# Management of anemia in heart failure

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**Current Opinion in Cardiology** 2010, 25:148–154

**Purpose of review**

Anemia is a relatively common finding in heart failure. Anemia in heart failure patients has been independently associated with reduced exercise tolerance, increased heart failure hospitalizations and increased all-cause mortality. Anemia would appear to be a reasonable treatment target for patients with heart failure. The review will discuss the potential causes of anemia in heart failure patients and give an up-to-date overview of treatment trials.

**Recent findings**

Studies assessing the pathophysiology of anemia in heart failure patients have recently demonstrated the potential importance of iron deficiency, abnormal iron metabolism and hemodilution. Treatment studies have focused on the use of erythropoiesis-stimulating agents, with recent trials showing mixed results.

**Summary**

Despite initial studies indicating a possible beneficial effect of erythropoiesis-stimulating agents in the treatment of anemic heart failure patients, clinical trial data, to date, have failed to show convincing evidence for morbidity or mortality benefit, and information on the long-term safety is lacking. Ongoing large-scale trials will have the potential to provide such information in the future.

**Keywords**

anemia, erythropoiesis-stimulating agents, heart failure

Curr Opin Cardiol 25:148–154

0268-4705

## Introduction

Heart failure is a very common illness, with a one in five lifetime risk of developing heart failure for those over the age of 40 years [1]. Heart failure is also a very costly illness, accounting for 25 billion dollars of healthcare expenditures annually.

Significant strides have been made in the treatment of heart failure, with the use of pharmacologic agents targeting the neurohormonal systems and application of device therapy. Clinical trial data in patients receiving optimal therapy demonstrate annual mortality rates that are only slightly greater than would be expected in an aged matched population without heart failure [2]. These trials, however, routinely exclude patients with significant comorbidities including anemia. Anemia is a relatively common finding in heart failure, and its treatment might provide additional improvements in outcomes.

## Prevalence

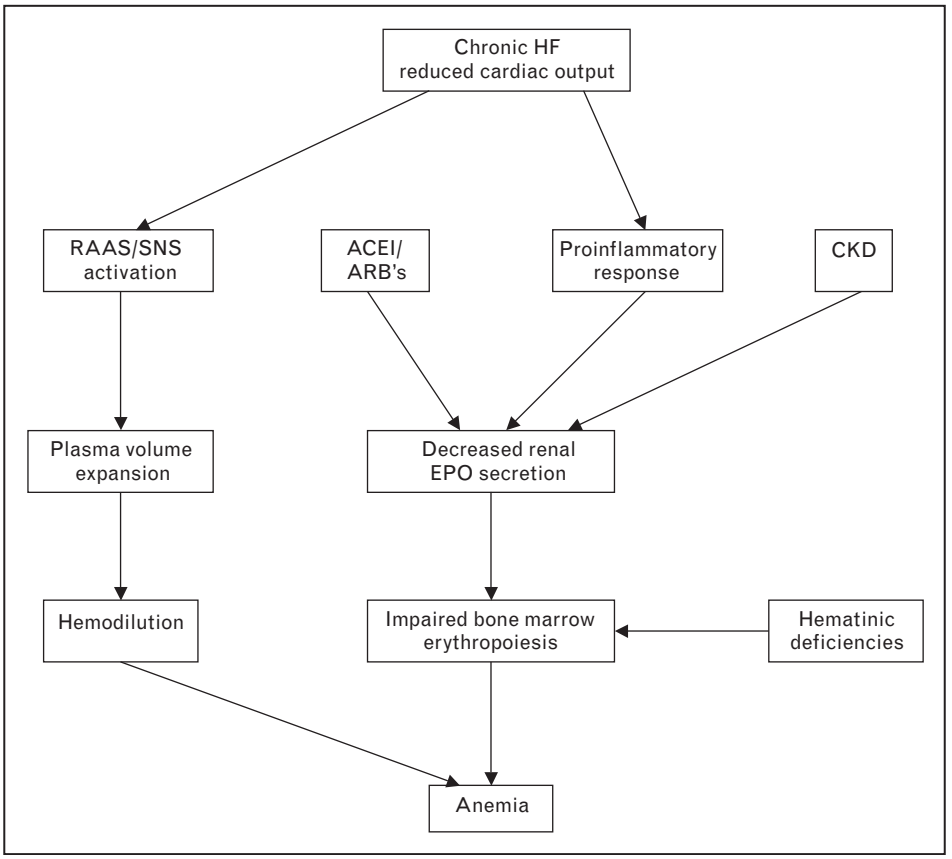
The prevalence of anemia in heart failure patients reported in the literature varies widely from 7 to over 50% [3••]. One of the reasons for this wide variation likely is related to the difference in criteria used to define anemia. The WHO defines anemia as a hemoglobin (Hb) concentration of less than 13 g/dl in men and less than 12 g/dl in postmenopausal women, whereas the National Kidney Foundation defines anemia as a Hb concentration of less than 12 g/dl in both men and postmenopausal women. Analysis of data from the Studies of Left Ventricular Dysfunction trial showed that when defining anemia as a hematocrit of less than 39% (approximately equivalent to a Hb of 13 g/dl), the prevalence of anemia was 22%, whereas when defining anemia as a hematocrit of less than 35% (approximately equivalent to a Hb of 12 g/dl), the prevalence of anemia was only 4% [4].

