Anemia and erythropoietin in cardiovascular disease
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Erythropoietin and heart failure: the end of a promise?

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For over a decade, anemia has been explored in heart failure (HF) patients. Anemia is observed in 25-40% of HF patients depending on severity of disease and definition of anemia. Furthermore, its presence is associated with increased mortality and HF hospitalizations.\(^1\) In patients with anemia, mortality risk is approximately doubled.\(^2\) The etiology of anemia in heart failure is multifactorial, including inflammation, medication, malnutrition, iron deficiency, renal insufficiency, hemodilution, and erythropoietin (EPO) resistance.\(^3\) Anemia is one of the reversible comorbidities associated with HF and correction is possible with erythropoiesis stimulating agents (ESA). Small studies indicated that treatment with ESA might reduce heart failure hospitalizations and improve exercise capacity and quality of life through correction of anemia.\(^8\)\(^-\)\(^10\) In a meta-analysis, patients treated with ESA showed a decreased risk of hospitalization for HF.\(^11\) To provide a final answer to the question whether ESA therapy in patients with anemia and heart failure is appropriate, the Reduction of Events With Darbepoetin Alfa in Heart Failure Trial (RED-HF) was designed.\(^12\)

Inclusion criteria of the RED-HF were HF of at least 3 months duration and of NYHA class II or more, hemoglobin levels between 9.0 g/dL and 12.0 g/dL and a left ventricular ejection fraction equal to or less than 40%. Patients with iron deficiency, defined as a transferrin saturation less than 15% were excluded. Furthermore, hypertension (blood pressure over 160/100 mm Hg) and renal dysfunction (serum creatinine > 265 µmol/L) or dialysis were major exclusion criteria.

The RED HF trial started including in 2006 and its primary endpoint was to determine the efficacy of darbepoetin alfa compared to placebo on the composite endpoint of time to death from any cause or first hospital admission for worsening HF in subjects with symptomatic left ventricular systolic dysfunction and anemia. Secondary endpoints included the effect of darbepoetin treatment on time to death from any cause, time to cardiovascular death or first admission for worsening HF and change in quality of life from baseline to 6 months measured by Kansas City Cardiomyopathy Questionnaire (KCCQ).

After 6 years of inclusion, 2278 patients were enrolled in 453 sites. Baseline characteristics did not differ between treatment and placebo groups.\(^13\) Patients had severe HF; about two thirds were in NYHA class III or IV. In the treatment group, median hemoglobin levels increased from 11.2 g/dL to 13 g/dL. Nevertheless, no difference in the primary composite endpoint of death or heart failure hospitalizations between treatment and placebo arms could be demonstrated.(HR 1.01, 95% confidence interval, 0.90 to 1.13; P=0.87).\(^14\) Fatal or nonfatal stroke occurred in 42 patients (3.7%) in the darbepoetin
alfa group and 31 patients (2.7%) in the placebo group (P=0.23). Furthermore, all cause thromboembolic events were reported in 153 patients (13.5%) in the darbepoetin alfa group and 114 patients (10.0%) in the placebo group (P=0.01). Darbepoetin alfa treatment was associated with a significant improvement in quality of life, as evidenced by a 2.2 point higher KCCQ score compared to the placebo group (P=0.005). However, the clinical significance of such a moderate improvement remains unclear.

The Trial to Reduce Cardiovascular Events With Aranesp® Therapy (TREAT) was the first study to evaluate the effect of chronic ESA treatment on cardiovascular events, although in patients with chronic kidney disease. The results showed that especially when patients had a poor initial hemoglobin response, ESA was associated with an increased incidence of the composite cardiovascular endpoint of death, myocardial infarction, stroke, heart failure or hospitalization for myocardial ischemia (HR 1.31; 95% CI 1.09-1.59). ESA treatment was also associated with an increased risk of stroke (HR 1.26; 95% CI 0.78–2.02). This finding is of relevance since in a previous study in which ESA was given to patients after a stroke, active treatment was associated with an increased incidence of stroke recurrence. The RED-HF trial corroborates with these results as thromboembolic adverse events occurred significantly more in the active treatment group than in the placebo group. Although not reaching statistical significance, more fatal and non fatal strokes were also observed in the treatment group.

The mechanism through which ESA is associated with adverse events is poorly understood. Several mechanisms can be hypothesized. First, ESA increases hematocrit levels by stimulating erythroid precursor production in the bone marrow and could therefore influence the rheology of the blood. Second, ESA are known for its pleiotropic effects including neovascularisation but these pleiotropic effects could also promote untoward effects including endothelial dysfunction, or hypercoagulability as well.

Despite the equivocal effects on the primary endpoint of death or HF hospitalizations and despite the slight increase in thromboembolic events, it remains unknown whether there are subgroups of HF patients that may benefit from ESA treatment. Earlier studies showed that patients with inappropriate high endogenous EPO levels and anemia are at the highest risk, probably reflecting bone marrow depression as a result of end stage disease or chronic inflammation. Further subgroup analysis may reveal that patients requiring only a low dose EPO to restore their hemoglobin values may have benefitted from ESA treatment, as their bone marrow is more responsive. More support for low dose EPO comes from research exploring extrahematopoietic effects; regardless of hematopoietic respons, ESA are able to induce neovascularization. As capillary density in HF patients is decreased, these patients may still benefit from low dose ESA. The first
clinical trials in patients with myocardial infarction remain however neutral. Another important anemia associated target is iron deficiency. The earlier published FAIR-HF trial showed that correction with ferric carboxymaltose in patients with HF, even in the absence of anemia, improves functional capacity and quality of life. As ESA treatment in HF does not improve outcome, one might therefore speculate that anemia in heart failure is a marker of severity of disease, rather than a mediator. On the other hand, ESA could elicit negative effects on its own, thereby offsetting possible beneficial effects of increasing hemoglobin levels.

In conclusion, RED-HF shows that increasing hemoglobin concentrations with ESA does not reduce morbidity and mortality in anemic HF patients. Anemia may therefore be a marker of disease severity rather than a therapeutic target in patients with HF and ESA treatment is therefore not recommended.

Fig 1. Percentage of primary composite endpoint and fatal and non fatal stroke in RED-HF and TREAT.
References


