Erythropoietin treatment in patients with chronic heart failure: a meta-analysis

van der Meer P, Groenveld HF, Januzzi JL, van Veldhuisen DJ

CRD summary
This review concluded that the treatment of anaemia in patients with chronic heart failure with erythropoiesis stimulating proteins reduced the risk for hospitalisation and had no effect on mortality rates. The authors' conclusions reflect the evidence presented, but should be viewed with caution given the small number of included trials, most of which had small sample sizes.

Authors' objectives
To determine if erythropoiesis stimulating proteins are associated with morbidity and mortality in the treatment of anaemic patients with chronic heart failure.

Searching
MEDLINE, Cochrane Controlled Clinical Trials Register Database (CENTRAL), Web of Science and ClinicalTrials.gov were searched from 1966 to July 2008. Search terms were reported. Bibliographies of relevant articles were handsearched for additional material. Experts in the field were contacted for further publications. Two authors independently performed the search strategy. Only studies in English were eligible for inclusion.

Study selection
Randomised controlled trials (RCTs) that assessed the effects of erythropoiesis stimulating proteins compared with placebo or usual care, in anaemic patients with chronic heart failure, were eligible for inclusion. Trials were not eligible if participants were under 18 years old or had a follow-up of less than three months. Outcomes measured were all-cause mortality, hospitalisation due to heart failure, venous thrombosis and hypertension.

Included erythropoiesis stimulating proteins were erythropoietin (alpha or beta) or darbepoetin. The majority of included trials had excluded patients with significant renal disease. Participants had haemoglobin levels of 9 to 12.5 g/dL. Follow-up ranged from three months to one year.

Two reviewers independently selected studies; disagreements were resolved by consensus.

Assessment of study quality
The quality of trials was assessed using the guidelines of the United States Preventative Task Force. The following criteria were used: duration of follow-up of more than six months; reporting loss of follow-up; definition of anaemia; full specification of outcome; trial sample representative for the mentioned population; full specification of clinical and demographic variables; explanation of sample selection; and clear inclusion and exclusion criteria. Trials were rated as good (more than seven criteria), fair (five to six criteria) or poor (less than five criteria).

Two reviewers performed the validity assessment.

Data extraction
Data was extracted to calculate risk ratios (RRs) and 95% confidence intervals (CI).

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Pooled risk ratios and 95% confidence intervals were calculated using fixed-effects (homogenous results) and random-effects (heterogeneous results) models. Heterogeneity was assessed using the $\chi^2$ and $I^2$ statistics. Bias was assessed using a funnel plot and the Egger test.
Results of the review
Seven RCTs were included in the review (total participants=650, range 23 to 319). All trials had a quality rating of fair.

The use of erythropoiesis stimulating proteins had no significant effect on mortality compared with placebo, but significantly decreased hospitalisation risk (RR 0.59, 95% CI 0.41 to 0.86). There was a small, non-significant risk of poorly controlled blood pressure in 4.7% of erythropoiesis stimulating protein treated patients and 4.2% of placebo treated patients. The trials were not significantly heterogeneous and publication bias was not detected.

Authors' conclusions
The use of erythropoiesis stimulating proteins to treat anaemia in patients with chronic heart failure reduced hospitalisation risk and was not associated with mortality rates.

CRD commentary
The review addressed clear research questions with clear inclusion criteria. Several sources were searched and attempts were made to obtain unpublished data. Only English-language publications were included, which introduced a risk of language bias. Attempts were made to minimise bias and error in the review process. Trial quality was assessed using described criteria and the trials were deemed fair. It was unclear which quality criteria the trials did not meet. The lack of heterogeneity between trials suggested that the synthesis was appropriate.

The authors' conclusions reflect the evidence presented, but results were based on seven trials, most of which had small sample sizes, so the conclusion should be viewed with caution.

Two authors disclosed receipt of fees from Amgen Inc. and Roche Inc. One author disclosed membership of the executive committee of the RED-HF (Reduction of Events with Darbepoetin Alfa in Heart Failure) trial.

Implications of the review for practice and research
Practice: The authors stated that erythropoiesis stimulating protein treatment appears to be safe.

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

Funding
The Netherlands Heart Foundation; The Netherlands Organisation for Scientific Research.

Bibliographic details

PubMedID
19168472

DOI
10.1136/hrt.2008.161091

Original Paper URL
http://heart.bmj.com/content/95/16/1309.abstract

Indexing Status
Subject indexing assigned by NLM

MeSH
Anemia /complications /drug therapy; Chronic Disease; Erythropoietin /adverse effects; Heart Failure /complications;
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.