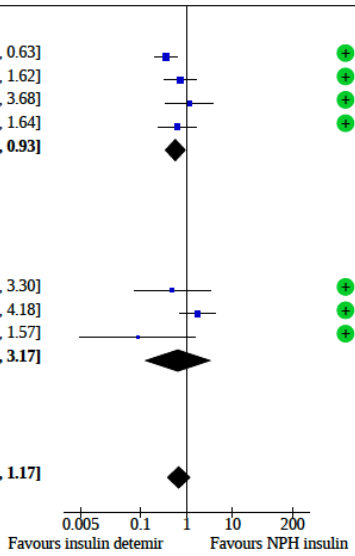
## Analysis 1.17. Comparison 1: Insulin detemir versus NPH insulin, Outcome 17: Nocturnal hypoglycaemia (symptoms)

| 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

| Study or Subgroup | Insulin detemir Events | Total | NPH insulin Events | Total | Weight | Risk Ratio M-H, Random, 95% CI | Risk of Bias A B C D E F |
|---|---|---|---|---|---|---|---|
| **1.18.1 Adults** | | | | | | | |
| Bartley 2008 | 18 | 331 | 25 | 164 | 23.9% | 0.36 [0.20 , 0.63] | + + + + + + |
| Russell-Jones 2004 | 14 | 491 | 10 | 256 | 19.3% | 0.73 [0.33 , 1.62] | + + + + + + |
| Standl 2004 | 6 | 236 | 5 | 224 | 13.1% | 1.14 [0.35 , 3.68] | + + + + + + |
| Vague 2003 | 9 | 301 | 7 | 146 | 16.2% | 0.62 [0.24 , 1.64] | + + + + + + |
| **Subtotal (95% CI)** | | **1359** | | **790** | **72.4%** | **0.57 [0.35 , 0.93]** | |
| Total events: | 47 | | 47 | | | | |
| Heterogeneity: Tau² = 0.07; Chi² = 4.18, df = 3 (P = 0.24); I² = 28% | | | | | | | |
| Test for overall effect: Z = 2.26 (P = 0.02) | | | | | | | |
| **1.18.2 Children** | | | | | | | |
| NCT00605137 | 2 | 55 | 2 | 27 | 6.6% | 0.49 [0.07 , 3.30] | + + + + + + |
| Robertson 2007 | 21 | 232 | 6 | 115 | 17.7% | 1.73 [0.72 , 4.18] | + + + + + + |
| Thalange 2013 | 0 | 177 | 5 | 170 | 3.3% | 0.09 [0.00 , 1.57] | + + + + + + |
| **Subtotal (95% CI)** | | **464** | | **312** | **27.6%** | **0.64 [0.13 , 3.17]** | |
| Total events: | 23 | | 13 | | | | |
| Heterogeneity: Tau² = 1.15; Chi² = 4.85, df = 2 (P = 0.09); I² = 59% | | | | | | | |
| Test for overall effect: Z = 0.54 (P = 0.59) | | | | | | | |
| **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 = 0.02, df = 1 (P = 0.88), I² = 0% | | | | | | | |

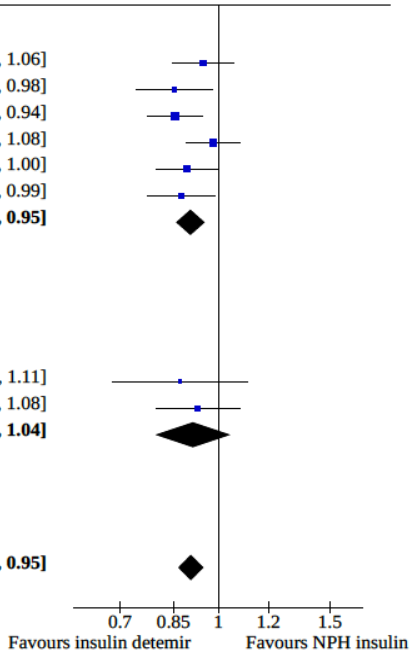



**Risk of bias legend**

(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 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% | | | | | | |

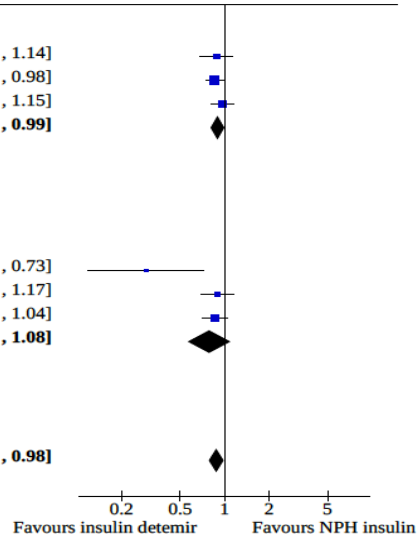



**Footnotes**

(1) Data from CSR after 6 months

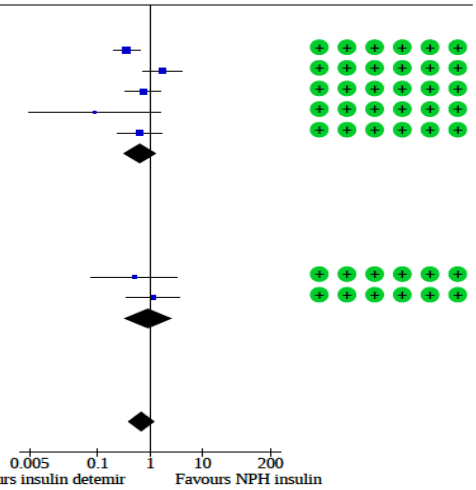
## Analysis 1.21. Comparison 1: Insulin detemir versus NPH insulin, Outcome 21: Nocturnal hypoglycaemia, symptoms only (published vs. unpublished data)