The characteristics of the patient population studied will also influence the observed prevalence. Anemia has been found to be more prevalent in heart failure patients with a higher New York Heart Association (NYHA) functional classification, greater degree of renal dysfunction, advanced age, female sex and African–American race [5]. The prevalence of anemia in patients with systolic and diastolic heart failure has been reported to be similar [6].

## Potential causes

There are a number of potential causes for the anemia seen in heart failure patients (Fig. 1). It is likely to be a

**Figure 1 Proposed causes for the anemia seen in heart failure patients**




ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; EPO, erythropoietin; RAAS, rennin–angiotensin–aldosterone system; SNS, sympathetic nervous system.

multifactorial problem in most patients. Identified causes of anemia in heart failure include proinflammatory state, chronic kidney disease (CKD), hemodilutional, the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) and gastrointestinal problems.

### Proinflammatory state

The heart failure syndrome is known to be associated with an increase in a number of proinflammatory cytokines, including tumor necrosis factor, interleukin (IL)-1 and IL-6 [7,8••]. This proinflammatory state can contribute to anemia through a number of mechanisms, including suppression of erythropoietin (EPO) secretion by the kidney, decrease bone marrow responsiveness to EPO and a decrease in iron bioavailability for Hb production [9–11]. IL-6 is also known to increase the production of hepcidin by the liver, which will lead to a decrease in gastrointestinal iron absorption, further decreasing iron bioavailability [12,13]. Evidence of the role of proinflammation as a contributing factor to anemia in heart failure patients includes the inverse relation seen between inflammatory cytokines and Hb levels in heart failure patients [14].

### Impaired renal function

Anemia is known to occur in patients with impaired renal function, largely related to decreased EPO production. Anemia occurs in patients who have moderate-to-severe renal dysfunction (defined as a glomerular filtration rate of $<60$ ml/min) [15]. Twenty to 40% of heart failure patient have this level of renal dysfunction [16,17••]. EPO levels in anemic heart failure patients are elevated as compared with nonanemic heart failure patients; however, when corrected for the level of anemia by calculating the observed/predicted EPO ratio, heart failure patients show an inappropriately low level of EPO, suggesting impaired renal production of EPO in anemic heart failure patients.

### Hematinic deficiencies

Vitamin $B_{12}$ and thiamine deficiency can lead to anemia; however, this appears to be the cause of anemia in only a small percentage of heart failure patients. [18]. The role of iron deficiency in heart failure patients has been debated. Heart failure patients are susceptible to iron deficiency due to poor nutrition and gastrointestinal loss, particularly those with an ischemic cause who are on

chronic aspirin therapy [19•]. The prevalence of low serum iron levels in heart failure has been reported to be between 4 and 21% [16,20]; however, detailed studies evaluating iron homeostasis are lacking. A recent study [21], which examined bone marrow biopsies in patients with advanced heart failure, found low iron stores in 27 of 37 patients (73%), despite normal ferritin levels. The normal ferritin levels suggest normal total body iron, despite low iron stores in the bone marrow. This is similar to the profile seen in patients with anemia of chronic disease, and results from the diversion and sequestration of iron from the bone marrow to other reticular–endothelial tissues. This is believed to be the result of the influences of various proinflammatory cytokines causing increased production of ferritin, increased uptake of iron, increased erythrophagocytosis and decreased release of iron from macrophage [22]. The extent to which nutritional iron deficiency or gastrointestinal iron loss plays in the anemia of heart failure patients will require further studies.

#### Medications

Angiotensin II decreases blood flow to the kidneys leading to increased EPO levels. Inhibition of angiotensin II using ACE inhibitors and ARBs will, therefore, lead to reduced EPO levels, resulting in a modest reductions of Hb levels [23]. In addition, ACE inhibitors can contribute to anemia by preventing the breakdown of N-acetyl-seryl-aspartyl-lysyl-proline, which is a suppressor of hemopoietic stem cell proliferation [24].

