Erythropoiesis stimulating agents in heart failure patients with anemia: a meta-analysis
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CRD summary
In patients with heart failure and anaemia, erythropoietin stimulating agent therapy appeared to have a positive effect on several important cardiovascular outcomes, particularly related to quality of life. Given limitations in the review (limited search, lack of consideration of trial quality and high levels of variation between trials), the authors’ conclusions should be treated cautiously.

Authors' objectives
To evaluate the clinical effects of treatment with erythropoietin stimulating agents in heart failure patients with anaemia.

Searching
PubMed was searched from 1966 to 2008 for English language studies; search and MeSH terms were reported. Reference lists of retrieved papers were searched manually. Studies published only as abstracts were excluded.

Study selection
Prospective clinical trials that investigated erythropoietin stimulating agents therapy in heart failure patients (aged 18 years or over) with anaemia were eligible for inclusion in the review. Trials of patients without heart failure, trials with patients who did not receive erythropoietin or darbopoetin, or trials with a follow-up of less than three months were excluded.

The included studies were all placebo randomised controlled trials (RCTs). The agents used were erythropoietin alfa, erythropoietin beta, darbopoietin alpha [darbepoietin alfa] and darbopoietin [darbepoietin]; in most trials both treatment groups were also given iron. Patient inclusion criteria varied and in most trials were based on the New York Heart Association (NYHA) classification of heart failure, or the left ventricular ejection fraction. Mean baseline haemoglobin ranged from 10.6 to 11.6. Trial duration ranged from 12 to 27 weeks. Outcomes assessed included days of hospitalisation, exercise performance or duration, NYHA functional class, renal function, oxygen use, increase in haemoglobin, echocardiographic evaluation, B-type natriuretic protein, six-minute walk test, hospitalisation due to heart failure, mortality and safety.

Studies were assessed for eligibility by two reviewers.

Assessment of study quality
Trial validity was assessed using the following criteria: reporting of loss to follow-up; multivariable analyses used to adjust for confounders; definition of treatment; definition of outcomes; representative sample of the population; complete description of clinical and patient characteristics; sample size calculation; temporality; and statement of inclusion and exclusion criteria. Poor quality trials were those meeting less than five criteria, fair quality five to seven criteria and good quality studies met eight or more criteria.

The authors did not report how many reviewers performed the validity assessment.

Data extraction
Standardised mean differences (SMD) with 95% confidence intervals (CI) were calculated for continuous outcomes based on results from post-intervention alone, post-intervention adjusted for baseline values, or change from baseline (depending on what was reported by the papers). Only outcomes reported by at least three trials were included in the analysis.

The authors did not report how many reviewers performed the data extraction.
Methods of synthesis
Standardised mean differences were pooled using random-effects meta-analysis. Heterogeneity was measured using the $I^2$ statistic; values greater than 50% were considered to indicate a large amount of inconsistency.

Results of the review
Seven RCTs were included in the review (n=663 patients). Four were single-centre and three were multi-centre RCTs.

Erythropoietin stimulating agent treatment led to a statistically significant increase in haemoglobin levels (MD 2.35g/dL, 95% CI 1.76 to 2.93), based on seven RCTs with a high level of heterogeneity ($I^2=83\%$).

Erythropoietin stimulating agent treatment increased exercise duration (SMD 0.91, 95% CI 0.08 to 1.73; four RCTs; $I^2=88\%$), improved NYHA functional class (SMD -1.46, 95% CI -2.32 to -0.60; five RCTs; $I^2=94\%$) and increased scores on the six-minute walk test (SMD 1.42, 95% CI 0.31 to 2.54; four RCTs; $I^2=91\%$).

Erythropoietin stimulating agent treatment reduced B-type natriuretic protein levels (SMD -0.54, 95% CI -1.03 to -0.05; three RCTs; $I^2=36\%$) and increased peak oxygen consumption (SMD 0.93, 95% CI 0.52 to 1.34; three RCTs; $I^2=0\%$).

The most significant side effect reported was death, but the deaths were not directly related to the effects of the particular treatment and were mostly due to complications of surgery, pneumonia or sepsis.

Authors’ conclusions
In patients with heart failure and anaemia, erythropoietin stimulating agent therapy appeared to have a positive effect on several important cardiovascular outcomes, particularly related to quality of life such as exercise tolerance, NYHA functional class and six-minute walk test.

CRD commentary
This review had a clearly specified research question and specified some inclusion and exclusion criteria, although not for outcomes. The search included only one database and was limited to English language publications, so language and publication bias were a risk of this review. Studies were assessed for eligibility by two reviewers, but it was not clear if this was done independently. It was unclear whether the processes of validity assessment and data extraction were performed in duplicate to reduce possible error or bias.

The authors assessed trial quality, but did not appear to use the most appropriate tool; they used a tool relevant for observational studies when all the studies included in the review were randomised controlled trials. The results of the quality assessment were not reported or discussed. Random-effects meta-analysis was used to combine results, but in many cases there was extremely high heterogeneity which was not fully explored by the authors.

Due to the limitations in the searching, lack of consideration of trial quality and high heterogeneity, the authors’ conclusions should be treated cautiously.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further adequately powered clinical trials are needed to comprehensively evaluate the effects of erythropoietin stimulating agent therapy on clinical outcomes in heart failure patients with anaemia.

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