Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine

Warren E, Weatherley-Jones E, Chilcott J, Beverley C

CRD summary
This review concluded there was some evidence that insulin glargine was more effective than once-daily neutral protamine Hagedorn in reducing nocturnal hypoglycaemia incidence, but there was no evidence of long-term glycaemic control improvement. The review methodology was poorly reported and the available data were limited, but the authors' cautious conclusions reflect the data presented and are likely to be reliable.

Authors' objectives
To assess the incremental clinical and cost-effectiveness of basal-bolus insulin glargine, a long-acting insulin analogue, compared with existing basal-bolus insulin treatments.

Searching
The following databases were searched to January 2002: Biological Abstracts, CINAHL, the Cochrane Library, DARE, EBM reviews, EMBASE, HEED, HTA database, MEDLINE, NHS EED, Science Citation Index and Social Science Citation Index. Search terms were reported (listed in report Appendix 3). No language or publication type restrictions were applied. The reference lists of included studies were searched for additional articles. Forty-five web-based health services research-related resources were scanned (listed in report Appendix 2).

Study selection
Systematic reviews, randomised controlled trials (RCTs), or economic evaluations, comparing insulin glargine with other long-acting basal insulins, in participants with type 1 diabetes or type 2 diabetes requiring insulin control, were eligible for inclusion. Included studies were required to report measures of glycaemic control (e.g. blood glucose, glycosylated haemoglobin) and/or incidence and severity of hypoglycaemic episodes. The minimum acceptable study duration was four weeks.

All included studies were prospective and the majority were RCTs. All studies compared one or more formulations of insulin glargine with each other and with neutral protamine Hagedorn. In the included studies, the mean age of participants with type 1 diabetes was from 24 to 39 years from 59 to 60 years for participants with type 2 diabetes, where reported. The mean baseline glycosylated haemoglobin, where reported, ranged from 7.7 to 8.1% for participants with type 1 diabetes, and from 8.5 to 9.1% for participants with type 2 diabetes.

The authors did not state how studies were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Included randomised controlled trials were assessed using three items of the five-point Jadad scale (it was not considered possible to blind participants to treatments, due to visible differences) and an additional item on blinding of outcome assessors.

The authors did not state how study quality was assessed, or how many reviewers undertook the assessment.

Data extraction
Data were extracted on baseline population characteristics (e.g. mean duration of illness, mean body mass index, mean baseline glycosylated haemoglobin), along with mean change from baseline, at end point, for primary outcome measures (fasting blood glucose, fasting plasma glucose and glycosylated haemoglobin) and between group differences were reported. Numbers of hypoglycaemic episodes in each treatment group were extracted (classified as nocturnal, symptomatic or severe) and between group differences were calculated. Data on adverse events were also extracted.
Data extraction was performed by one reviewer using a standard extraction form.

**Methods of synthesis**
Study results were presented in tables and a narrative synthesis, grouped by diabetes type and outcome measure.

**Results of the review**
Thirteen studies were included in the review of clinical effectiveness including: seven studies (1,691 participants in six studies plus one study not reported) of adults with type 1 diabetes; one study of 349 children with type 1 diabetes; five studies of 1,399 adults with type 2 diabetes.

Of the randomised controlled trials (RCTs) published as full reports, which could be assessed for methodological quality, the highest score was 3 points (one RCT), four RCTs scored 2 points, and one RCT scored one point (lowest quality). No study reported whether clinical assessors were blinded.

In type 1 diabetes, insulin glargine appeared to be more effective than neutral protamine Hagedorn for control of fasting plasma glucose (four studies, out of five reporting data, reported a significant difference in favour of insulin glargine) and fasting blood glucose (six studies, out of seven reporting data, reported a significant difference in favour of insulin glargine). However, insulin glargine did not appear to be more effective than neutral protamine Hagedorn in reducing glycosylated haemoglobin (six out of eight data sets showed no significant difference).

In type 2 diabetes, there was no evidence that insulin glargine was more effective than neutral protamine Hagedorn for control of fasting plasma glucose, fasting blood glucose or glycosylated haemoglobin.

Evidence on the control of hypoglycaemia was inconclusive for both types of diabetes; studies which showed insulin glargine to be superior to neutral protamine Hagedorn in reducing incidence of nocturnal hypoglycaemia, indicated that this may only be the case for the HOE901[80] formulation of insulin glargine, compared with once-daily neutral protamine Hagedorn (not twice-daily). There was no conclusive evidence that insulin glargine performed better than neutral protamine Hagedorn in reducing incidence of symptomatic, or severe hypoglycaemia.

Injection site pain/reaction was the most commonly reported adverse event. This was generally higher in groups treated with insulin glargine than in those treated with neutral protamine Hagedorn, where reported.

**Cost information**
Modelling suggested that the cost-effectiveness of insulin glargine, for patients with type 1 diabetes, was £3,496 to £4,978 per quality-adjusted life-year (QALY). For patients with type 2 diabetes, the cost-effectiveness was £32,508 to £43,411 per QALY. Cost per QALY was dependent upon mode of administration (vial, cartridge, or insulin pen). The cost-effectiveness of insulin glargine, in both types of diabetes, was highly sensitive to the utility assigned to reducing the fear of hypoglycaemia.

**Authors’ conclusions**
There is some evidence that insulin glargine was more effective than once-daily neutral protamine Hagedorn in reducing the incidence of nocturnal hypoglycaemic episodes. There appeared to be no improvement in long-term glycaemic control, so insulin glargine was unlikely to reduce the incidence of long-term microvascular and cardiovascular complications.

**CRD commentary**
The review addressed a clearly stated research question and defined appropriate inclusion criteria. The search strategy was extensive and unrestricted, and abstracts, as well as published papers, were included in the review, minimising the potential for language and publication bias. Reporting of the review process was limited and data extraction was conducted by a single reviewer, leaving open the potential for error and/or bias. The methodological quality of included studies was assessed, where possible, and the results of this assessment were included in the narrative. The use of a narrative summary, rather than formal meta-analyses, seemed appropriate, given the small numbers of studies in each group reporting common interventions and outcome measures. However, the authors provided no reasoning in their
methods section to justify their approach to synthesis. The results of individual studies were clearly reported for each outcome measure. The authors' cautious conclusions reflect the data presented and are likely to be reliable.

**Implications of the review for practice and research**

**Implications for practice:** The authors did not state any implications for practice.

**Research:** The authors stated that further research on insulin glargine is needed with respect to the quality of life associated with fear of hypoglycaemia, the economic impact of the trade-off between hypoglycaemia and long-term glycosylated haemoglobin control, and the incidence of hypoglycaemia achieved in practice.

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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.