| 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% | | | | | | |

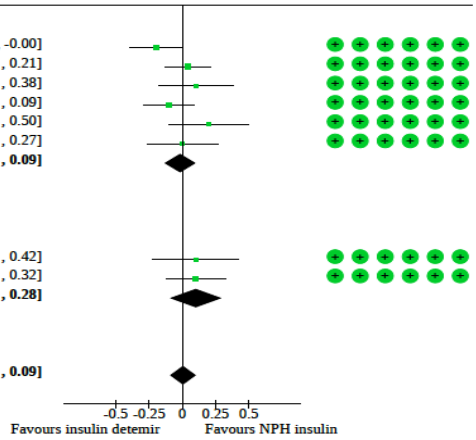



**Risk of bias legend**

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

| Study or Subgroup | Insulin detemir Mean | SD | Total | NPH insulin Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.27.1 Published** | | | | | | | | |
| Bartley 2008 (1) | 7.4 | 1.1 | 320 | 7.6 | 1 | 159 | 15.9% | -0.20 [-0.40 , -0.00] |
| Kobayashi 2007 (1) | 7.33 | 0.7 | 195 | 7.29 | 0.7 | 98 | 19.7% | 0.04 [-0.13 , 0.21] |
| Robertson 2007 | 8 | 1.5 | 232 | 7.9 | 1.1 | 115 | 9.0% | 0.10 [-0.18 , 0.38] |
| Russell-Jones 2004 | 8.3 | 1.1 | 491 | 8.4 | 1.3 | 256 | 17.2% | -0.10 [-0.29 , 0.09] |
| Thalange 2013 (1) | 8.8 | 1.4 | 171 | 8.6 | 1.4 | 168 | 8.0% | 0.20 [-0.10 , 0.50] |
| Vague 2003 (1) | 7.6 | 1.5 | 280 | 7.6 | 1.2 | 139 | 9.8% | 0.00 [-0.27 , 0.27] |
| **Subtotal (95% CI)** | | | **1689** | | | **935** | **79.7%** | **-0.02 [-0.13 , 0.09]** |
| Heterogeneity: Tau² = 0.01; Chi² = 7.22, df = 5 (P = 0.20); I² = 31% | | | | | | | | |
| Test for overall effect: Z = 0.32 (P = 0.75) | | | | | | | | |
| **1.27.2 Unpublished** | | | | | | | | |
| NCT00605137 (2) | 7.6 | 0.7 | 55 | 7.5 | 0.7 | 27 | 7.0% | 0.10 [-0.22 , 0.42] |
| Standl 2004 (3) | 7.7 | 1.1 | 210 | 7.6 | 1.2 | 206 | 13.3% | 0.10 [-0.12 , 0.32] |
| **Subtotal (95% CI)** | | | **265** | | | **233** | **20.3%** | **0.10 [-0.08 , 0.28]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 1.07 (P = 0.28) | | | | | | | | |
| **Total (95% CI)** | | | **1954** | | | **1168** | **100.0%** | **0.00 [-0.09 , 0.09]** |
| Heterogeneity: Tau² = 0.00; Chi² = 8.67, df = 7 (P = 0.28); I² = 19% | | | | | | | | |
| Test for overall effect: Z = 0.09 (P = 0.93) | | | | | | | | |
| Test for subgroup differences: Chi² = 1.17, df = 1 (P = 0.28), I² = 14.9% | | | | | | | | |




**Footnotes**

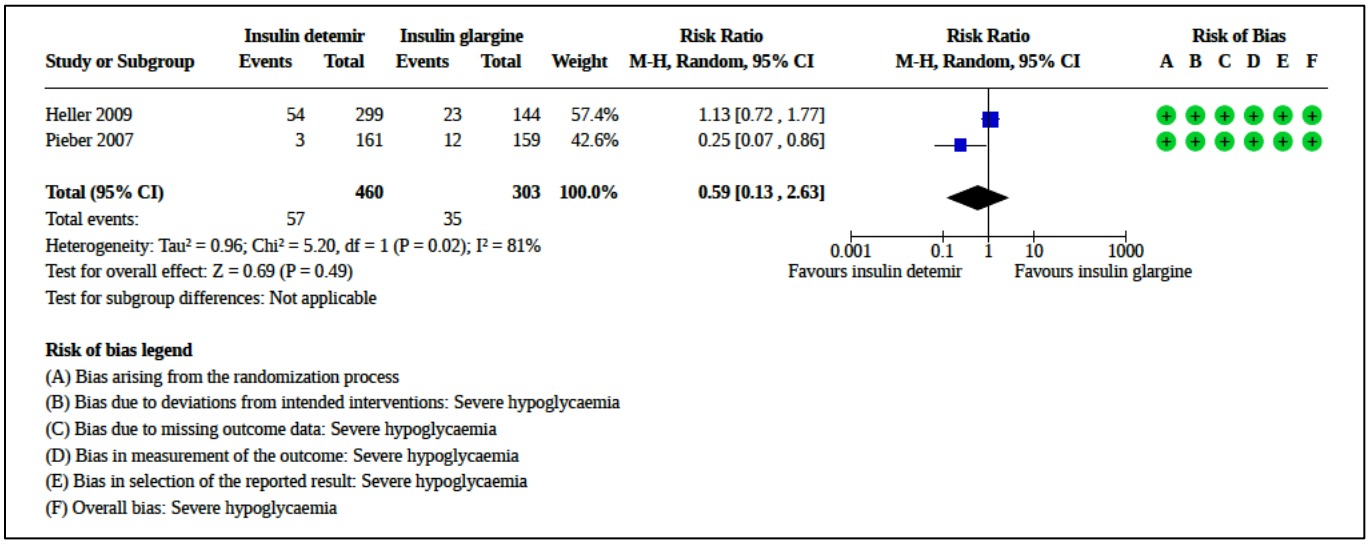
(1) SD calculated from SE
(2) Data from study synopsis. LS mean adjusted for baseline value. SD calculated from SE.
(3) Data after 26 weeks of intervention from FDA medical review and CSR

