CRD summary
The authors concluded that metabolic control and hypoglycaemia were associated with intensity of treatment. Basal regimens had less effect on metabolic control but were associated with lower frequency of hypoglycaemia. Newer analogues yielded better control and less hypoglycaemia. The authors’ conclusions are reasonable based on the evidence presented but the unexplained variability across trials in several analyses, the lack of high quality studies and the lack of information on long-term complications mean they should be interpreted with some caution.

Authors’ objectives
To evaluate the effect of different insulin regimens and insulin analogues.

Searching
The Cochrane Library, MEDLINE and EMBASE were searched from inception to June 2010 for studies published in English. Search terms were reported. Reference lists of retrieved articles, reviews, editorials and proceedings of international conferences were searched.

Study selection
Randomised controlled trials (RCTs) that compared different insulins or insulin regimens in patients with type 2 diabetes were eligible for inclusion. Treatment was required to last between 12 and 52 weeks. Included studies had to report a predefined target of fasting blood glucose level. Only insulin-based arms were considered; placebo and oral antidiabetic drugs arms were not considered.

The outcomes of interest were final HbA1c and hypoglycaemia reported as absolute frequency of hypoglycaemia, nocturnal hypoglycaemia or severe hypoglycaemia (frequency or episodes/patient/year).

Only insulin-treated or insulin-naive patients (not a mixture of both in the trial) were included. Three regimens were investigated in the included studies basal (defined as once a day insulin injection), twice a day injection and prandial (three to four injections per day). Target fasting blood glucose ranged from 86 to 144mg/dL. Most patients also received oral antidiabetic drugs. Various types of insulins (rapid-, short-, intermediate- and long-acting) were used. The mean age of the participants in each arm ranged from 51 to 70 years.

Three reviewers were involved in study selection. Disagreements were resolved by discussion.

Assessment of study quality
Study quality was assessed using the Jadad scale of random allocation, blinding, validated outcomes, drop-outs and withdrawals.

It appeared that more than one reviewer assessed the study quality.

Data extraction
Data were extracted to calculate the standardised mean difference and 95% confidence interval (CI) for HbA1c and for hypoglycaemia outcomes reported as episodes per patient year. The odds ratio (OR) was extracted where hypoglycaemia was reported as a frequency.

Three authors extracted data. Disagreements were resolved by discussion.

Methods of synthesis
A random-effects model was used to pool studies and calculate standardised mean differences (SMD) and odds ratios, each with 95% CIs. Studies were grouped according to regimen (basal versus twice-a-day, basal versus prandial, twice-a-day versus prandial) and within each regimen according to the analogues (detemir and glargine versus comparators, new
combinations versus older combinations). Statistical heterogeneity was assessed using the Q and $I^2$ statistics. $P<0.05$ indicated the presence of statistical heterogeneity and was investigated using subgroup analysis. Regression analyses investigated the relationship between the outcomes of final HbA1c and hypoglycaemia and a range of clinical and methodological variables were undertaken (not summarised in this abstract).

**Results of the review**

Sixty-seven studies (21,347 patients, 143 treatment arms) were included in the review. Study quality scores ranged from 1 to 3. Only one study was double-blinded.

**Basal versus twice-a-day:** Compared to basal regimen, twice-a-day regimen was significantly more effective for final HbA1c (SMD 0.24, 95% CI 0.10 to 0.39; $I^2=77.2%$; 14 studies) but basal regimen had lower risk of hypoglycaemia (OR 0.63, 95% CI 0.49 to 0.81; $I^2=66%$; 13 studies) and severe hypoglycaemia (OR 0.35, 95% CI 0.15 to 0.83; $I^2=36%$; three studies) compared with twice-a-day regimen.

**Basal versus prandial:** Compared to basal regimen, prandial was more effective for final HbA1c (SMD 0.57, 95% CI 0.35 to 0.78; $I^2=78%$; nine studies) but basal regimen was associated with lower frequency of hypoglycaemia (OR 0.37, 95% CI 0.24 to 0.58; $I^2=69%$; eight studies).

**Twice-a-day versus prandial:** Compared to twice-a-day, prandial was more effective on final HbA1c (SMD 0.65, 95% CI 0.25 to 1.05; $I^2=89%$; nine studies). There was no statistically significant difference between twice-a-day and prandial regimens for risk of hypoglycaemia and severe hypoglycaemia.

**Comparisons within treatment regimens:** Within basal regimens, newer analogues (detemir and glargine) had similar effects compared to older insulins on HbA1c ($I^2=80%$) with lower risk of hypoglycaemia (OR 0.71, 95% CI 0.59 to 0.85; $I^2=48%$; 10 studies) and nocturnal hypoglycaemia (SMD -0.65, 95% CI -0.82 to -0.47; $I^2=85%$; nine studies). For prandial regimens, newer analogues were more effective than older insulins on final HbA1c (SMD -0.21, 95% CI -0.40 to -0.03; $I^2=86%$; 10 studies). Low risk of nocturnal hypoglycaemia was observed in prandial regimen with newer analogues (SMD -0.36, 95% CI -0.60 to -0.13; $I^2=85%$; four studies).

Analyses that compared detemir and glargine to other comparators were also presented.

Substantial heterogeneity was found for most of the analyses presented and this was explored using subgroup analyses. In most instances there was still heterogeneity in the subgroups.

**Authors' conclusions**

The authors concluded that metabolic control and hypoglycaemia were associated with intensity of treatment. Basal regimens had a reduced effect on metabolic control but were associated with lower frequency of hypoglycaemia than twice daily or prandial regimens. Newer analogues (short- and long-acting) yielded better control and less hypoglycaemia than older analogues.

**CRD commentary**

The review question and inclusion criteria were clear. The search covered a range of relevant sources. Unpublished studies and studies in languages other than English were not searched for so relevant studies may have been missed. Appropriate methods to reduce reviewer error and bias were used for some stages of the study selection process and data extraction and quality assessment.

Most of the included studies received a low quality score; lack of double-blinding was the specific area of weakness reported. There was substantial unexplained heterogeneity in several analyses and inspection of the forest plots suggested that there were important differences between trials for some comparisons. For some analyses, single trial arms were used more than once to allow multiple comparisons from individual trials and this may have resulted in an underestimation of variability (confidence interval) in a pooled estimate. This was less likely to have had an impact on results from analyses that compared different regimens than for some of the comparisons between types of insulin. The review included interventions that lasted up to one year; long-term implications for diabetes related complications were unknown.

The authors’ conclusions are reasonable based on the evidence presented but the unexplained variability across trials in
several analyses, the lack of high quality studies and the lack of information on long-term complications mean they should be interpreted with some caution.

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

**Practice:** When the glycaemic target has been decided, the preferable regimen should be the one associated with the lowest hypoglycaemic risk.

**Research:** The authors stated that future RCTs should be double-blinded.

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