#### Hemodilution

Hemodilution likely plays a role in the development of anemia in heart failure patients. A number of recent studies [25,26,27•] have shown hemodilution as a causal factor in nearly half of all heart failure patients.

## Prognosis and pathophysiologic consequences

Anemia in heart failure patients has been independently associated with reduced exercise tolerance, increase heart failure hospitalizations and increase all-cause mortality [16,28,29•,30]. Many, but not all, studies have shown an inverse linear relationship between Hb levels and mortality. One study [29•] found that in patients with a hematocrit of less than 37.5%, a 1% decrease in hematocrit was associated with an 11% increase in mortality.

The reason for worsening outcomes in anemic heart failure patients is likely to be multifactorial. Anemia results in peripheral vasodilatation and decreased blood pressure, which will cause neurohormonal activation. This leads to salt and water retention, as well as adverse cardiac remodeling, thereby worsening the heart failure syndrome [7,31,32]. Anemia might also be a marker of more advanced disease, including poor nutritional status and cardiac cachexia, which can also worsen outcomes [33–35].

## Treatment using iron

A few small studies have evaluated the use of iron therapy in the treatment of anemia in heart failure patients. Bolger *et al.* [36] treated 16 anemic heart failure patients with intravenous (i.v.) iron in an uncontrolled, open-label study. Patients were treated for 12–17 days and followed for $92 \pm 6$ days. Treatment was associated with an increase in Hb level ($11.2 \pm 0.7$–$12.6 \pm 1.2$ g/dl) and improvement in NYHA class, Minnesota Living with Heart Failure Questionnaire (MLHFQ) score and 6-min walk distance (6MWD).

Toblli *et al.* [37] performed a randomized, double-blind, placebo-controlled trial in 40 anemic heart failure patients. Patients were treated with either i.v. iron ($n = 20$) or physiologic saline ($n = 20$) for 5 weeks. After 6 months, treatment with iron resulted in a significant increase in Hb levels ($10.3 \pm 0.6$–$11.8 \pm 0.7$ g/dl), improvement in creatinine clearance and MLHFQ score, decrease in C-reactive protein and N-terminal-pro-B-type natriuretic peptide (BNP) and increase in left ventricular ejection fraction (LVEF) and 6MWD.

The ferric iron sucrose in heart failure study [38•] was a randomized, open-label, observer-blinded study in 35 patients with heart failure, anemic and nonanemic, all of whom were iron deficient. Patients were randomly assigned in a 2:1 ratio to receive 16 weeks of i.v. iron sucrose or to the control group. Unlike the previous two trials, treatment did not result in an increase in Hb levels, and there was a trend towards improvement in $VO_{2_{max}}$ ($P = 0.08$) and treadmill exercise duration ($P = 0.08$), with significant improvements seen in NYHA class ($P = 0.007$) and Patient Global Assessment ($P = 0.002$).

This series of small studies, although not definitive, are intriguing. Larger studies are clearly needed before definitive recommendations regarding this treatment approach can be made. The yet to be completed Iron Supplementation in Heart Failure Patients With Anemia (Iron-HF) trial [39] might provide additional information in this area. This is a multicenter study in patients with heart failure and anemia-randomizing patients to receive either iron therapy or placebo.

## Treatment using erythropoietic-stimulating agents

As stated early, EPO levels in anemic heart failure patients are inappropriately low, suggesting a possible benefit from the exogenous administration of EPO. A

series of small studies pointing to the benefits of EPO in heart failure patients raised initial enthusiasm for this treatment strategy (Table 1).

The first study was by Silverberg *et al.* [40] performed in 26 patients with severe resistant heart failure and anemia. This was an unblended, uncontrolled study in which patients were given subcutaneous EPO and iron for a mean duration of $7.2 \pm 5.5$ months. Treatment resulted in an increase in Hb from 10.2 to 12.1 g/dl. Compared with prior to treatment, patients had an improvement in NYHA functional class and LVEF, with a decrease in diuretic dose and hospitalizations. The same authors [41] performed a randomized, open-label study on 32 patients with anemia and NYHA functional class III–IV heart failure. Patients received either subcutaneous EPO and i.v. iron ($n = 16$) or usual care ($n = 16$). Treatment with EPO and iron resulted in an increase in Hb from 10.3 to 12.9 g/dl, with improvements in NYHA class and LVEF, with a decrease in diuretic requirements.