**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)

## Insulin detemir vs insulin glargine

**Severe hypoglycaemia:**



| Study or Subgroup | Insulin detemir Events | Total | Insulin glargine Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| 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 | | | |

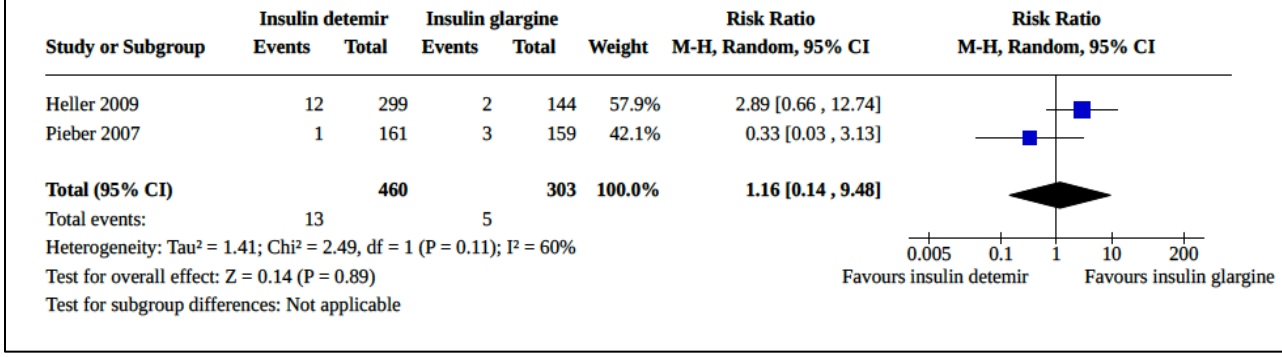
Heterogeneity: Tau² = 0.96; Chi² = 5.20, df = 1 (P = 0.02); I² = 81%
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable

Risk Ratio M-H, Random, 95% CI: 0.001, 0.1, 1, 10, 1000 — Favours insulin detemir / Favours insulin glargine

Risk of Bias: A B C D E F

**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 3.4. Comparison 3: Insulin detemir versus insulin glargine, Outcome 4: Hypoglycaemia reported as a serious adverse event**

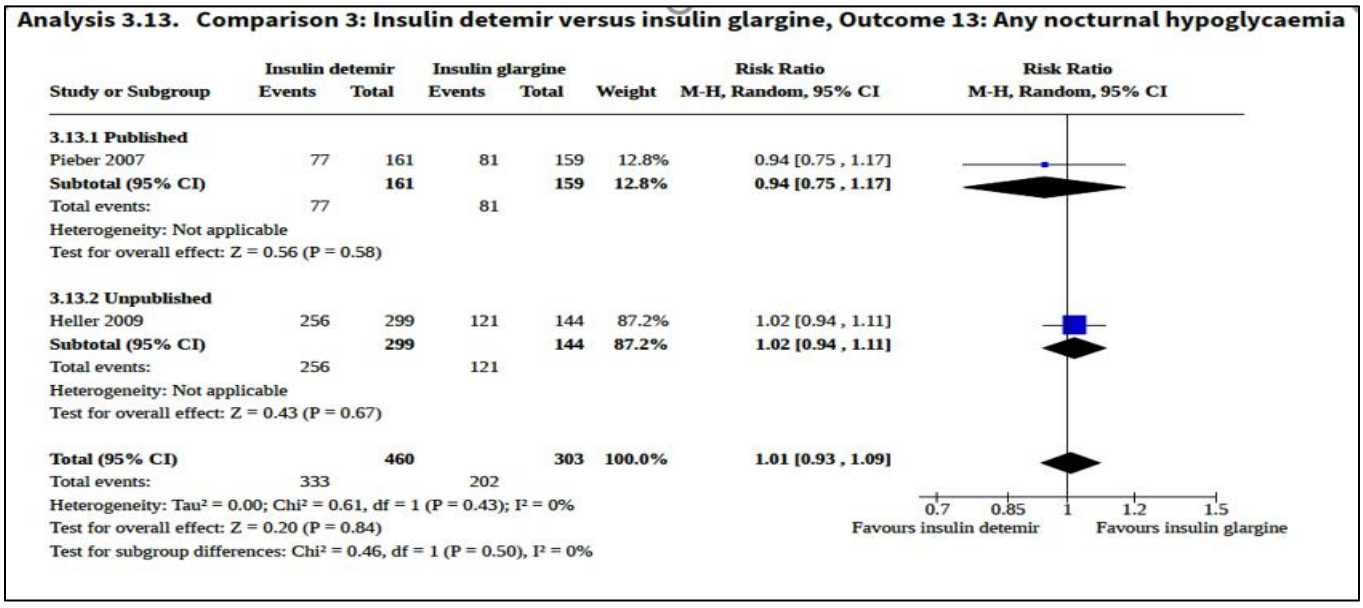


| Study or Subgroup | Insulin detemir Events | Total | Insulin glargine Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Heller 2009 | 12 | 299 | 2 | 144 | 57.9% | 2.89 [0.66 , 12.74] |
| Pieber 2007 | 1 | 161 | 3 | 159 | 42.1% | 0.33 [0.03 , 3.13] |
| **Total (95% CI)** | | **460** | | **303** | **100.0%** | **1.16 [0.14 , 9.48]** |
| Total events: | 13 | | 5 | | | |

Heterogeneity: Tau² = 1.41; Chi² = 2.49, df = 1 (P = 0.11); I² = 60%
Test for overall effect: Z = 0.14 (P = 0.89)
Test for subgroup differences: Not applicable

Risk Ratio M-H, Random, 95% CI: 0.005, 0.1, 1, 10, 200 — Favours insulin detemir / Favours insulin glargine

