Correcting anemia in heart failure: the efficacy and safety of erythropoiesis-stimulating agents

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CRD summary
The authors concluded that in patients with chronic heart failure and anaemia, erythropoiesis-stimulating agents were associated with decreased chronic heart failure-related hospitalisations and improved quality of life and exercise tolerance. Mortality data were inconclusive. The conclusions reflected the limited evidence, but should be interpreted with caution due to potential biases in the review process and unclear quality of included studies.

Authors' objectives
To evaluate the efficacy and safety of erythropoiesis-stimulating agents (ESAs) for correcting anaemia in patients with chronic heart failure.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to June 2009 for published articles in English. Search terms were reported. Additional studies were sought from ClinicalTrials.gov and by scanning bibliographies of retrieved articles.

Study selection
Randomised controlled trials (RCTs) that compared ESAs with control in patients with chronic heart failure (left ventricular ejection fraction <40%, or symptomatic heart failure) and comorbid non-critical anaemia (haemoglobin between 9.0 and 12.5g/dL) were eligible for inclusion. Follow-up had to be at least 12 weeks. Patients had to be receiving stable optimal medical chronic heart failure management at the time of randomisation.

Trials were conducted in USA, Israel and Europe; there were no UK studies. Most patients were reported to be men with a mean age range between 60 and 75 years. All trials used either recombinant erythropoietin or analogue darbepoetin with various dosing regimens. All trials administered iron supplements to the ESA group; most also administered iron supplements to the control group. Control group regimens were not specified in most cases.

Outcomes were all-cause mortality, hospitalisation as a result of chronic heart failure, chronic heart failure exacerbations, change in New York Heart Association symptom severity, exercise tolerance, haemoglobin, left ventricular ejection fraction, brain-natriuretic peptide, quality of life (Minnesota Living with Heart Failure Questionnaire) and adverse events. Extended mortality and morbidity periods were included in some studies.

The authors did not state how many reviewers were involved in study selection.

Assessment of study quality
Trial quality was assessed using the Jadad scale of randomisation, blinding and withdrawals/drop-outs. The maximum possible score was 5. Scores between zero and 2 were classed as low quality and scores between 3 and 5 were high quality.

The authors did not state how many reviewers carried out the quality assessment.

Data extraction
Data were extracted to enable calculation of odds ratios (OR) or mean differences and 95% confidence intervals. Missing data were sought from authors or published data sources.

Two reviewers extracted data. Disagreements were resolved by consensus or with the involvement of a third reviewer.
**Methods of synthesis**
Summary odds ratios, weighted mean differences (WMD) and 95% CIs were estimated using a random-effects meta-analysis. A narrative synthesis was presented for other selected outcomes. Statistical heterogeneity was quantified using the $I^2$ statistic. Sensitivity analyses were conducted to explore the impact of correcting for zero events trials, inclusion of only high-quality trials, inclusion of trials where iron supplementation was given to both study groups and where patients had both chronic heart failure and low left ventricular ejection fraction. Publication bias was assessed using funnel plots.

**Results of the review**
Nine RCTs (n=747 participants) were included in the meta-analysis. Six trials were considered to be high quality. Six trials were double-blind, two were single-blind and one was open-label. Follow-up ranged from three to 13 months.

ESAs were associated with a statistically significant reduction in hospitalisation due to chronic heart failure (OR 0.41, 95% CI 0.24 to 0.69, $I^2=19%$; seven trials) and improved quality of life (WMD -2.29, 95% CI -2.64 to -1.94, $I^2=0%$; three trials).

In terms of chronic heart failure hospitalisation, sensitivity analyses revealed significant influences of trials that included iron supplementation to both study groups and where only patients with chronic heart failure (OR 0.54, 95% CI 0.35 to 0.84; $I^2=0%$) and low left ventricular ejection fraction (OR 0.50, 95% CI 0.32 to 0.77, $I^2=2%$) were included. ESAs were associated with decreased mortality, but this was not statistically significant. There was no evidence of increase in the overall adverse event rate.

Other results showed that ESAs were beneficial in terms of exercise tolerance, left ventricular ejection fraction, symptom severity and levels of brain-natriuretic peptide.

There was no evidence of publication bias.

**Authors’ conclusions**
In patients with chronic heart failure and anaemia, ESAs were associated with a decrease in chronic heart failure-related hospitalisations and improved quality of life and exercise tolerance. Mortality data were inconclusive.

**CRD commentary**
The review question was clear and supported by sufficiently detailed inclusion criteria to allow replication for all aspects apart from outcomes. The search strategy included relevant sources, but there was a risk of language bias and potential for missed studies. There was no evidence of publication bias. The review process was poorly reported in terms of procedures for study selection and quality assessment. Data extraction was conducted with efforts to minimise error and bias. Quality assessment was carried out, but only the results for blinding were reported. Study characteristics were presented.

Statistical heterogeneity was assessed and taken into account in the chosen method of synthesis. Although trials were deemed largely higher quality, the absence of full details on quality made this difficult to verify. The authors advised appropriate caution to the review findings based on a small number of trials and limited sample sizes.

The authors’ conclusions reflected the limited evidence presented, but should be interpreted with some caution due to potential biases in the review process and the unclear quality of the included studies.

**Implications of the review for practice and research**
**Practice:** The authors stated that there was insufficient evidence to recommend routine use of ESAs to chronic heart failure patients with anaemia.

**Research:** The authors stated that further large randomised controlled trials were needed to assess the effect of ESAs on mortality and drew attention to on-going research.