Mancini *et al.* [42] performed another small study included 26 heart failure patients with anemia and randomized patients in a single-blinded fashion (patients, but not investigators were blinded). Patients had NYHA class II–IV symptoms and received either EPO and oral iron and folate or placebo. Active treatment resulted in an increase in Hb from 11.0 to 14.3 g/dl, and increases in peak $VO_{2_{max}}$ and 6MWD, and improvement in MLHFQ.

Following the initial encouraging results of these small and mostly uncontrolled studies, a series of randomized, double-blinded, placebo-controlled trails have been completed. Palazzuoli *et al.* [43] performed a study including 51 patients with heart failure and anemia in a single center, double-blind study of EPO and iron ($n = 26$) or placebo and iron ($n = 25$). After 12 months, active treatment resulted in an increase in Hb level and LVEF, with a decrease in left ventricular (LV) dimensions, LV volume, LV mass, pulmonary artery pressure and BNP levels [43].

Ponikowski *et al.* [44] randomized patients to treatment with darbepoetin ($n = 19$) or placebo ($n = 22$) for 26 weeks. All patients had heart failure and anemia (Hb between 9.0 and 12.0 g/dl) and a peak $VO_{2_{max}}$ of less than 16 ml/kg/min [44]. Mean Hb levels increased significantly in the darbepoetin group (from 11.8 to 13.9 g/dl); however, there was no significant change in peak $VO_{2_{max}}$, exercise duration, Kansas City Cardiomyopathy Questionnaire (KCCQ) or MLHFQ scores.

van Veldhuisen *et al.* [45] randomized patients to darbepoetin given every 2 weeks for 26 weeks at a weight-adjusted dose ($n = 56$), a fixed dose ($n = 54$) or placebo ($n = 55$). The combined darbepoetin group showed an increase in Hb level (11.5–13.3 g/dl), with an associated

**Table 1 Summary of published trials assessing effects of erythropoiesis-stimulating agents in patients with heart failure and anemia**

| Ref. | Study design | Patients ($n$) | NYHA class | Follow-up (months) | Baseline Hb (g/dl) | Study drug | Outcome |
|---|---|---|---|---|---|---|---|
| Silverberg *et al.* [40] | Single-center, uncontrolled, open-label | 26 | III–IV | 8 | 10.2 | Epoetin + iron | Decreased serum creatinine; improved Hb, NYHA class, LVEF, $VO_{2_{max}}$ and exercise capacity |
| Silverberg *et al.* [41] | Single-center, randomized, open-label | 32 | III–IV | 8 | 10.3 | Epoetin | Decreased serum creatinine; improved Hb, LVEF and NYHA class |
| Mancini *et al.* [42] | Single-center, single-blind, randomized, placebo-controlled | 26 | NA | 3 | 11.0 | Epoetin alfa vs. placebo | Improved Hb, QoL, $VO_{2_{max}}$ and exercise capacity |
| Palazzuoli *et al.* [43] | Single-center, randomized, double-blind, placebo-controlled | 51 | III–IV | 12 | 10.4 | Epoetin beta + iron vs. placebo + iron | Decreased BNP, hospitalization rate; improved Hb, NYHA class and LVEF |
| Ponikowski *et al.* [44] | Multicenter, randomized, double-blind, placebo-controlled | 41 | I–III | 6 | 11.8 | Darbepoetin vs. placebo | No change in NYHA class, $VO_{2_{max}}$; improved Hb, QoL |
| van Veldhuisen *et al.* [45] | Multicenter, randomized, double-blind, placebo-controlled | 165 | II–III | 6 | 11.5 | Darbepoetin vs. placebo | No change in NYHA class, LVEF and exercise capacity; improved Hb, QoL |
| Ghali *et al.* [46•] | Multicenter, randomized, double-blind, placebo-controlled | 319 | I–IV | 6.5 | 11.4 | Darbepoetin vs. placebo | No change in NYHA class, exercise capacity and QoL; improved Hb |

BNP, B-type natriuretic peptide; Hb, hemoglobin; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; QoL, quality of life.

improvement in KCCQ total symptom score, but no improvement in LVEF, NYHA class, MLHFQ score, 6MWD or Patient's Global Assessment score. In addition, there were six deaths in the darbepoetin group and no deaths in the placebo group.