**Analysis 3.13. Comparison 3: Insulin detemir versus insulin glargine, Outcome 13: Any nocturnal hypoglycaemia**

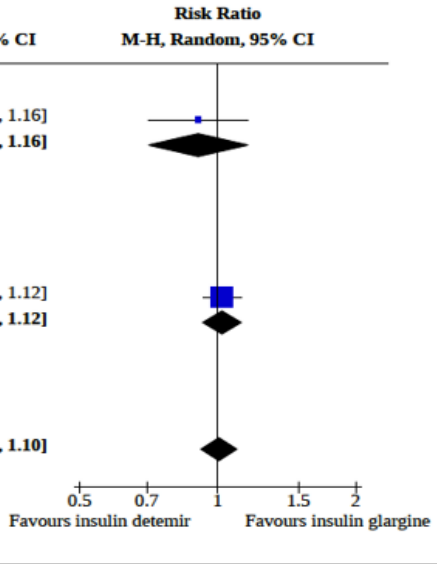


| Study or Subgroup | Insulin detemir Events | Total | Insulin glargine Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **3.13.1 Published** | | | | | | |
| Pieber 2007 | 77 | 161 | 81 | 159 | 12.8% | 0.94 [0.75 , 1.17] |
| **Subtotal (95% CI)** | | **161** | | **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%

Risk Ratio M-H, Random, 95% CI: 0.7, 0.85, 1, 1.2, 1.5 — Favours insulin detemir / Favours insulin glargine

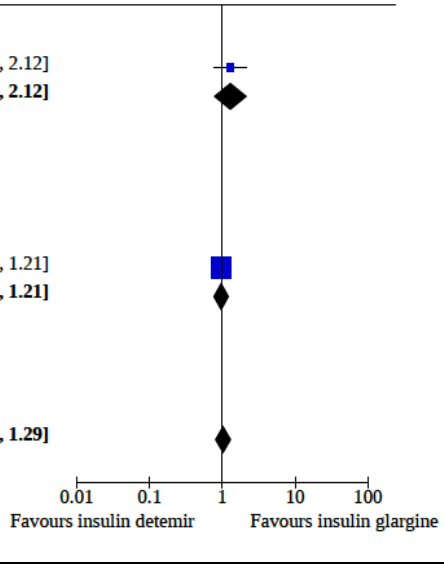
**Analysis 3.14. Comparison 3: Insulin detemir versus insulin glargine, Outcome 14: Confirmed nocturnal hypoglycaemia (PG < 3.1 mmol/L and no assistance)**



| 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% | | | | | | |



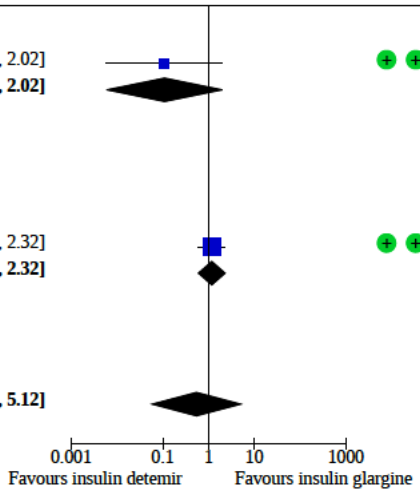
**Analysis 3.15. Comparison 3: Insulin detemir versus insulin glargine, Outcome 15: Symptomatic nocturnal hypoglycaemia (PG ≥ 3.1 or no PG and no assistance required)**



| 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 |
|---|---|---|---|---|---|---|
| **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% | | | | | | |

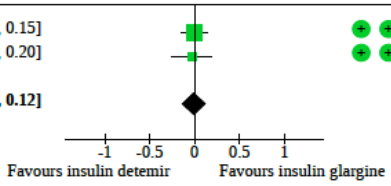



Risk of Bias: A B C D E F

**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 3.18. 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 | | | | | | | | |




Risk of Bias: A B C D E F

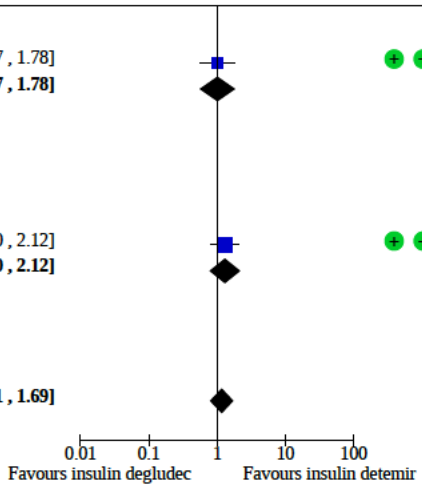
**Footnotes**
(1) SD calculated from SE

**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

## Insulin degludec vs insulin detemir

**Analysis 4.3. Comparison 4: Insulin degludec versus insulin detemir, Outcome 3: Severe hypoglycaemia**

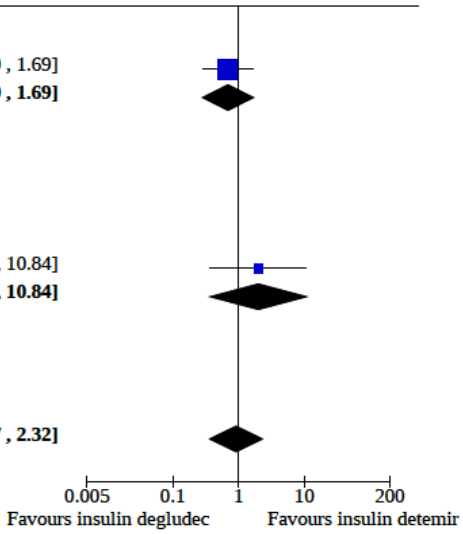
| Study or Subgroup | Insulin degludec Events | Insulin degludec Total | Insulin detemir Events | Insulin detemir Total | Weight | Risk Ratio M-H, Random, 95% CI | Risk of Bias A B C D E F |
|---|---|---|---|---|---|---|---|
| **4.3.1 Adults** | | | | | | | |
| Davies 2014 | 32 | 301 | 16 | 152 | 42.7% | 1.01 [0.57 , 1.78] | + + + + + + |
| **Subtotal (95% CI)** | | **301** | | **152** | **42.7%** | **1.01 [0.57 , 1.78]** | |
| Total events: | 32 | | 16 | | | | |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: Z = 0.03 (P = 0.97) | | | | | | | |
| **4.3.2 Children** | | | | | | | |
| BEGIN Young | 31 | 174 | 24 | 175 | 57.3% | 1.30 [0.80 , 2.12] | + + + + + + |
| **Subtotal (95% CI)** | | **174** | | **175** | **57.3%** | **1.30 [0.80 , 2.12]** | |
| Total events: | 31 | | 24 | | | | |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: Z = 1.05 (P = 0.30) | | | | | | | |
| **Total (95% CI)** | | **475** | | **327** | **100.0%** | **1.17 [0.81 , 1.69]** | |
| Total events: | 63 | | 40 | | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 1 (P = 0.51); I² = 0% | | | | | | | |
| Test for overall effect: Z = 0.81 (P = 0.42) | | | | | | | |
| Test for subgroup differences: Chi² = 0.43, 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: 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

