Erythropoiesis-stimulating agents for anemia of chronic kidney disease: systematic review and economic evaluation


CRD summary
This review concluded that treatment with erythropoiesis-stimulating agents for anaemia from chronic kidney disease in adult patients was likely to be optimal when a haemoglobin target of 110g/L was adopted. This conclusion reflects the results of a well-conducted review and appears to be reliable.

Authors’ objectives
To assess the clinical efficacy and safety, and the economic implications of erythropoiesis-stimulating agents for anaemia from chronic kidney disease in adult patients.

Searching
MEDLINE (from 1966), EMBASE (from 1988) and all EBM reviews were searched, with no language restrictions, up to December 2006. Many sources of grey literature were searched (full details were provided in the report). References of included studies and relevant reviews were checked. Canadian manufacturers and study authors were contacted.

Study selection
Parallel design randomised controlled trials (RCTs), with at least 30 participants in each group, were eligible for inclusion if they assessed epoetin alpha or beta, or darbepoetin in adults with anaemia who were at least 16 years old and had chronic kidney disease. Eligible comparators were a different drug or haemoglobin target; placebo; or a different dose, schedule, or route of administration. Included outcomes were all-cause or cardiovascular mortality; myocardial infarction, stroke, heart failure or revascularisation; hospitalisation, vascular access loss, or dialysis dependence; glomerular filtration rate, creatinine clearance, or serum creatinine; quality of life assessed by the Kidney Disease Questionnaire (KDQ) fatigue section or the Short Form (SF-36) health survey; red blood cell transfusions; systolic and diastolic blood pressure; left ventricular mass index; and adverse events.

Trials of transplant recipients were excluded from the review. Trials of both dialysis-dependent and non-dependent patients were included. Target haemoglobin strategies were classified as follows: high (over 120g/L), intermediate (110g/L; range 105g/L to 120g/L) and low (around 90g/L to 105g/L).

Two reviewers independently assessed the trials for inclusion and disagreements were resolved through consensus with a third reviewer.

Assessment of study quality
Two reviewers independently assessed the trials for validity, using a modified form of the Chalmers Index. Criteria assessed were allocation concealment, randomisation, double-blinding, and description of withdrawals and dropouts. Statistical analysis, including sample size calculations, use of intention-to-treat analysis, and model type, was also assessed, as was the reporting of accrual dates, confidence intervals, and adverse events. Information on funding sources was also recorded.

Disagreements between reviewers were resolved through consensus and in consultation with a third reviewer.

Data extraction
Data were extracted to permit the calculation of relative risk (RR) with 95% confidence interval (CI) for each dichotomous outcome and mean difference with 95% CI for continuous outcomes. Where standard deviations were missing, single value imputations were substituted. Where multiple time points were reported for an outcome the latest value was used.
One reviewer extracted the data using a standardised method. This extraction was checked by a second reviewer and a statistical reviewer checked the numerical data. Authors were contacted for missing information.

**Methods of synthesis**
The trials were combined using a random-effects model meta-analysis to calculate pooled RR with 95% CI for dichotomous outcomes and weighted mean difference (WMD) with 95% CI for continuous outcomes. Statistical heterogeneity between trials was assessed using the $I^2$ statistic. Meta-regression explored the impact of numerous variables on the relationship between therapy and outcomes. Indirect comparisons, using logistic regression techniques, explored the effect of haemoglobin target levels and mean required dose on mortality outcomes. Sensitivity analyses assessed the impact of duration of follow-up; publication year; and dose, schedule and route of administration. Quality of life data was analysed by imputing the change from baseline to be zero and the standard deviation to be the maximum available value from the trial, where only a non-significant result was reported. Where no trial specific information was presented the maximum standard deviation from all trials was used. Publication bias was assessed using a regression test and a funnel plot.

**Results of the review**
Thirty-seven RCTs (n=10,180 patients) were included. Trials were of poor to moderate quality and detailed results of the quality assessment were reported for each question.

**Erythropoiesis-stimulating agents (ESA) versus no ESA** (10 RCTs, n=1,553): ESA for intermediate or low haemoglobin target strategies resulted in lower cardiovascular mortality (RR 0.15, 95% CI 0.03 to 0.69), but no difference in all cause mortality. A clinically relevant improvement was noted for groups treated with ESA in quality of life (WMD 1.10, 95% CI 0.76 to 1.44) and fatigue, but they had increased blood pressure (systolic WMD 6.1mmHg, 95% CI 1.8 to 10.4 and diastolic WMD 5.5mmHg, 95% CI 3.0 to 8.1) and frequency of requiring an increase of anti-hypertensive therapy (RR 1.76, 95% CI 1.37 to 2.26). There was no significant difference in kidney failure.

**High versus intermediate or low target haemoglobin** (13 RCTs, n=5,605): There were no statistically significant differences between the groups in the outcomes of all-cause or cardiovascular mortality, or kidney failure, but indirect comparisons suggested an increased risk of death with higher targets (OR 1.24, 95% CI 1.02 to 1.50). High targets showed mixed effects on quality of life, but were associated with an increased risk of hospitalisation (RR 1.06, 95% CI 1.00 to 1.13), adverse events (RR 1.03, 95% CI 1.00 to 1.05) and vascular access thrombosis (RR 1.34, 95% CI 1.16 to 1.54).

**Assessment of other comparisons**: Epoetin versus darbepoetin (three RCTs, n=775), dose (six RCTs, n=732), schedule (four RCTs, n=1,207), and route of administration (three RCTs, n=426) provided little evidence to inform optimal treatment.

The funnel plot was suggestive of possible publication bias, but no statistical evidence for this was found using the regression test (p=0.16).

**Cost information**
A full economic evaluation was carried out. The cost of treating all dialysis-dependent patients in Canada to an intermediate target was estimated to be Canadian $174 million per annum. The cost of treating all patients not dependent on dialysis to an intermediate target was estimated to be between Canadian $1.4 and $6.7 million annually.

**Authors' conclusions**
The authors concluded that treatment to a haemoglobin target of 110g/L was likely to produce optimal results, but further research was required to determine the maximum dose of ESA above which treatment would not be increased even if the target was not met.

**CRD commentary**
The review question and the inclusion criteria were clearly stated. The authors searched two relevant databases and other sources, without language restrictions, and made systematic attempts to identify unpublished trials. These factors
make it unlikely that publication or language bias was introduced into the review, or that relevant studies were omitted. The authors reported using methods designed to reduce reviewer bias and error at all stages of the review process. A thorough validity assessment using appropriate criteria was conducted and used to inform the synthesis. The use of meta-analyses was appropriate and heterogeneity between trials was assessed and explored. The authors’ conclusions reflect the results of this well-conducted review and are likely to be reliable.

Implications of the review for practice and research

Practice: The authors stated that it might be prudent to consider a maximum ESA dose, which should not be exceeded even if haemoglobin targets were not reached, and that until this limit is determined only a low haemoglobin target strategy should be reimbursed.

Research: The authors stated that research should focus on determining an optimum ESA dose for anaemia in patients with chronic kidney disease. This dose should not be exceeded even if haemoglobin targets were not reached and the impact of haemoglobin targets on quality of life would be key to determining this threshold. The impact of this threshold on ESA use, blood transfusions, and other resources used should also be considered. Head-to-head comparisons of epoetin and darbepoetin should also be evaluated.

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