Long-acting insulin analogues versus human insulin for type 2 diabetes mellitus: update of a Cochrane review

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Background:

In persons with type 2 diabetes mellitus (T2DM) insulin treatment is frequently performed by administering basal insulin. Common adverse effects are hypoglycaemia and weight gain. Long-acting insulin analogues have been developed to minimise side effects and allow for better blood glucose control.

Objectives:

To assess the effects of long-term treatment with long-acting insulin analogues (insulin glargine U100 and U300, insulin detemir and insulin deglutec) compared to NPH (Neutral Protamine Hagedorn) insulin on all-cause mortality, late diabetic complications, quality of life and metabolic control in persons with type 2 diabetes mellitus.

Methods:

We included randomized controlled trials comparing the effects of treatment with long-acting insulin analogues to NPH treatment in adult persons with type 2 diabetes mellitus.

We searched CENTRAL, MEDLINE, Embase as well as ICTRP Search Portal and ClinicalTrials.gov. The date of the last search of all databases was January 26, 2017. No language restrictions were applied. We contacted authors of included trials and main pharmaceutical companies to obtain additional information and to determine if further trials existed. We considered additional information based on original trial reports published in a report by the German Institute for Quality and Efficiency in Health Care (IQWiG 2009). We tried to identify other potentially eligible trials or ancillary publications by searching the reference lists of included trials, systematic reviews, meta-analyses and health technology assessment reports. We did not use abstracts or conference proceedings.
Two authors independently selected trials, assessed risk of bias, extracted data and evaluated the overall quality of evidence using GRADE. Studies were pooled using random-effects meta-analyses.

Results:

16 studies compared insulin glargine to NPH insulin and 8 studies compared insulin detemir to NPH insulin. In these trials 3419 and 1321 persons with type 2 diabetes were randomised to insulin glargine and to insulin detemir respectively. We found no studies comparing insulin glargine U300 or insulin degludec with NPH insulin. Duration of the included trials ranged from 24 weeks to 5 years. All trials had an unclear or high risk of bias for several domains.

Information on myocardial infarction, stroke, amputations, ESRD and QoL was available only from few studies with a small number of events. When available, study results did not suggest any differences in the effects. Meta-analyses on retinopathy did not result in statistically or clinically significant differences between treatments. The number of deaths were low and meta-analyses did not show a significant difference between treatments: glargine versus NPH OR 1.06 (0.62; 1.82), detemir versus NPH OR 0.74 (0.20; 2.65).

Treatment with insulin glargine compared to NPH insulin treatment showed an OR for severe hypoglycaemia of 0.65 (95% CI 0.48 to 0.57); P = 0.004; 14 trials; 6164 participants, very low-quality evidence. The OR for serious hypoglycaemia was 0.73 (95% CI 0.50 to 1.07); P = 0.11; 10 trials; 4685 participants; low-quality evidence. Treatment with glargine reduced the incidence confirmed nocturnal hypoglycaemia. (All see table 1.) Treatment with insulin detemir compared to NPH insulin showed an OR for severe hypoglycaemia of 0.37 (95% CI 0.15 to 0.92); P = 0.03; 5 trials; 1804 participants; very low-quality evidence. The OR for serious hypoglycaemia was 0.16 (95% CI 0.04 to 0.61); P = 0.007; 5 trials; 1777 participants; very low-quality evidence. Treatment with detemir also reduced the incidence of confirmed and confirmed nocturnal hypoglycaemia. (All see table 2.)
Changes in glycosylated haemoglobin A1c were about the same whether treating with long-acting insulin analogues or NPH (table1 and table 2).

The incidence of adverse events, including weight gain, was (clinically) comparable for persons treated with glargine, or detemir, and persons treated with NPH.

Discussion:

Duration of follow-up was 12 months or less for all studies but one which lasted for 60 months. For most patient-important outcomes, information was available only in a small number of studies.
The reported frequency of such outcomes was low.