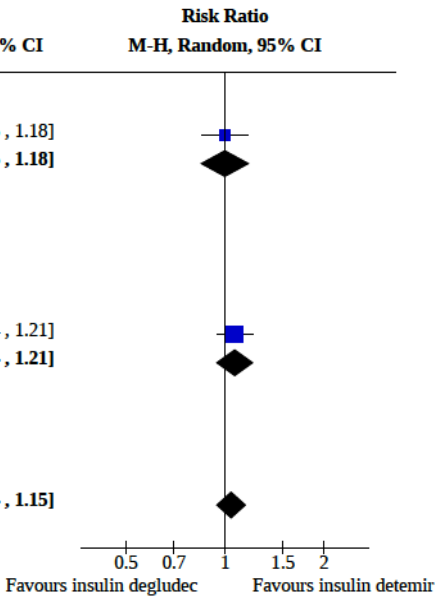
**Analysis 4.4. Comparison 4: Insulin degludec versus insulin detemir, Outcome 4: Hypoglycaemia reported as a serious adverse event**

| Study or Subgroup | Insulin degludec Events | Insulin degludec Total | Insulin detemir Events | Insulin detemir Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **4.4.1 Adults** | | | | | | |
| Davies 2014 | 11 | 301 | 8 | 152 | 73.4% | 0.69 [0.29 , 1.69] |
| **Subtotal (95% CI)** | | **301** | | **152** | **73.4%** | **0.69 [0.29 , 1.69]** |
| Total events: | 11 | | 8 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.80 (P = 0.42) | | | | | | |
| **4.4.2 Children** | | | | | | |
| BEGIN Young | 4 | 174 | 2 | 175 | 26.6% | 2.01 [0.37 , 10.84] |
| **Subtotal (95% CI)** | | **174** | | **175** | **26.6%** | **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%** | **0.92 [0.37 , 2.32]** |
| Total events: | 15 | | 10 | | | |
| Heterogeneity: Tau² = 0.10; Chi² = 1.20, df = 1 (P = 0.27); I² = 17% | | | | | | |
| Test for overall effect: Z = 0.17 (P = 0.86) | | | | | | |
| Test for subgroup differences: Chi² = 1.20, df = 1 (P = 0.27), I² = 16.5% | | | | | | |



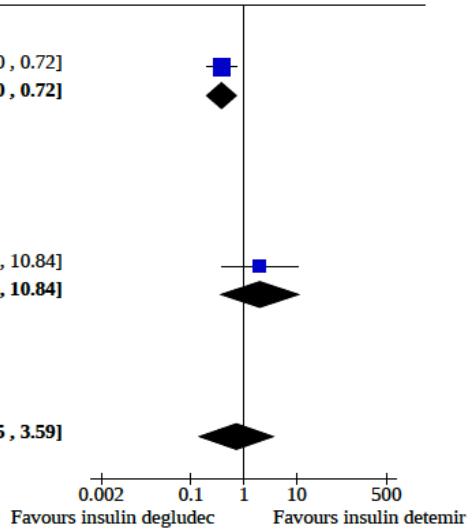
**Analysis 4.14. Comparison 4: Insulin degludec versus insulin detemir, Outcome 14: Nocturnal hypoglycaemia**

| 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% | | | | | | |



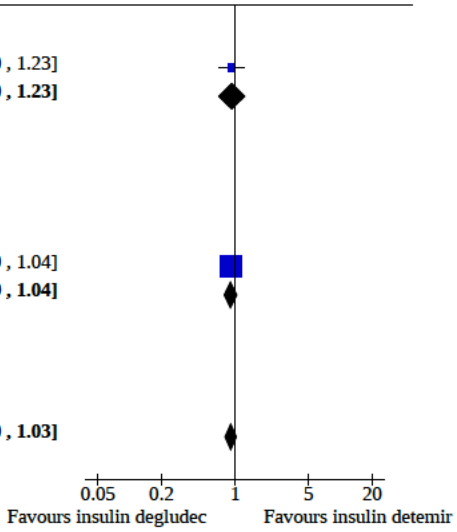

**Analysis 4.16. Comparison 4: Insulin degludec versus insulin detemir, Outcome 16: Nocturnal hypoglycaemia (symptomatic)**

| 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% | | | | | | |



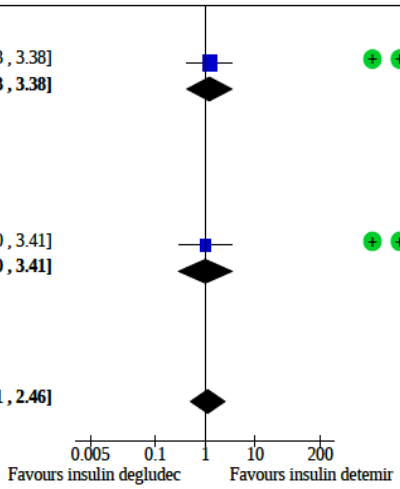
## Analysis 4.17. Comparison 4: Insulin degludec versus insulin detemir, Outcome 17: Nocturnal hypoglycaemia (asymptomatic)

| 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

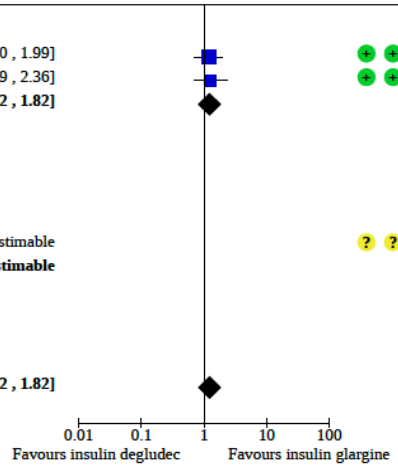
(E) Bias in selection of the reported result: Severe nocturnal hypoglycaemia

