Long-acting insulin analogues for diabetes mellitus: meta-analysis of clinical outcomes and assessment of cost-effectiveness

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CRD summary
Long-acting insulin analogues (specifically insulin glargine and insulin detemir) were investigated for the treatment of diabetes mellitus. The authors found that long-acting insulin analogue use did not result in clinically important outcomes for all patients with diabetes mellitus. This review was generally well-conducted and the authors' conclusions are likely to be reliable.

Authors' objectives
To investigate the clinical efficacy and economic implications of long-acting insulin analogues (specifically insulin glargine and insulin detemir) for the treatment of diabetes mellitus. This abstract relates primarily to the review of clinical efficacy.

Searching
MEDLINE, EMBASE, BIOSIS Previews, PASCAL and the Cochrane Database of Systematic Reviews were searched from 1990. Search terms reported. Grey literature was also scanned through websites of regulatory agencies, Health Technology Assessment Agency, near-technology assessment agencies and additional specialised databases. In addition, professional association websites and their associated conference sites were searched. Manufacturers were also contacted.

Study selection
Randomised controlled trials (RCTs) of patients with diabetes mellitus (type 1 or 2, or gestational) that compared long-acting insulin analogues (insulin glargine or insulin detemir) with conventional human insulin or oral anti-diabetic agents were eligible for inclusion. Outcomes were glycaemic control level (glycated haemoglobin $A_1c$), blood glucose level, quality of life, hypoglycaemic episodes, adverse events, complications of diabetes, or mortality.

The included trials were parallel and cross-over multicentre RCTs conducted mainly in the US or Europe. Trial duration ranged from four weeks to one year. The included patients had a mean age of 11.5 to 62 years, were Caucasian (where reported) and the proportion of males ranged from 38.7 to 82%. The mean duration of diabetes ranged from 8.5 to 18.6 years, where reported. The long-acting analogues evaluated were: insulin detemir with insulin aspart, human insulin or oral anti-diabetic agent; insulin glargine with insulin lispro, human insulin, insulin aspart, oral anti-diabetic agent, glimepiride, metformin or sulfonylurea (with or without metformin). The comparator in the majority of trials was neutral protamine Hagedorn with insulin aspart, insulin lispro, human insulin, oral anti-diabetic agent, glimepiride or metformin.

Two reviewers independently selected studies. Disagreements resolved by consensus.

Assessment of study quality
Methodological quality of the primary trials was assessed using the Jadad scale, which evaluates randomisation, blinding, withdrawals and drop-outs, to give a quality score out of a maximum of 5 points. Concealment of allocation, blinding of assessors and intention to treat were also recorded.

The authors did not state how the validity assessment was performed.

Data extraction
Data were extracted for the outcomes haemoglobin $A_1c$, blood glucose, hypoglycaemia, adverse events, mortality and quality of life into a data extraction form and relative risks and corresponding 95% confidence intervals calculated.
Data were extracted by one reviewer and checked by a second. Disagreements were resolved by consensus.

**Methods of synthesis**
Statistical heterogeneity was assessed with the $I^2$ test. Where the $I^2$ value was less than 75%, the trials were pooled to generate weighted mean difference for continuous data, and relative risks and risk difference for binary data. Results from the random effects model were presented.

**Results of the review**
Thirty-four randomised controlled trials (RCTs) were included in the review (n=11,971 patients). The number of patients in the RCTs ranged from between 14 to 756. The mean Jadad score was 2.3 (indicating generally low quality). None of the trials were double-blinded.

**Type 1 diabetes mellitus:** Five of 11 RCTs found that insulin glargine treatment was significantly associated with reductions in haemoglobin A$_1c$ levels when compared with neutral protamine Hagedorn (results not pooled due to heterogeneity. However, these differences were not clinically significant (defined as 1.0 reduction in haemoglobin A$_1c$). There were no differences in overall, severe or nocturnal hypoglycaemia between treatments. Subgroup analysis of human insulin as the bolus found a statistically significant difference in severe hypoglycaemia (relative risk 0.73, 95% confidence interval (CI): 0.55 to 0.95; five RCTs). No significant differences were found in haemoglobin A$_1c$ levels with insulin detemir compared with neutral protamine Hagedorn. When insulin detemir was compared with neutral protamine Hagedorn, with insulin aspart as the bolus, this was associated with a significant reduction in nocturnal hypoglycaemia (relative risk 0.84, 95% CI: 0.73 to 0.95; five RCTs) and severe hypoglycaemia (relative risk 0.70, 95% CI: 0.52 to 0.95; five RCTs).

**Type 2 diabetes mellitus:** There was no significant difference in glycated haemoglobin A$_1c$ with insulin glargine or insulin detemir compared with neutral protamine Hagedorn. Insulin glargine was associated with a significant reduction in nocturnal hypoglycaemia compared with neutral protamine Hagedorn, regardless of additional human insulin or oral anti-diabetic agent (relative risk 0.57, 95% CI: 0.44 to 0.74; five trials). There was no statistically significant difference in severe hypoglycaemia with insulin glargine compared with neutral protamine Hagedorn.

Adverse events were similar in type 1 and type 2 diabetes mellitus patients with insulin analogues and conventional insulin. Mortality and quality of life data were inconclusive.

**Cost information**
Comparison of insulin glargine and insulin detemir suggested that patient benefit derived from avoidance of severe hypoglycaemic events with the insulin analogue offset the increased cost of this drug and resulted in cost savings.

One trial, that compared insulin detemir and neutral protamine Hagedorn in type 1 diabetes mellitus, found that insulin detemir-based basal and bolus therapy would result in an incremental cost equivalent to C$51,427 per life-year gained, with an incremental cost of C$44,130 per quality-adjusted life-year. It concluded that this was likely to be good value for money.

The estimated provincial budget impact over three years (2006 to 2008), if more patients switched to long-acting insulin analogues, would range from C$605,708 to C$13,921,951 (if 10% switched), and from C$3,534,906 to C$79,115,423 (if 100% switched), depending on province.

**Authors’ conclusions**
Long-acting insulin analogue use did not result in clinically important outcomes for all individuals with diabetes mellitus.

**CRD commentary**
The research question was well defined and supported by inclusion criteria for participants, outcomes, interventions and study design. Published and unpublished sources were searched, reducing the possibility of publication bias (but this
was not assessed). The authors did not specify whether language restrictions were used, so the presence of language bias cannot be ruled out.

Data extraction and study selection were performed by two reviewers, reducing the possibility of error and bias. The process of validity assessment was not described, so it is not known whether similar steps were taken. Statistical differences between trials were assessed and pooling appeared to be appropriate. Details of the study populations were available for examination of clinical differences. The quality of trials was assessed and taken into consideration. Generally, this appeared to be a well-conducted review and the authors’ conclusions are likely to be reliable.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that long-term high-quality comparative studies are needed to determine the benefit and harm of long-acting insulin analogues.

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Other publications of related interest


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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.