**STATE-OF-THE-ART PAPER**

# Anemia and Chronic Heart Failure

## Implications and Treatment Options

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Anemia is a common comorbidity in patients with heart failure and is associated with worse long-term outcomes. Although the cause of anemia in heart failure is unclear, the weight of evidence suggests that renal dysfunction, along with neurohormonal and proinflammatory cytokine activation in heart failure, favors the development of anemia of chronic disease, with defective iron utilization, inappropriate erythropoietin production, and depressed bone marrow function. Similarly, the mechanisms by which anemia worsens heart failure outcomes are unknown but may be related to increased myocardial workload. If anemia is a mediator and not just a marker of poor outcomes, correcting anemia could become an important and novel therapeutic target to improve long-term outcomes in such patients. Indeed, several small-sized studies have shown the beneficial effects of empirically treating anemia in heart failure patients with recombinant erythropoietin and intravenous iron. However, the ideal threshold at which therapy should be initiated and the extent of correction considered safe and desirable in the individual patient with heart failure need to be known. These issues become more important because of increasing safety concerns that recombinant erythropoietin therapy for treating anemia may be associated with adverse cardiovascular outcomes in patients with chronic kidney disease and may worsen cancer in patients receiving chemotherapy to treat various types of cancer. Therefore, further prospectively designed studies are required to address some of these questions. Fortunately, 2 large mortality morbidity trials, TREAT (Trial to Reduce Cardiovascular Events with Aranesp Therapy) in patients with chronic kidney disease and RED-HF (Reduction of Events with Darbepoetin alfa in Heart Failure) in heart failure patients, are in progress and are likely to provide definitive answers. (J Am Coll Cardiol 2008;52:501–11) © 2008 by the American College of Cardiology Foundation

The annual mortality in patients with chronic heart failure (HF) who are randomized in clinical trials has shown a remarkable decrease to approximately 8% with the use of beta-blockers and renin-angiotensin-aldosterone antagonists (1). However, the mortality in clinical practice remains very high (2). One reason for this disparity is the exclusion of patients from clinical trials with comorbid conditions that contribute to high mortality. Anemia is one such comorbidity and a novel therapeutic target in HF. This review will summarize the magnitude of the problem of anemia in HF and examine the factors that are associated with the development of anemia and the mechanisms by which anemia may worsen HF. The risks and benefits of treating anemia with erythropoietin-stimulating agents (ESA), a subject of much recent debate, also will be discussed.

## Prevalence of Anemia in HF

The World Health Organization defines anemia as hemoglobin (Hgb) <13.0 g/dl in men and <12.0 g/dl in women (3). Using this definition, Sarnak et al. (4) found 9% (men 5%; women 13%) of a normal population ages 45 to 64 years in the U.S. to have anemia. However, a more appropriate age-, gender-, and race-specific definition identified anemia in approximately 5% of the NHANES (National Health and Nutrition Examination Survey) population (5). The prevalence of anemia during HF varies depending on the definition and sample selection, as summarized in previous reviews (6–8). In clinical trials and large HF registries, the prevalence ranged from 15% to 61% and 14% to 70% among hospitalized patients. During the course of 1 year, new anemia developed in 9.6% of SOLVD (Studies Of Left Ventricular Dysfunction) patients (9), 16.9% of Val-HeFT (Valsartan Heart Failure Trial) patients (10), and 14.2% of COMET (Carvedilol Or Metoprolol European Trial) patients (11). The prevalence of anemia is similar in patients with impaired or preserved left ventricular (LV) function (12–15). In a large community study, 58% of HF patients had anemia of chronic disease, on the basis of International Classification of Diseases-9th Edition (285.9) code alone (16).

Anemia during HF has been associated with older age, diabetes, chronic kidney disease (CKD), greater New York Heart Association (NYHA) functional class, lower exercise capacity, worse health-related quality of life, greater edema, lower blood pressure, greater use of diuretics, and greater levels of neurohormones, proinflammatory cytokines, and C-reactive protein (CRP) (10,17–21). Importantly, Hgb has a weak inverse relation to ejection fraction (EF) (10,15), and an increase in Hgb over time is associated with a decrease, not an increase, in EF (10,22).