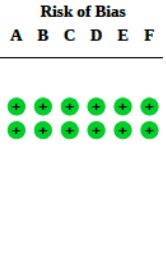
(F) Overall bias: Severe nocturnal hypoglycaemia

## Insulin degludec vs insulin glargine

### 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 | | | | | | |



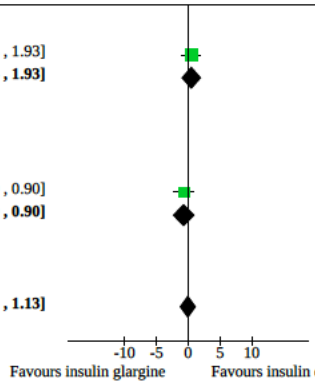




**Risk of bias legend**

(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 5.3. 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% | | | | | | | | |



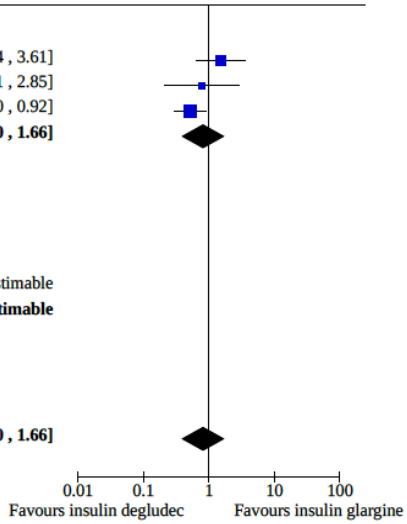


**Risk of bias legend**

(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)

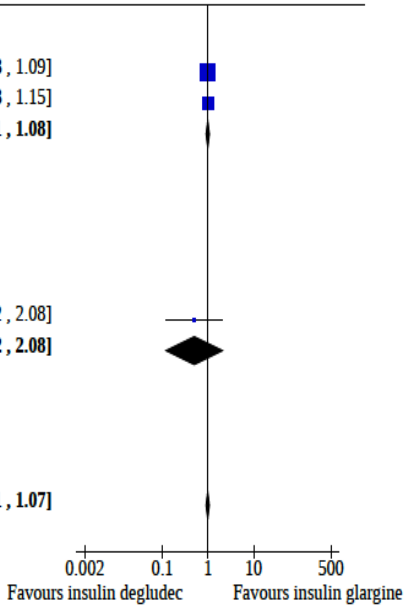
## Analysis 5.6. Comparison 5: Insulin degludec versus insulin glargine, Outcome 6: Hypoglycaemia reported as a serious adverse event

| 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 5.15. 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% | | | | | | |

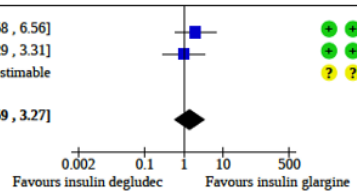



**Footnotes**

(1) Data provided by study author

## Analysis 5.19. 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 | | | | |



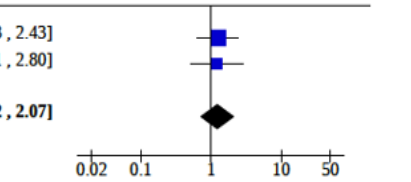

Heterogeneity: Tau² = 0.00; Chi² = 0.64, df = 1 (P = 0.42); I² = 0%
Test for overall effect: Z = 0.75 (P = 0.46)
Test for subgroup differences: Not applicable

**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 5.18. 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

References:


1. Patterson CC, Karuranga S, Salpea P, Saeedi P, Dahlquist G, Soltesz G, et al. Worldwide estimates of incidence, prevalence and mortality of type 1 diabetes in children and adolescents: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract. 2019 Nov 1;157:107842.

2. The Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Intensive Diabetes Treatment and Cardiovascular Outcomes in Type 1 Diabetes: The DCCT/EDIC Study 30-Year Follow-up. Diabetes Care. 2016 May;39(5):686–93.

3. Orchard TJ, Nathan DM, Zinman B, Cleary P, Brillon D, Backlund J-YC, et al. Association Between 7 Years of Intensive Treatment of Type 1 Diabetes and Long-term Mortality. JAMA. 2015 Jan 6;313(1):45.

4. Sheldon B, Russell-Jones D, Wright J. Insulin analogues: an example of applied medical science. Diabetes Obes Metab. 2009 Jan 1;11(1):5–19.

5. Miles HL, Acerini CL. Insulin analog preparations and their use in children and adolescents with type 1 diabetes mellitus. Pediatr Drugs. 2008;10(3):163–76.

6. Hartman I. Insulin analogs: impact on treatment success, satisfaction, quality of life, and adherence. Clin Med Res. 2008;6(2):54–67.

7. Northam EA, Anderson PJ, Jacobs R, Hughes M, Warne GL, Werther GA. Neuropsychological profiles of children with type 1 diabetes 6 years after disease onset. Diabetes Care. 2001;24(9):1541–6.

8. Kalra S, Mukherjee JJ, Venkataraman S, Bantwal G, Shaikh S, Saboo B, et al. Hypoglycemia: The neglected complication. Indian J Endocrinol Metab. 2013;17(5):819.

