The impact of selecting a high hemoglobin target level on health-related quality of life for patients with chronic kidney disease: a systematic review and meta-analysis


CRD summary
This generally well-conducted review concluded that using erythropoietin-stimulating agents in adult patients with chronic kidney disease with a final target haemoglobin greater than 12.0 g/dL produced small and clinically meaningless improvements in health-related quality of life. Despite some concerns about the reporting of the review process, the authors' conclusions are likely to be reliable.

Authors' objectives
To compare the impact of targeting different haemoglobin levels with erythropoietin-stimulating agents in patients with chronic kidney disease.

Searching
MEDLINE (1966 to 2006), EMBASE (1988 to 2006), Evidence Based Medicine reviews and a range of grey literature sources were searched to identify relevant trials in any language for inclusion in the review. Search terms were reported. The reference lists of included trials and relevant reviews were scanned and trial authors and drug manufacturers were contacted to locate further trials of interest.

Study selection
Parallel design randomised controlled trials (RCTs) of anaemic adults (aged 18 years or over) with chronic kidney disease (including those dependent and non-dependent on haemodialysis) and treated with epoetin (alpha and beta) or darbepoetin were eligible for inclusion in the review. Study groups were required to have at least 30 participants in each treatment group, with the control arm using either a different agent or haemoglobin target or placebo. The comparison of interest was between a low/intermediate haemoglobin target level (9.0 to 12.0 g/dL) and a high target level (greater than 12.0 dL). The outcome of interest was health-related quality of life, using a validated measure. There were several different outcome measures among the included trials, the most frequently reported being the short form 36-item instrument (SF-36). Approximately half of included participants were male. The mean age of all participants ranged from 43 to 66 years. Two independent reviewers selected trials for inclusion in the review; disagreements were resolved by consensus.

Assessment of study quality
Trial quality was assessed using the Jadad criteria (maximum possible score of 5). The authors did not state how many reviewers assessed trial quality.

Data extraction
Data were extracted largely on mean changes from baseline in each domain of the SF-36 outcome measure in order to calculate mean differences and 95% confidence intervals (CI). The last time point was recorded where multiple reporting existed. All trial authors were contacted for additional data. Unpublished material was supplied in two cases. The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Weighted mean differences (WMDs) were calculated in a random-effects meta-analysis, along with 95% CIs for each domain of the SF-36. The results of other outcome measures were synthesised narratively. Heterogeneity was explored using the I² statistic. Sensitivity analyses were performed for trials reporting all domains of the SF-36, and for trials where any SF-36 data were reported. No change over time was assumed for domains that were not reported, or reported as p>0.05. Where possible, changes in health-related quality of life were also compared with the minimally clinically important difference (this being a five point change for the SF-36 score).

Results of the review
Eleven RCTs were included in the review (n=5,214). Samples sizes ranged from 78 to 1,432 participants. Follow up
ranged from six to 29 months. The mean Jadad score was four, indicating high quality. In general, the reporting of data was poor; differences between groups were small, and were below the minimally clinically important difference specified for each measure.

Six trials (n=3,784) using the SF-36 measure (including three with complete data on all domains) provided sufficient data for inclusion in the meta-analysis.

Statistically significant changes in favour of targeting high haemoglobin levels were noted in terms of the impact of treatment on: physical function, WMD 2.91 (95% CI: 1.29, 4.53); general health, WMD 2.71 (95% CI: 1.26, 4.15); vitality, WMD 3.17 (95% CI: 1.89, 4.44); and mental health, WMD 0.44 (95% CI: 0.06, 0.83).

No significant differences were found for the domains of physical role, pain, social function and emotional role.

Significant heterogeneity was reported in analyses for: physical role (I² = 68.8%, p=0.02); social function (I² = 72.6%, p=0.01); and mental health (I² = 70.5%, p=0.02). Smaller differences between study groups were noted in sensitivity analyses where all domains of the SF-36 were included, or where no difference was assumed. These analyses favoured targeting the low/intermediate target level in more domains.

The authors reported that none of the results were clinically meaningful.

Authors' conclusions
Targeting erythropoietin-stimulating agent treatment in patients with chronic kidney disease and haemoglobin levels in excess of 12.0 g/dL produced small improvements in health-related quality of life, but these were not clinically meaningful.

CRD commentary
This review addressed a clear question supported by explicit and potentially reproducible inclusion criteria. The search strategy was balanced to include published and unpublished material in any language, thus minimising the potential for language and publication biases. An appropriate validity assessment tool was applied to the included study designs, and the results of this assessment were used to highlight the strength of the review findings. The process of study selection was carried out with adequate attempts to minimise error and bias, but the same was not reported for the processes of data extraction and validity assessment. Study details were provided. The chosen method of synthesis appeared to be appropriate in the presence of heterogeneity. Sensitivity analyses were applied to address the difficulties of variably reported data. The reporting of results usefully distinguished between clinical and statistically meaningful changes. The authors pointed out the potential limitation of including trials that were powered to detect differences in outcomes other than the primary measure of interest. Although there were some methodological limitations in the reporting of the review process, this appeared to be a largely well-conducted review and the authors' conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that given the safety concerns of targeting high haemoglobin levels it was preferable to target treatment at patients with levels in the range of 9.0 to 12.0 g/DL.

Research: The authors did not state any implications for future research.

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Record Status
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.