## Potential Causes of Anemia During HF

**Hematinic abnormalities.** Serum vitamin B12 and folic acid levels are low in only a minority of anemic patients with HF (23–25). Malabsorption and aspirin-induced gastrointestinal bleeding can cause iron deficiency. Detailed studies of iron homeostasis are not available. Lacking standard criteria (i.e., transferrin saturation, soluble transferrin receptor or ferritin levels), the reported prevalence of iron deficiency has varied from 5% to 21% (16,17,23,24,26). In a recent study, 43% of patients had either low serum iron ($<8$ $\mu$mol/l) or ferritin ($<30$ $\mu$g/l), but microcytic anemia was observed in only 6% patients (27). In contrast, Nanas et al. (28) found depleted iron stores in the bone marrow of 73% patients despite normal serum iron, ferritin, and erythropoietin. The mean corpuscular volume was at the lower limit of normal, suggesting that microcytic anemia was not present in all patients. These findings might be explained by diversion of iron from the bone marrow to the other reticuloendothelial stores, where it is not available for erythropoiesis even though serum iron and ferritin are normal or increased, a feature of anemia of chronic disease (29). Therefore, either absolute or relative iron deficiency may be more common than previously thought.

**Renal dysfunction and impaired erythropoietin production.** Erythropoietin is produced primarily in the kidney by specialized peritubular fibroblasts situated within the cortex and outer medulla (30). The primary stimulus for erythropoietin production is low $PO_2$ that activates hypoxia-inducible factor-1 in the peritubular fibroblasts, which induces transcription of the erythropoietin gene. The kidney is very susceptible to hypoxia despite the fact that it receives nearly 25% of the cardiac output and uses less than 10% of the oxygen delivered. To maintain the osmotic gradient generated by the loop of Henle, the arterial and venous blood vessels supplying it run countercurrent and in close contact, which leads to shunt diffusion of oxygen between the arterial and venous circulations, causing $PO_2$ to decrease across the renal parenchyma, reaching around 10 mm Hg at the tips of the cortical pyramids where the erythropoietin is produced (30). This area is very sensitive to small changes in the $PO_2$, resulting from an imbalance between oxygen supply and oxygen demand related to increased proximal tubular sodium reabsorption caused by low renal blood flow (RBF) and glomerular filtration rate.

During HF, RBF is decreased (31), and some renal dysfunction is common (7,32), but structural renal disease that could reduce erythropoietin production is infrequent. Therefore, reduced RBF should increase erythropoietin. Indeed, erythropoietin is increased, in proportion to the severity of HF, but is lower than expected for the degree of anemia, suggesting a blunted erythropoietin production (17,33,34). Studies of the complex relationship between RBF and erythropoietin secretion during HF have been inconsistent (25,35,36).

**Anemia and the renin-angiotensin system.** Angiotensin II decreases $PO_2$ by reducing RBF and increasing oxygen demand, thereby stimulating erythropoietin production. Angiotensin II also stimulates bone marrow erythroid progenitor cells (37). Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers cause a modest reduction in Hgb (10,38) by decreasing erythropoietin (39) and by preventing the breakdown of the hematopoiesis inhibitor N-acetyl-seryl-aspartyl-lysyl-proline (40).

**Proinflammatory state, bone marrow dysfunction, and anemia of chronic diseases.** Tumor necrosis factor-$\alpha$, interleukin (IL)-6, and several other proinflammatory cytokines (17,41) and CRP are increased in HF (42) and inversely related to Hgb (18). Interleukin-6 and tumor necrosis factor-$\alpha$ inhibit erythropoietin production in the kidney by activating GATA-2 and nuclear factor-$\kappa$B (43), which could explain the blunted erythropoietin response in HF. These cytokines also inhibit proliferation of bone marrow erythroid progenitor cells (44). Indeed, bone marrow in rats with HF show impaired erythropoiesis and have decreased number of erythropoietic progenitor cells, but the mechanisms remain unknown (45). Moreover, IL-6 stimulates the production of hepcidin in the liver that blocks duodenal absorption of iron (29). Furthermore, IL-6 down-regulates the expression of ferroportin, preventing the release of iron from body stores (29). Thus, an activated proinflammatory state, an essential component of anemia of chronic disease (29), can contribute to the development of anemia by several mechanisms (Fig. 1).