9. Executive summary. The Selection and Use of Essential Medicines 2021. Report of the 23rd WHO Expert Committee on the Selection and Use of Essential Medicines, virtual meeting, 21 June–2 July 2021. Geneva: World Health Organization; 2021 (WHO/MHP/HPS/EML/2021.01). Licence: CC BY-NC-SA 3.0 IGO. In.

10. Mochizuki M, Kikuchi T, Urakami T, Kikuchi N, Kawamura T, Yokomichi H, et al. Improvement in glycemic control through changes in insulin regimens: findings from a Japanese cohort of children and adolescents with type 1 diabetes: M. M OCHIZUKI ET AL . Pediatr Diabetes. 2017 Sep;18(6):435–42.

11. Garg S, Moser E, Dain M-P, Rodionova A. Clinical experience with insulin glargine in type 1 diabetes. Diabetes Technol Ther. 2010 Nov;12(11):835–46.

12. Semlitsch T, Engler J, Siebenhofer A, Jeitler K, Berghold A, Horvath K. (Ultra-)long-acting insulin analogues versus NPH insulin (human isophane insulin) for adults with type 2 diabetes mellitus. Cochrane Database Syst Rev [Internet]. 2020;(11). Available from: http://dx.doi.org/10.1002/14651858.CD005613.pub4

13. Harris S, Snoek F, Meneghini L, Lauand F, Westerbacka J, Khunti K. Treatment satisfaction in people with type 2 diabetes receiving basal insulin: results from real-world studies and randomised controlled trials with insulin glargine 300 u/ml. Diabetes Technol Ther. 2021;23(SUPPL 2):A86-.

14. Harris S, Snoek F, Meneghini L, Lauand F, Westerbacka J, Roborel De Climens A, et al. Treatment satisfaction in people with type 2 diabetes receiving basal insulin: results from real-world and randomised controlled studies with insulin glargine 300 U/ml. Diabetologia. 2020;63(SUPPL 1):S331-.

15. Swinnen S, Simon A, Holleman F, Hoekstra J, DeVries J. Insulin detemir versus insulin glargine for type 2 diabetes mellitus. Cochrane Database Syst Rev [Internet]. 2011;(7). Available from: http://dx.doi.org/10.1002/14651858.CD006383.pub2

16. Vardi M, Jacobson E, Nini A, Bitterman H. Intermediate acting versus long acting insulin for type 1 diabetes mellitus. Cochrane Database Syst Rev [Internet]. 2008;(3). Available from: http://dx.doi.org/10.1002/14651858.CD006297.pub2

17. McCance D, Hod M, Ivanisevic M, Duran-Garcia S, Jovanovic L, Mathiesen E, et al. Maternal efficacy and safety outcomes, and perinatal outcomes, in a randomised trial comparing insulin detemir with neutral protamine Hagedorn insulin in 310 pregnant women with Type 1 diabetes. Diabet Med. 2012;29:26.

18. Bartley P, Bogoev M, Larsen J, Philotheou A. Long-term efficacy and safety of insulin detemir compared to Neutral Protamine Hagedorn insulin in patients with Type 1 diabetes using a treat-to-target basal-bolus regimen with insulin aspart at meals: a 2-year, randomized, controlled trial. Diabet Med. 2008;25(4):442-449.

19. Arutchelvam V, Heise T, Dellweg S, Elbroend B, Minns I, Home P. Plasma glucose and hypoglycaemia following exercise in people with Type 1 diabetes: a comparison of three basal insulins. Diabet Med. 2009;26(10):1027-1032.

20. Thalange N, Bereket A, Larsen J, Hiort LC, Peterkova V. Insulin analogues in children with Type 1 diabetes: a 52-week randomized clinical trial. Diabet Med J Br Diabet Assoc. 2013 Feb;30(2):216–25.

21. Fajardo Montañana C, Hernández Herrero C, Rivas Fernández M. Less weight gain and hypoglycaemia with once-daily insulin detemir than NPH insulin in intensification of insulin therapy in overweight Type 2 diabetes patients: the PREDICTIVE BMI clinical trial. Diabet Med. 2008;25(8):916-923.

22. Hermansen K, Davies M. Does insulin detemir have a role in reducing risk of insulin-associated weight gain? Diabetes Obes Metab. 2007;9(3):209-217.

23. Ridderstråle M, Jensen M, Gjesing R, Niskanen L. Cost-effectiveness of insulin detemir compared with NPH insulin in people with type 2 diabetes in Denmark, Finland, Norway, and Sweden. J Med Econ. 2013;16(4):468-478.

24. Saravanan P, Rodbard H, Tripathy D, Velazquez M, Demissie M, Can Tamer S, et al. Adding faster-acting insulin aspart to basal insulin significantly improved glycaemic control in adults with Type 2 diabetes: the onset 3 trial. Diabet Med. 2017;34:69-.

25. Hoogma R, Hammond P, Gomis R, Kerr D, Bruttomesso D, Bouter K, et al. Comparison of the effects of continuous subcutaneous insulin infusion (CSII) and NPH-based multiple daily insulin injections (MDI) on glycaemic control and quality of life: results of the 5-nations trial. Diabet Med. 2006;23(2):141-147.

26. Dixon S, Peters J. Evaluating the 'real' cost-effectiveness of health technology: reconciling the public interest with patients' interests. Curr Med Res Opin Suppl. 2007;23(1):S1-S6.

27. Thalange N, Bereket A, Larsen J, Hiort L, Peterkova V. Treatment with insulin detemir or NPH insulin in children aged 2-5 yr with type 1 diabetes mellitus. Pediatr Diabetes. 2011;12(7):632-641.

28. Pedersen-Bjergaard U, Kristensen P, Beck-Nielsen H, Nørgaard K, Perrild H, Christiansen J, et al. Effect of insulin analogues on risk of severe hypoglycaemia in patients with type 1 diabetes prone to recurrent severe hypoglycaemia (HypoAna trial): a prospective, randomised, open-label, blinded-endpoint crossover trial. Lancet Diabetes Endocrinol. 2014;2(7):553-561.