Most studies limited NPH to a single injection per day. However, standard clinical practice and the summary of product characteristics indicate that the number of daily NPH injections should be adjusted as necessary.
Target blood glucose levels were not adjusted individually in any of the trials. (Since all study participants had had the disease for a relatively long time, higher target levels may well have been more appropriate.)

Definitions of hypoglycaemia were bias-prone. Even for confirmed hypoglycaemia, the risk of bias is high as participants may choose not to report events, or may make mistakes when transcribing blood glucose readings.
All trials had an unclear or high risk of bias for several domains.

Conclusion:

Whether treatment with long-acting insulin analogues rather than NPH insulin will result in a reduction of diabetic complications remains unclear: Information on patient-relevant outcomes was insufficient and no safe inferences can be drawn from the effects on metabolic control alone.
Treatment with insulin glargine or insulin detemir resulted in fewer participants experiencing severe, overall and nocturnal hypoglycaemia when compared to treatment with NPH insulin. The effects on HbA1c were comparable. But low-quality evidence and trial designs that did not conform with current clinical practice mean it remains unclear if the same effects will be observed in daily clinical practice.

Table 1: Summary of findings, NPH versus glargine

Outcomes	Comparative risks		NNT	Relative effect [OR (95% CI)]	Quality of evidence (GRADE)
	NPH	Glargine			
Severe hypoglycaemia	37 per 1000	24 per 1000	77	0,65 (0.48; 0.57)	very low
Serious* hypoglycaemia	27 per 1000	20 per 1000	-	0.73 (0.50; 1.07)	low
Confirmed hypoglycaemia (BG < 55mg/dl)	180 per 1000	159 per 1000	48	0.88 (0.81; 0.96)	low
Confirmed nocturnal hypoglycaemia (BG < 55mg/dl)	115 per 1000	85 per 1000	33	0.74 (0.64; 0.85)	low
HbA1c (%)	Mean change ranged across control groups from -2.1 to +0.1	Mean change in the intervention groups was **0.07 lower** (0.18 lower to 0.03 higher)	-	-	very low

HbA1c: glycosylated A1c; NNT: number needed to treat; OR: odds ratio; * required to fulfil at least one criteria of a serious adverse event

Table 2: Summary of findings, NPH versus detemir

Outcomes	Comparative risks		NNT	Relative effect [OR (95% CI)]	Quality of evidence (GRADE)
	NPH	Glargine			
Severe hypoglycaemia	17 per 1000	6 per 1000	91	0,37 (0.15; 0.92)	very low
Serious* hypoglycaemia	11 per 1000	2 per 1000	111	0.16 (0.04; 0.61)	very low
Confirmed hypoglycaemia (BG < 55mg/dl)	493 per 1000	237 per 1000	4	0.48 (0.32; 0.71)	low
Confirmed nocturnal hypoglycaemia (BG < 55mg/dl)	255 per 1000	82 per 1000	6	0.32 (0.16; 0.63)	low
HbA1c (%)	Mean change ranged across control groups from -1.9 to -0.32	Mean change in the intervention groups was **0.13 higher** (0.02 lower to 0.28 higher)	-	-	very low

HbA1c: glycosylated A1c; NNT: number needed to treat; OR: odds ratio; * required to fulfil at least one criteria of a serious adverse event

Declarations of Interests:
KH: was involved in the preparation of the report on long-acting insulin analogues for the treatment of type 2 diabetes mellitus for the Institute for Quality and Efficiency in Health Care (www.iqwig.de); JE: none known; TS: none known; KJ: was involved in the preparation of the report on long-acting insulin analogues for the treatment of type 2 diabetes mellitus for the Institute for Quality and Efficiency in Health Care (www.iqwig.de); AB: none known; AS: was involved in the preparation of the report on long-acting insulin analogues for the treatment of type 2 diabetes mellitus for the Institute for Quality and Efficiency in Health Care (www.iqwig.de)

IQWiG 2009: Institute for Quality and Efficiency in Health Care (IQWiG). Long-acting insulin analogues in the treatment of diabetes mellitus type 2 (IQWiG Reports - Commission No. A05-03). Cologne: Institute for Quality and Efficiency in Health Care (IQWiG), 2009.