In 148 patients with stable HF, a specific cause of anemia was identified in only 43% of cases (17). Iron deficiency was found in only 5% of patients. In the remaining 57%, proinflammatory cytokine activation, inadequate erythropoietin production, and/or defective iron utilization was found despite adequate iron stores,
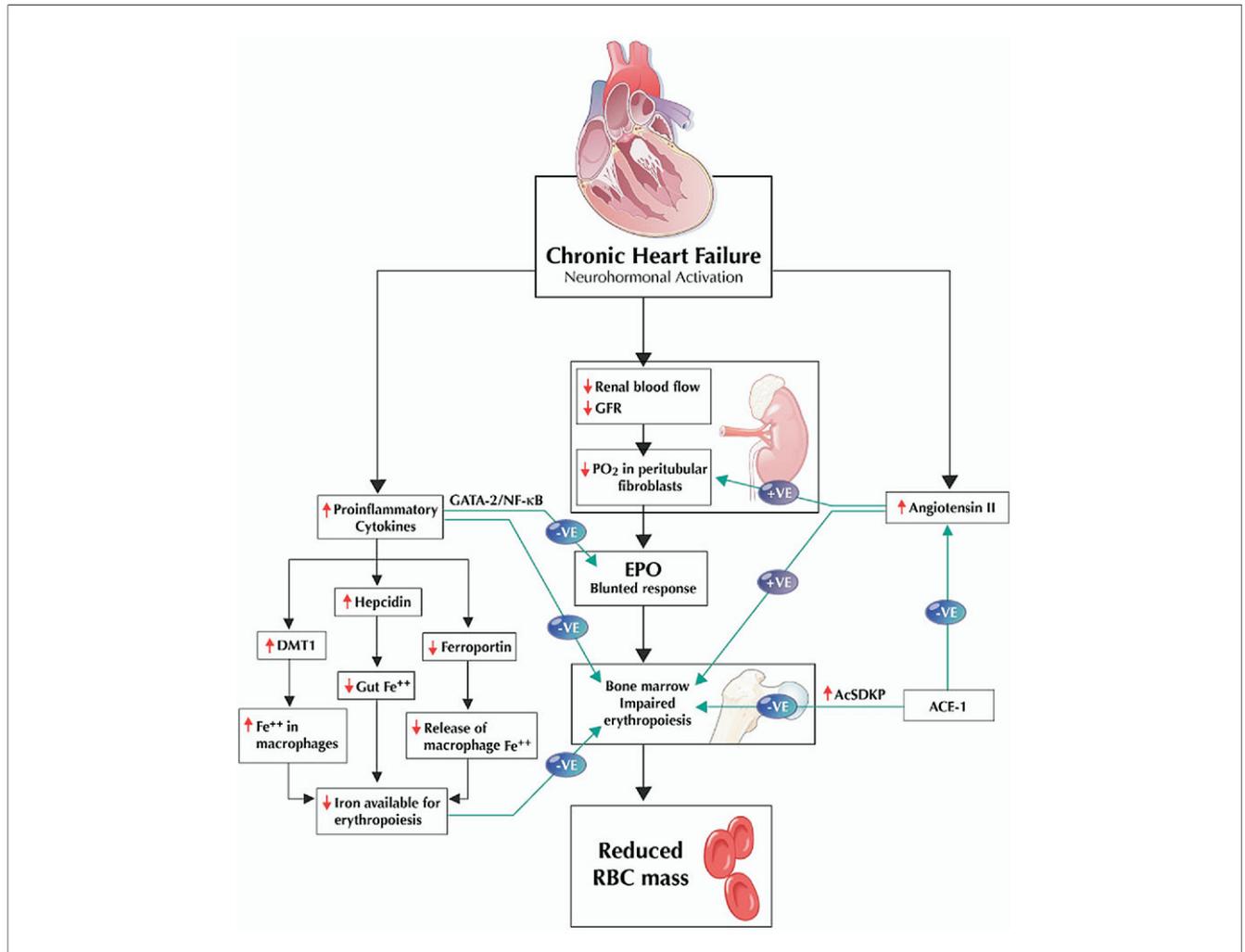
**Figure 1**  **Possible Mechanisms Involved in the Genesis of Anemia in Heart Failure**

Shown is a diagram of the possible mechanisms of anemia in patients with heart failure. ACE-I = angiotensin-converting enzyme inhibitor; AcSDKP = N-acetyl-seryl-aspartyl-lysyl-proline; ARB = angiotensin receptor blocker; DMT1 = divalent metal transporter 1; EPO = epoetin; GFR = glomerular filtration rate; HF = heart failure; NF-κB = nuclear factor-kappa B; RBC = red blood cell mass. Figure illustration by Rob Flewell.

suggesting anemia of chronic disease (29). Therefore, anemia of chronic disease could be the most frequent cause of anemia during HF.

**Hemodilution.** Anemia might be due to hemodilution (25,46). Androne et al. (46) found that nearly one-half of the clinically euvolemic patients referred for cardiac transplant had hemodilution induced "pseudoanemia." However, others have found that clinically euvolemic patients have normal plasma volume (47).

