Efficacy and safety of degludec insulin: a meta-analysis of randomised trials

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CRD summary
The authors of this review concluded that degludec was associated with a lower incidence of hypoglycaemia than glargine insulin for similar levels of glycaemic control in diabetes. It could represent one step further in insulin therapy but more research was necessary. Their conclusions follow from the evidence presented but should be approached with caution given limitations identified with the review.

Authors' objectives
To evaluate the efficacy and safety of degludec insulin for patients with diabetes.

Searching
The authors searched MEDLINE and The Cochrane Library up to July 1st 2012. One search term was presented: degludec.

Study selection
Eligible studies needed to be randomised controlled trials (RCTs) of at least 16 weeks' duration that enrolled patients with type 1 or type 2 diabetes. Trials needed to compare degludec to other basal insulins and combine treatment with oral hypoglycaemic agents or with a prandial insulin. The main outcomes were glycated haemoglobin (HbA1c) and nocturnal, overall and severe hypoglycaemia. Secondary outcomes included body mass index (BMI), fasting plasma glucose (FPG) and insulin doses at the end of the trial.

Mean ages of trial participants ranged between 43 and 59 years. Baseline HbA1c varied from 7.7% to 8.7%. Mean BMI was between 26.3 kg/m² and 32.1 kg/m². Most of the trials compared degludec with glargine insulin. Trial duration was either 16 or 52 weeks.

Study selection was performed by two reviewers independently; disagreements were resolved by discussion.

Assessment of study quality
Quality was assessed using Jadad criteria.

It was unclear whether more than one reviewer was involved in assessing study quality.

Data extraction
Standardised mean differences (SMD) were calculated for the outcomes of HbA1c and BMI and odds ratios (OR) for hypoglycaemia, each with 95% confidence intervals (CI).

Data extraction was performed by two reviewers independently; disagreements were resolved by discussion.

Methods of synthesis
Random-effects models were used for meta-analysis of primary and secondary outcomes.

Results of the review
Five RCTs (2,105 participants, range 123 to 992) were included in the review. The authors stated that randomisation, allocation and blinding procedures were reported adequately and described in all included trials.

Degludec versus glargine (four trials): Levels of HbA1c were similar in the two treatment groups (SMD 0.04, 95% CI -0.05 to 0.13). Degludec was associated with a lower rate of overall hypoglycaemia in patients with type 2 diabetes (OR 0.81, 95% CI 0.78 to 0.85) and a lower rate of nocturnal hypoglycaemia in patients with type 1 diabetes (OR 0.66, 95% CI 0.49 to 0.88).

FPG was significantly lower in degludec-treated groups (SMD -0.38, 95% CI -0.71 to -2.27). No significant differences
were observed in BMI, cardiovascular events and cancer. Doses of insulin at the end of the trial were significantly higher for degludec than for glargine in patients with type 2 diabetes.

**Authors' conclusions**
Degludec appeared to be associated with a lower incidence of hypoglycaemia in comparison with glargine insulin for similar levels of overall glycaemic control. Use of this agent could represent one step further in insulin therapy but more research was necessary.

**CRD commentary**
This review was based on defined inclusion criteria for participants, intervention, outcomes and study designs. Searching was based on two resources. It is possible that studies were missed and it is unclear whether unpublished studies and papers in languages other than English were eligible for the review. This left the review open to publication bias which was not assessed. All included trials were sponsored by the manufacturer of degludec. Study quality was assessed using a basic tool and the full results were not reported. The authors stated that all trials were open-label (neither researchers nor participants were blinded to treatment). Study selection and data extraction were carried out by two reviewers (which helps to minimise bias) but it was unclear whether study quality assessment was carried out in the same way. Meta-analysis appeared to be appropriate but studies varied in duration and it was unclear why the authors chose to standardise the continuous outcomes. No forest plots or details of statistical heterogeneity were provided.

The authors' conclusions follow from the evidence presented but should be approached with caution given these limitations.

**Implications of the review for practice and research**
**Practice:** The authors stated that results obtained should be considered preliminary as trials were few in number and exposure to degludec was of limited duration.

**Research:** The authors stated a need for further research before conclusions could be drawn on cardiovascular and cancer risks with degludec.

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