Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis

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CRD summary
This well-conducted review examined the effect of targeting low and high levels of haemoglobin when treating patients with anaemia resulting from chronic kidney disease with erythropoietin. The authors concluded that targeting a high haemoglobin level increases patient overall mortality. These conclusions are likely to be reliable.

Authors' objectives
To determine the impact of targeting different haemoglobin concentrations when treating patients with anaemia caused by chronic kidney disease with erythropoietin.

Searching
MEDLINE, EMBASE, the Cochrane Controlled Trials Register, the Cochrane Renal Group's Specialised Register of RCTs and ClinicalTrials.gov were searched from inception to November 2006; some search terms were reported. The references of retrieved articles were screened and the abstracts of three relevant scientific meetings were searched (2000 to November 2006). Only studies published in the English language were eligible for inclusion.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with at least 100 recruited patients and a follow-up period of at least 12 weeks were eligible for inclusion. The included studies contained between 146 and 1,432 patients and the follow-up ranged from 12 to 48 months.

Specific interventions included in the review
Studies that assessed the effects of targeting different haemoglobin concentrations with recombinant human erythropoietin were eligible for inclusion. The specific therapies eligible for inclusion were epoetin alfa, epoetin beta, darbepoetin, or placebo. All of the included studies compared different doses of epoetin alfa or epoetin beta given subcutaneously or intravenously.

Participants included in the review
Studies of patients with anaemia resulting from chronic kidney disease were eligible for inclusion. The proportion of male patients in the included studies ranged from 42 to 70%, and the mean ages ranged from 50 to 65 years. The included studies contained patients with differing degrees of cardiac co-morbidity and diabetes. All but one study recruited patients with a moderately to severely reduced glomerular filtration rate or kidney failure; the exception was a study that included patients with a mildly reduced glomerular filtration rate. Several studies in which patients had very low baseline levels of haemoglobin (70 to 80 g/L) were excluded from the main analysis but were included in the sensitivity analyses.

Outcomes assessed in the review
Studies that reported all-cause mortality or cardiovascular events were eligible for inclusion. The studies included in the review reported the following outcomes: all-cause mortality, myocardial infarction (MI), changes in blood-pressure (BP), arteriovenous access thrombosis and effects on left ventricular mass. The included studies employed differing criteria for defining some outcomes. Quality-of-life measures were not assessed since the included studies had used different scales to assess these.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.
Assessment of study quality
Two reviewers independently assessed the studies for validity, and any disagreements were resolved by consensus. The studies were assessed using the following criteria: allocation concealment, blinding of the assessors and method of adjudication for adverse events, intention-to-treat analysis, loss to follow-up, early termination of study, responsibility for study design and control of database.

Data extraction
Two reviewers independently extracted the data for the review. Data were extracted on patient characteristics, type and mode of erythropoiesis-stimulating agents, method of dialysis, cointerventions and outcomes. Relative risks (RRs) and 95% confidence intervals (CIs) were calculated for each outcome.

Methods of synthesis
How were the studies combined?
The studies were combined using both random-effects (DerSimonian and Laird) and fixed-effect (Mantel-Haenszel) meta-analyses. Significance was determined using the random-effects model unless statistical heterogeneity was detected, in which case the fixed-effect model was used.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared and I-squared statistics. Sensitivity analyses were conducted to assess the impact of having excluded 5 trials from the review: four because of low haemoglobin baselines, and one because it recruited fewer than 100 patients. Subgroup analyses were conducted to assess the impact of differences between groups of patients on particular characteristics.

Results of the review
Nine RCTs with a total of 5,143 patients were included in the review.

In terms of study quality: 1 study was double-blinded; 3 studies used independent adjudication of adverse events; all studies used an intention-to-treat analysis; and 2 studies were terminated early due to safety issues.

All-cause mortality (8 studies).
All-cause mortality was significantly higher in the higher haemoglobin target group than in the lower target group (RR 1.17, 95% CI: 1.01, 1.35, p=0.031). No statistically significant heterogeneity was detected (I-squared 27%, p=0.213). A subgroup analysis showed no statistically significant difference between the two haemoglobin target groups in either pre-dialysis patients (RR 1.33, 95% CI: 0.98, 1.81, p=0.067) or those currently undergoing dialysis (RR 1.11, 95% CI: 0.94, 1.31, p=0.22). A sensitivity analysis that included the 5 excluded studies only had a small impact on the results (RR 1.14, 95% CI: 0.99, 1.32, p=0.07).

MI (7 studies).
There was no significant difference in the occurrence of MI between the two groups (RR 0.98, 95% CI: 0.73, 1.31, p=0.88). There was no statistical evidence of heterogeneity (I-squared 0%, p=0.965). A subgroup analysis in the pre-dialysis patients also showed similar results (RR 0.90, 95% CI: 0.58, 1.41, p=0.66). Only 2 trials with dialysis patients reported MI. A sensitivity analysis that included the 2 excluded trials reporting on MI did not significantly change the results of the analysis.

Poorly controlled BP (4 studies).
There was a significantly higher risk of poorly controlled BP in the higher haemoglobin target group than in the lower target group, based on a fixed-effect meta-analysis (RR 1.27, 95% CI: 1.08, 1.50, p=0.004). There was some suggestion of statistical heterogeneity (I-squared 48%, p=0.119). The random-effects analysis showed no significant difference between the two groups (RR 1.31, 95% CI: 0.97, 1.78, p=0.075). A sensitivity analysis that included the 4 excluded trials reporting on BP did not significantly change the results of the fixed-effect analysis, although the random-effects
analysis showed evidence of a beneficial effect of the higher haemoglobin target group (RR 1.62, 95% CI: 1.16, 2.26, p=0.005).

Arteriovenous access thrombosis (6 studies).

There was a significantly higher risk of arteriovenous access thrombosis in the higher haemoglobin target group than in the lower target group (RR 1.34, 95% CI: 1.16, 1.54, p=0.0001). No statistically significant heterogeneity between the trials was detected (I-squared 0%, p=0.612). A sensitivity analysis that included the 2 excluded trials reporting on arteriovenous access thrombosis showed similar results.

Left ventricular mass (5 studies).

None of the studies showed a difference between the higher and lower haemoglobin target groups in the change in left ventricular mass over the study period.

**Authors’ conclusions**
The targeting of higher haemoglobin levels when treating patients with anaemia caused by chronic kidney disease puts patients at an increased risk of death.

**CRD commentary**
The review question and the inclusion criteria were extremely clear. The search was reasonably extensive. However, the decision to limit the search to published studies reported in English may have increased the likelihood that some relevant studies might not have been included in the review. The authors used appropriate methods to reduce the possibility of bias and error in the assessment of study validity and the extraction of data, although they did not report using such measures when selecting studies for the review. Appropriate criteria were used to assess study validity, but the results of this assessment were not incorporated into the evidence synthesis.

The decision to employ meta-analyses for study synthesis appeared appropriate, and an extensive exploration of both study heterogeneity and the appropriateness of decisions on the relevance of studies for inclusion in the review was undertaken. The authors' conclusions appear justified and, overall, 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 an upper limit for target haemoglobin concentration should be considered in the formulation of future guidelines.

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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.