Treatment regimens with insulin analogues and haemoglobin A1c target of <7% in type 2 diabetes: a systematic review
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CRD summary
This review found that glycated haemoglobin targets of less than 7% could be achieved with the use of insulin analogues depending on the insulin regimen used. The authors’ conclusions should be interpreted with caution due to the poor quality of the trials and the indirect comparisons made in the review analyses.

Authors’ objectives
To assess the effectiveness of different regimens using insulin analogues to reach haemoglobin A1c (glycated haemoglobin) targets of below 7% in patients with type 2 diabetes mellitus.

Searching
MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL) and CINAHL were searched from inception to January 2010; search terms were reported. The clinical trials public registries www.clinicaltrials.gov and www.clinicalstudyresults.org and the websites of the United Stated Food and Drug Administration (FDA) and the European Medicines Agency were also searched. Reference lists of retrieved articles were checked for additional studies. There were no language restrictions.

Study selection
Randomised controlled trials (RCTs) of patients (18 years and over) with type 2 diabetes that evaluated insulin regimens (basal, biphasic, prandial or basal-bolus) using insulin analogues were eligible for inclusion. Trials had to measure the proportions of patients who achieved glycated haemoglobin levels of 7% or lower. Secondary outcomes were hypoglycaemic events and weight gain. Abstracts and trials with less than 30 patients in any treatment arm or with intervention durations of less than three months were excluded from the review.

The included RCTs were published from 2000 to 2010 and were multinational studies. Most included trials were sponsored by industry. The duration of trials ranged from three to 31 months. The mean age of included patients was 57.5 years. At baseline, the baseline median glycated haemoglobin was 8.7% (interquartile range 8.4 to 8.9%). The trials included insulin-naive patients, insulin-treated patients, and one trial enrolled a mixture of insulin-naive and insulin-treated patients.

Basal insulin regimens evaluated were glargine, detemir, and lispro NPL. Biphasic insulin regimens consisted of pre-mixed insulin analogues (lispro 25/75, lispro 50/50, aspart 50/50 and aspart 70/30; the figures denoted proportions of rapid-acting and long-acting components). Prandial insulin regimens consisted of the short-acting insulin analogues lispro, aspart and glulisine. Basal-bolus regimens were any combination of prandial and basal insulin analogues. Most of the included trials used combined treatment regimens of oral drugs and insulin; the most commonly used oral drugs were metformin, a sulfonylurea or a glitazone.

Two reviewers independently performed the study selection; any disagreements were resolved by consensus with a third reviewer.

Assessment of study quality
Methodological quality was assessed using the Jadad 5-point scale for randomisation, use of double-blinding, completeness of follow-up and use of intention-to-treat analyses. Trials with Jadad scores of 2 points or less were considered to be of low quality; trials assigned a score of 3 or more points were regarded as high quality.

It was not clear how many reviewers performed the quality assessment.

Data extraction
Data were extracted to transform the proportions of patients who achieved glycated haemoglobin levels of under 7% to
quantities suitable for meta-analyses, and to calculate the mean differences between groups for the outcomes of hypoglycaemic episodes and weight gain, with 95% confidence intervals (CIs) for the summary estimates.

It was not clear how many authors performed the data extraction

**Methods of synthesis**

Pooled percentage reductions weighted mean differences, with 95% confidence intervals, were calculated for each summary estimates using fixed-effect and DerSimonian and Laird random-effects models. Heterogeneity was assessed using $\chi^2$ and $I^2$. Meta-regression analyses were also used to explore potential sources of heterogeneity.

**Results of the review**

Forty-eight trials, with 85 treatment arms (n=30,588 patients), were included in the review. Intention-to-treat analyses were used in 38 trials. Methodological quality scores on the 5-point Jadad scale ranged from 1 point to 4 points; the median score was 3 points. Twenty studies were allocated Jadad scores of 2 points or less. Predefined titration steps of insulin doses were used in 41 trials.

**Basal insulin** (29 RCTs, 38 arms, n=17,588): The proportion of patients with glycated haemoglobin levels of less than 7% was 41.4% (95% CI 35.6 to 47.4), with substantial heterogeneity ($I^2$=95.7%). Meta-regression analyses found that first insulin treatment (46.1%, 95% CI 40.1 to 52.3), lower insulin dose (42.8%, 37.0 to 48.8) and the use of two oral drugs (45.9%, 95% CI 39.2 to 52.7) were also associated with beneficial responses. The median number of hypoglycaemic events per patient per 30 days was 0.5 (interquartile range (0.39 to 0.62) and weight gain was 1.75kg (1.2 to 2.1).

**Biphasic insulin** (20 RCTs, 26 treatment arms, n=9,237): The proportion of patients with glycated haemoglobin levels of less than 7% was 46.5% (95% CI 40.8 to 52.3), with substantial heterogeneity ($I^2$=89.3%). Higher insulin doses were the only variable that was significantly associated with beneficial response (52.8%, 95% CI 45.9 to 59.6). The median number of hypoglycaemic events per patient per 30 days were 0.37 (interquartile range 0.07 to 0.70) and weight gain was 3kg (1.7 to 4.0).

**Prandial insulin** (eight RCTs, nine arms, n=1,605): The proportion of patients attaining glycated haemoglobin levels of less than 7% was 39.6% (95% CI 28.6 to 51.3), with substantial heterogeneity ($I^2$=94.6%). Due to the small number of trials, meta-regression analyses were performed only on baseline glycated haemoglobin, final insulin dose and concomitant oral drug use, but none of these were associated with the response observed in glycated haemoglobin levels. The median number of hypoglycaemic events per patient per 30 days was 0.67 (interquartile range 0.44 to 1.0) and weight gain was 2.3kg (1.87 to 3.8).

**Basal-bolus insulin** (eight RCTs, 12 arms, n=2,114): The proportion of patients attaining glycated haemoglobin levels of less than 7% was 53.9% (95% CI 43.5 to 64), with substantial heterogeneity observed across trials ($I^2$=92.1%). There were non-significant trends found (using meta-regression analyses) for final insulin dose and concomitant use of oral drugs associated with the response. The median number of hypoglycaemic episodes per patient per 30 days was 0.88 (interquartile range 0.35 to 1.3) and weight gain was 2.75 kg (0.78 to 1.3)

**Authors' conclusions**

Glycated haemoglobin targets of less than 7% could be achieved with the use of insulin analogues depending on the insulin regimen used. Further achievement could be obtained in insulin-naïve patients with the concomitant use of at least two oral drugs when basal insulin analogue regimens were used

**CRD commentary**

The review addressed a clear question. Criteria for the inclusion of studies were defined. Appropriate databases were searched for relevant studies with no language restrictions. Attempts were made to identify unpublished studies. Steps were taken by the reviewers to minimise errors and biases for study selection, but were not explicitly reported for data extraction and the assessment of methodological quality.

The authors published summary scores of the quality assessment; nearly half of the included trials were judged to be of poor quality. However, data were only extracted for one treatment arm for the proportions of patients who attained the treatment objective of glycated haemoglobin levels of less than 7%. Direct comparisons with the control arm were not
reported, which meant that indirect comparisons were made. There was substantial heterogeneity present across the trials in the results. The authors explored potential sources of heterogeneity using meta-regression analyses. The limitations of the review were acknowledged by the authors for the heterogeneity of the results and the exclusion of potentially relevant trials based on the lack of reporting of the primary outcome.

Although the authors' conclusions were based on the evidence presented, the poor quality of many of the included trials and the indirect comparisons made in the synthesis mean that the conclusions should be interpreted with some caution.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further studies were required to understand the impact of insulin analogues on long-term complications.

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