Treatment of anaemia in chronic heart failure—optimal approach still unclear

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This editorial refers to ‘Randomized, double-blind, placebo-controlled study to evaluate the effect of two dosing regimens of darbepoetin alfa in patients with heart failure and anaemia’ by D.J. van Veldhuisen et al., on page 2208

Anaemia, most commonly defined using the WHO definition as a haemoglobin <13 g/dL in men and <12.0 g/dL in women, has variable prevalence in heart failure. Rates vary between 4 and 55% dependent on the population studied and the definition of anaemia used.1,2 Anaemia is more common in patients with NYHA functional class III or IV symptoms and in those with renal dysfunction.1 The increasing interest in this subject reflects the observations that anaemia is associated with worse symptoms, reduced exercise capacity, and an increased risk of hospital admission. In addition, anaemia also portends a worse prognosis, with a 2–3% increased risk of death per 1% reduction in haematocrit.3

A number of factors contribute to the pathogenesis of anaemia in heart failure. Expansion of blood volume can result in haemodilution, producing ‘anaemia’ without a reduction in actual red cell volume. Other causes include renal dysfunction, and iron and other haematinics deficiencies. Angiotensin-converting enzyme inhibitors, commonly prescribed in heart failure patients, are also associated with a low haemoglobin possibly by suppressing erythropoietin production. In addition, proinflammatory cytokines such as interleukin-1 and -6 and tumour necrosis factor-α, significantly elevated in more severe forms of heart failure, can result in decreased erythropoietin production or, alternatively, resistance to the actions of erythropoietin. Finally, chronic gastrointestinal blood loss, made more likely as a result of antiplatelet and antithrombotic agents, can also contribute to anaemia in these patients.

The association between anaemia and poorer outcome has led to the hypothesis that treating anaemia of no definable cause in heart failure may improve outlook. Two specific therapies have been considered, supplementing haematinics such as iron, and using subcutaneous erythropoiesis-stimulating agents (ESAs). The latter have received most attention recently. Erythropoietin is produced by the kidney in response to hypoxia and acts on the bone marrow to promote the survival and proliferation of erythroid precursor cells therefore increasing red blood cell production.4 Several studies have investigated the treatment of anaemia in heart failure patients with ESAs, using either recombinant human erythropoietin (rh-EPO) or a newer analogue of erythropoietin, darbepoetin alfa, which has the advantage of a longer half-life, therefore requiring less frequent administration. Silverberg et al.5 were the first investigators to assess the role of ESAs in treating anaemia in heart failure patients. In a randomized open-label study of 32 patients with moderate to severe heart failure and haemoglobin 10–11.5 g/dL, treatment with rh-EPO and intravenous iron improved NYHA class, increased left ventricular ejection fraction, and reduced hospitalizations and diuretic dose requirement. Mancini et al.6 again in a single-centre study, randomized 26 patients with advanced heart failure and a haematocrit <35%, and observed an improved peak VO2 and exercise duration with rh-EPO. Palazzuoli et al.7 randomized 40 patients with moderate to severe heart failure and haemoglobin <11 g/dL to receive rh-EPO or placebo for 3 months. All patients received daily oral iron. Erythropoietin treatment improved NYHA functional class, increased exercise tolerance and VO2 max, improved renal function, and reduced B-type natriuretic peptide levels. In the first multicentre trial. Ponikowski et al.8 randomized 41 patients with symptomatic heart failure (VO2 max <16 mL/kg/min) and a haemoglobin between 9 and 12 g/dL to receive darbepoetin alfa or placebo, in addition to iron, every 2 weeks for 26 weeks. While ESA therapy improved health-related quality of life, as measured using Patient’s Global Assessment of Change, there was no significant impact on the primary end-point of VO2 max.

Van Veldhuisen et al.9 have reported on the effect of two different dosing regimens of darbepoetin alfa on the rise of haemoglobin in heart failure patients with anaemia. One
hundred and sixty-five patients with a haemoglobin between 9.0 and 12.5 g/dL were randomized to receive either a weight-adjusted dose or a fixed dose of darbepoetin alfa or placebo every 2 weeks for 26 weeks to achieve and maintain target haemoglobin of 14 g/dL. As anticipated, they showed that treatment with darbepoetin alfa raised haemoglobin, with similar effects from both the fixed dose and weight-adjusted dose regimens. Whilst darbepoetin alfa improved some quality of life indices (Kansas City Cardiomyopathy Questionnaire total symptom score), there was no significant improvement in the 6 min walk test, NYHA classification, Minnesota Living with Heart Failure Questionnaire, Patient’s Global Assessment score, or Kansas City Cardiomyopathy Questionnaire overall summary score.