The largest study, to date, evaluating erythropoietic-stimulating agents (ESAs) in heart failure was the Study of Anemia in Heart Failure–Heart Failure Trial [46•]. In this multicenter trial, patients with NYHA class II–IV heart failure, LVEF less than 40%, serum creatinine more than 3 mg/dl and Hb between 9.0 and 12.5 g/dl were randomized to receive darbopoetin ($n = 162$) or placebo ($n = 157$). Treatment resulted in an increase in Hb, however, at 27 weeks, there was no improvement in treadmill exercise time, NYHA class or MLHFQ score.

Two recent studies in patients without heart failure have raised potential concerns regarding the risks of ESAs therapy in patients with chronic renal insufficiency (CRI). In the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin beta (CREATE) trial, 603 patients with CRI and anemia were randomized to either receive epoetin beta to normalize Hb (13.0–15.0 g/dl) or only if Hb decreased to less than 10.5 g/dl [47]. There was a trend toward increased mortality with a relative risk of 35% ($P = 0.14$) in the group attempting to normalize Hb levels. In the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial [48], 1432 patients with CRI and anemia were randomized to either receive a dose of epoetin alfa targeted to achieve a Hb level of 13.5 g/dl or a dose targeted to achieve a level of 11.3 g/dl. The higher Hb group had a 34% increase in the composite endpoint of death, myocardial infarction, hospitalization for heart failure and stroke ($P = 0.03$).

In November 2007, following a review of all safety information, the US Food and Drug Administration issued a 'black box warning' in the prescribing information for all ESAs in the management of anemia in patients with CKD. The warning recommended the lowest possible dose to slowly raise the Hb concentration to the lowest level that will avoid the need for a blood transfusion, in order to avoid serious cardiovascular and arterial and venous thromboembolic events.

Benefits seen in early small, nonrandomized studies using ESAs in anemic heart failure patients were not confirmed in larger randomized studies. Recent concerns have been raised regarding the risks of ESAs in patients with CKD. However, it should be noted that in CREATE and CHOIR, only a small percentage of patients had heart failure. Whether these results can be extrapolated to heart failure patients remains unclear. The Reduction of Events with Darbepoetin Alfa in Heart Failure trial [49•] is a randomized multicenter study enrolling 3400 patients with heart failure and anemia to receive either darbepoetin or placebo. This ongoing trial may help address some of the unanswered questions regarding the treatment of anemia in heart failure patients.

## Heart failure guidelines and recommendations for treatment

The most recent heart failure guidelines from both Europe and the United States make only passing mention of anemia. The 2008 European Society of Cardiology Heart Failure guidelines [50] indicate that anemia may aggravate the pathophysiology of heart failure by adversely affecting myocardial function, activating neurohormonal systems, compromising renal function and contributing to circulatory failure. However, they point out that correction of anemia has not been established as routine therapy in heart failure. Simple blood transfusion is not recommended to treat the anemia of chronic disease in heart failure. Among potential therapies, they indicate the use of ESAs, usually together with iron, to increase red blood cells production represents an unproven option.

The 2009 Focused Update to the American College of Cardiology/American Heart Association Heart Failure guidelines [51] indicates the severity of anemia may contribute to the increasing severity of heart failure. They point out several studies have demonstrated worse outcomes in patients with heart failure and anemia, but state that it is unclear whether anemia is the cause of decreased survival or a result of more severe disease. Finally, they state that several small studies have suggested benefit from the use of erythropoietin and iron for treatment of mild anemia in heart failure, but state that there is concern that thromboembolic events may be increased. They conclude by simply stating that this therapy is undergoing further investigation.

It is clear that on the basis of the currently available data, these organizations do not recommend routine treatment of anemia in heart failure patients. It is reasonable to monitor Hb levels in all heart failure patients on an annual basis, with an evaluation to assess for nutritional deficiencies and other correctable forms of anemia. In heart failure patients with CKD, treatment with ESAs can be considered. The current National Kidney Foundation guidelines [52] recommend considering ESAs and iron therapy in patients with moderate-to-severe CKD (estimated glomerular filtration rate $< 60$ ml/min) with a goal Hb level of 11.0 g/dl.

## Conclusion

Anemia is a relatively common finding in heart failure patients and is associated with poor outcome. The cause

of anemia in heart failure is likely multifactorial, with contributing factors including renal dysfunction, pro-inflammatory state, hematinic abnormalities, hemodilution and medications. Although treatment of anemia would appear to be a reasonable therapeutic target, clinical trial data, to date, have failed to show convincing evidence for morbidity or mortality benefit, and information on the long-term safety of ESAs is lacking. Hopefully, ongoing large-scale trials will provide such information, as well as guidance regarding at what Hb level treatment should be started, and what Hb level should be targeted after treatment.

## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 171–172).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