29. Home P, Bolli G, Mathieu C, Deerochanawong C, Landgraf W, Candelas C, et al. Modulation of insulin dose titration using a hypoglycaemia-sensitive algorithm: insulin glargine versus neutral protamine Hagedorn insulin in insulin-naïve people with type 2 diabetes. Diabetes Obes Metab. 2015;17(1):15-22.

30. Fulcher G, Gilbert R, Yue D. Glargine is superior to neutral protamine Hagedorn for improving glycated haemoglobin and fasting blood glucose levels during intensive insulin therapy. Intern Med J. 2005;35(9):536-542.

31. Rosenstock J, Fonseca V, McGill J, Riddle M, Hallé J, Hramiak I, et al. Similar progression of diabetic retinopathy with insulin glargine and neutral protamine Hagedorn (NPH) insulin in patients with type 2 diabetes: a long-term, randomised, open-label study. Diabetologia. 2009;52(9):1778-1788.

32. Ling J, Ozaki R, Luk A, Chan J, Chow E. Glycaemic variability and time-in-range during self-titration of once daily insulin glargine 300u/ml versus NPH (neutral protamine hagedorn)

insulin in insulinnaive chinese type 2 diabetes patients. Diabetes Technol Ther. 2020;22:A23-A24.

33. Chatterjee S, Tringham J, Davies M. Insulin glargine and its place in the treatment of Types 1 and 2 diabetes mellitus. Expert Opin Pharmacother. 2006;7(10):1357-1371.

34. Mathiesen E, Damm P, Jovanovic L, McCance D, Thyregod C, Jensen A, et al. Basal insulin analogues in diabetic pregnancy: a literature review and baseline results of a randomised, controlled trial in type 1 diabetes. Diabetes Metab Res Rev. 2011;27(6):543-551.

35. Dunn CJ, Plosker GL, Keating GM, McKeage K, Scott LJ. Insulin glargine: an updated review of its use in the management of diabetes mellitus. Drugs. 2003;63(16):1743–78.

36. Group H 901/2004 SI. Safety and efficacy of insulin glargine (HOE 901) versus NPH insulin in combination with oral treatment in Type 2 diabetic patients. Diabet Med. 2003;20(7):545–51.

37. Simpson D, McCormack P, Keating G, Lyseng-Williamson K. Insulin lispro: a review of its use in the management of diabetes mellitus. Drugs. 2007;67(3):407-434.

38. ji J, He Z, Yang Z, Mi Y, Guo N, Zhao H, et al. Comparing the efficacy and safety of insulin detemir versus neutral protamine hagedorn insulin in treatment of diabetes during pregnancy: a randomized, controlled study. BMJ Open Diabetes Res Care. 2020 Apr;8(1):e001155.

39. Robertson KJ, Schoenle E, Gucev Z, Mordhorst L, Gall M-A, Ludvigsson J. Insulin detemir compared with NPH insulin in children and adolescents with Type 1 diabetes. Diabet Med J Br Diabet Assoc. 2007 Jan;24(1):27–34.

40. Monami M, Marchionni N, Mannucci E. Long-acting insulin analogues vs. NPH human insulin in type 1 diabetes. A meta-analysis. Diabetes Obes Metab. 2009 Apr;11(4):372–8.

41. Chapman TM, Perry CM. Spotlight on insulin detemir in type 1 and 2 diabetes mellitus. BioDrugs Clin Immunother Biopharm Gene Ther. 2005;19(1):67–9.

42. Petit-Bibal C, Rothenbuhler A, Lucchini P, Aboumrad B, Castell AL, Le Fur S, et al. Decrease in clinical hypoglycemia in young children with type 1 diabetes treated with free-mixed aspart and detemir insulin: an open labeled randomized trial. Pediatr Diabetes. 2015 Aug;16(5):345–53.

43. Hassan K, Rodriguez LM, Johnson SE, Tadlock S, Heptulla RA. A randomized, controlled trial comparing twice-a-day insulin glargine mixed with rapid-acting insulin analogs versus standard neutral protamine Hagedorn (NPH) therapy in newly diagnosed type 1 diabetes. Pediatrics. 2008 Mar;121(3):e466-472.

44. Schober E, Schoenle E, Van Dyk J, Wernicke-Panten K, Pediatric Study Group of Insulin Glargine. Comparative trial between insulin glargine and NPH insulin in children and adolescents with type 1 diabetes mellitus. J Pediatr Endocrinol Metab JPEM. 2002 Apr;15(4):369–76.

45. Philotheou A, Arslanian S, Blatniczky L, Peterkova V, Souhami E, Danne T. Comparable efficacy and safety of insulin glulisine and insulin lispro when given as part of a Basal-bolus insulin regimen in a 26-week trial in pediatric patients with type 1 diabetes. Diabetes Technol Ther. 2011 Mar;13(3):327–34.

46. Murphy NP, Keane SM, Ong KK, Ford-Adams M, Edge JA, Acerini CL, et al. Randomized Cross-Over Trial of Insulin Glargine Plus Lispro or NPH Insulin Plus Regular Human Insulin in Adolescents With Type 1 Diabetes on Intensive Insulin Regimens. Diabetes Care. 2003 Mar 1;26(3):799–804.

47. Hemmingsen B, Metzendorf M-I, Richter B. (Ultra-)long-acting insulin analogues for people with type 1 diabetes mellitus. Cochrane Metabolic and Endocrine Disorders Group, editor. Cochrane Database Syst Rev [Internet]. 2021 Mar 4 [cited 2021 Dec 3];2021(4). Available from: http://doi.wiley.com/10.1002/14651858.CD013498.pub2

48. Lee T, Kuo S, Yang C, Ou H. Cost-effectiveness of long-acting insulin analogues *vs* intermediate/long-acting human insulin for type 1 diabetes: A population-based cohort followed over 10 years. Br J Clin Pharmacol. 2020 May;86(5):852–60.