**Compensatory mechanisms and pathophysiological consequences of anemia.** Nonhemodynamic responses to anemia include increase in erythropoiesis to enhance oxygen carrying capacity, and increase in RBC 2,3-diphosphoglycerate that shifts the hemoglobin-oxygen dissociation curve to the right and improves oxygen delivery to the tissues (48). Because erythropoiesis is defective in HF, hemodynamic responses may predominate. In chronic severe anemia, low Hgb reduces systemic vascular resistance (SVR) (49) as the result of de-

creases in blood viscosity and enhanced nitric oxide-mediated vasodilation (50,51). Low SVR reduces blood pressure (BP) and causes baroreceptor-mediated neurohormonal activation (49), identical to that seen in low output HF (31,52). The increased sympathetic and renin-angiotensin activity decreases RBF and glomerular filtration rate, resulting in salt and water retention by the kidneys and expansion of the extracellular and plasma volumes. The combined effect of volume expansion and vasodilation increases the cardiac output (49), which may help to increase oxygen transport (53). Correction of anemia in patients with normal LV function causes a rapid and complete regression of the syndrome of high output HF (49,51). Although these hemodynamic and neurohormonal responses were observed in patients with severe anemia, it is unclear whether these mechanisms are also operative in HF patients with less severe anemia. However, similar changes have also been reported in CKD patients with mild-to-moderate anemia. McMahon et al. (22) found that in patients with CKD,
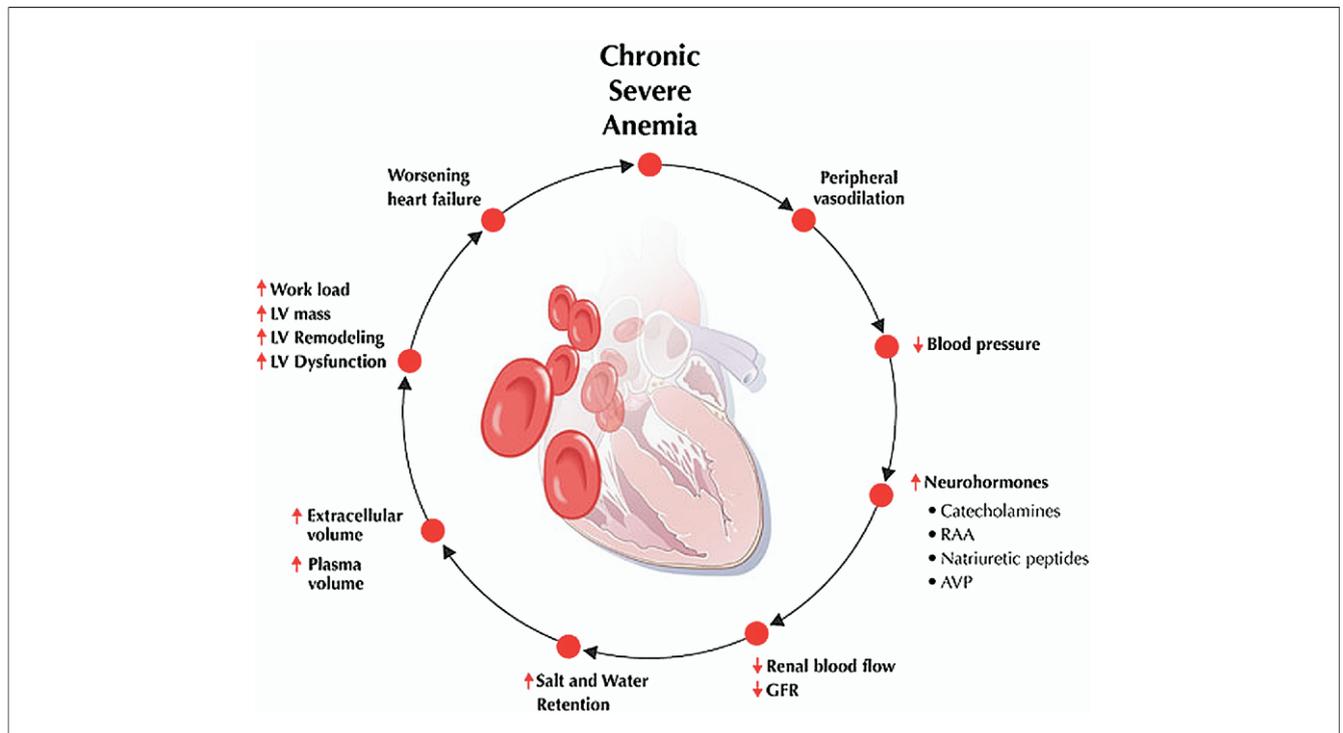
**Figure 2**    Possible Sequence of Events Involved in the Pathogenesis of Heart Failure in Chronic Severe Anemia