In summary, the results of multicentre trials have not convincingly supported the findings of the single-centre studies. The explanation for this is unclear, but the powering of the multicentre studies may have played a role. Van Veldhuisen’s study was not powered for clinical end-points. Furthermore, Ponikowski et al. also addressed this issue as a potential explanation for the failure to achieve the primary end-point, with greater variability of peak VO2 in the placebo group compromising the power of the study.8

A further issue from the van Veldhuisen study that requires comment was the occurrence of six deaths (5.5%) in the darbepoetin group during the study period. Five of these deaths were in the weight-based dosing group, where the median dose of the ESA was higher. However, the absolute amount of erythropoietin received by these patients is not provided. The increased case-fatality could be a matter of chance or related to either increasing red blood cell volume or to the ESA itself. Erythropoietin therapy increases blood pressure and is associated with an increased risk of thrombosis which could increase cardiovascular risk. It is of interest that there have also been recent concerns about the safety of ESAs for the correction of anaemia in chronic kidney disease. In the CHOIR study10 of 1432 patients treated with rh-EPO, compared with partial correction of anaemia, a higher target haemoglobin level of 13.5 g/dL was associated with an increased risk of death, myocardial infarction, chronic heart failure (CHF) hospitalization and stroke. In a subsequent meta-analysis of nine randomized controlled trials (n = 5143) of patients with anaemia and chronic kidney disease treated with ESAs, a higher target haemoglobin resulted in an increased risk of death, uncontrolled blood pressure, and arteriovenous access thrombosis (compared with a lower target haemoglobin).11 There is also recent evidence in oncology patients that ESAs used to treat anaemia were associated with a reduction in survival, increased rate of tumour growth, and increased risk of thromboembolic events.12 In the context of all the above, it should be noted that the adverse event profile of darbepoetin alfa was similar to that of placebo in the other heart failure studies, with no evidence of an excess risk of mortality.

Several questions remain unanswered; while there is no doubt that low haemoglobin is associated with an adverse outcome in heart failure, it remains unclear whether increasing the haemoglobin improves prognosis. Furthermore, the optimal strategy of raising haemoglobin in this population remains unclear. Are ESAs the correct treatment for anaemia in patients with heart failure and, if so, what are the treatment threshold and target haemoglobin values and which is the correct ESA agent? In contrast to chronic kidney disease, erythropoietin levels are modestly elevated in patients with CHF.13 It is interesting to hypothesize that the response of patients with heart failure to ESAs could depend on baseline erythropoietin levels, and this requires further analysis. The long-term safety issues with ESAs in heart failure also need to be clarified. Many of the above issues will be addressed by the Reduction of Events with Darbepoetin Alfa in Heart Failure Trial (RED-HF) presently enrolling, which plans to recruit 3400 patients to determine the efficacy of treatment of anaemia with darbepoetin alfa compared with placebo in subjects with symptomatic left ventricular systolic dysfunction. An alternative therapy to improve anaemia in heart failure may be administration of iron alone. In patients with heart failure, there is dysregulation of iron homeostasis. Proinflammatory cytokines divert iron to the reticuloendothelial system from the blood and the bone marrow, where the iron is unavailable for erythropoiesis—termed reticuloendothelial iron block. In a small study of 16 patients with anaemia and heart failure, intravenous iron sucrose increased haemoglobin, reduced symptoms, and improved exercise capacity.14 The Iron-HF study is an ongoing multicentre randomized placebo-controlled trial investigating the potential of correcting anaemia in heart failure patients with iron therapy.15

Therefore, the approach to the management of anaemia in heart failure remains unclear. At this stage, we should focus on excluding modifiable causes of low haemoglobin and optimizing management of the heart failure syndrome. Until the results of ongoing trials are available we must remain circumspect about the role of ESAs in the management of anaemia in this syndrome.

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References


Clinical vignette

An unusual case of punctiform chest pain

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Case presentation

Punctiform thoracic pain modified by respiration and digital compression is normally atypical pain due to angina and generally requires no further diagnostic investigation. In this article, we present the case of a young patient of 44, a non-EU citizen, with no available cardiological history and who came to the emergency department complaining of pain in the thorax, with atypical characteristics. No other medical details were available on account of the difficulty the patient had in communicating with medical staff for linguistic reasons. The electrocardiogram showed regular sinus rhythm at a normal rate, a right branch block, and repolarization within normal limits. Cardiac enzyme assay indicated a slight increase in troponin (0.07 ng/mL), whereas chest X-ray revealed the presence of a foreign body in the form of a needle at the level of the cardiac shadow (Panel A). The patient then underwent cardiac CT-scan (GE 64 × 0.625) which indicated the presence of a ‘needle’ running through the whole thickness of the anterior wall of the left ventricle to the anterior leaflet of the mitral valve (Panels B and C). Furthermore, there was fibrous thickening of the anterior leaflet of the mitral valve due to the presence of the foreign body (Panel D).

The patient later on declared that he was wounded by an industrial mattress needle during a fight. The foreign body was removed by surgery, and after 30 days, the patient’s general condition was satisfactory.

Panel A. Chest X-ray: lateral incidence, showing the presence of a foreign body in the form of a needle at the level of the cardiac shadow (red circle).

Panel B. CT-volume rendering reconstruction of the heart: the entry site of the foreign body was very close to the proximal left anterior descending artery (arrow).

Panel C. Oblique cut-plane of CT-volume rendering reconstruction: this view allows the precise identification of the foreign body trajectory passing through the left ventricular anterior wall into the left ventricular cavity very close to the anterior mitral leaflet.

Panel D. Echocardiographic three-chamber apical view. The anterior mitral leaflet appears thickened and fibrous in its distal segment as a traumatic reaction to the tip of the needle.