AVP = arginine vasopressin; GFR = glomerular filtration rate; LV = left ventricle;
RAA = renin-angiotensin-aldosterone. Data from Anand et al. (49). Figure illustration by Rob Flewell.

when Hgb was increased progressively from 8.5 to 10 to 14 g/dl with epoetin, the cardiac output (7.0 to 6.6 to 5.2 l/min) and the LV fractional shortening (36% to 33% to 29%) decreased significantly. Therefore, these data suggest that correction of anemia is unlikely to improve LV function. The possible sequence of events in the pathogenesis of HF in anemia is shown in Figure 2.

## Implications of Anemia and Lower Hemoglobin on Outcomes

Anemia and low Hgb have consistently been shown to be independently associated with increased risk of mortality and hospitalizations for HF in acute and chronic HF with LV dysfunction. The data are summarized in recent reviews (6–8). Anemia increased the relative risk of death in these studies by 20% to 50%. A similar relationship has also been shown in patients with preserved LV function (13–15,54). New-onset anemia and a decrease in Hgb over time are also associated with increased mortality (9,10).

The association of Hgb with mortality is not linear, and most of the increased risk occurs at low Hgb concentrations (10,11,55). In Val-HeFT, the risk of death were nearly identical in the 2 upper Hgb quartiles, 13.7 to <14.7 g/dl and >14.7 g/dl, whereas increased risk was found in the lower 2 Hgb quartiles (<12.8 g/dl) and (12.8 to <13.7 g/dl) (10). Some studies have reported a "J"-shaped relationship between Hgb and mortality in the normal population (56),

patients with coronary artery disease (57), acute coronary syndromes (58), and HF (54,55). The lowest mortality risk was observed in the Hgb range of 13 to 16 g/dl and the risk increased with Hgb concentrations below or above this range. Thus, the concern that excessive increases in hemoglobin may be associated with increased mortality.

## Why Is Anemia Associated With Poor Outcomes?

The increased myocardial workload due to hemodynamic and neurohormonal alterations observed in chronic anemia (49) could cause adverse LV remodeling. LV hypertrophy and dilation are observed in animal models of severe anemia (59,60), and they may contribute to poor outcomes. Whereas LV hypertrophy is consistently found in anemic patients with CKD, it is unclear whether it is related to anemia or hypertension (61). Although there are no data directly linking LV hypertrophy and anemia in HF, a 1-g/dl increase in Hgb over the course of 24 weeks was associated with a 4.1-g/m$^2$ decrease in LV mass in the RENAISSANCE (Randomized Etanercept North American Strategy to Study Antagonism of Cytokines) trial (19). However, treatment of anemia with ESA does not reverse LV hypertrophy in CKD (61). Hemoglobin may be inversely related to EF (10,15,22), and whereas anemia is related to brain natriuretic peptide (BNP), a marker of LV dysfunction, anemia remains an independent predictor of adverse outcomes in the presence of BNP and EF, suggesting that these variables

may have their effect through different mechanisms (10). Taken together, these findings suggest that changes in LV structure and function might not entirely explain the pathogenesis of worse outcomes in anemia.

Chronic kidney disease is a common comorbidity in HF patients with anemia (7,20), and both anemia and renal dysfunction remain independent predictors of outcomes in multivariate models (10,15,20). The relative risk of death at 2 years was increased by a factor of 1.6 in anemic patients with heart failure who also had CKD in a large Medicare database (62). In addition, anemia is often associated with poor nutritional status, low albumin (10,15), and cardiac cachexia (63), all of which could worsen outcomes. Finally, anemic patients have worse neurohormonal and proinflammatory cytokine profile that may also contribute to worse outcomes (18,41,49). Thus, although anemia may be related to a worse prognosis through multiple mechanisms, it is not clear whether anemia is a mediator or just a marker of poor outcomes.

## Treatment Options

Because anemia is strongly associated with poor clinical status and high mortality, it is logical to consider whether correcting anemia can improve outcomes. Only a few options are available to increase Hgb. Although blood transfusion can be used as an acute therapy, transfusions are associated with many risks and provide only temporary benefit (64). The correction of hematinic abnormalities might help; however, most patients are thought to have anemia of chronic disease, where stimulating erythropoiesis with ESAs is a rational strategy. Several small studies in HF have tested the effects of increasing Hgb with ESAs. Three studies investigated epoetin alfa, 1 study used epoetin beta, and 3 examined darbepoetin alfa (Table 1).

Silverberg et al. (65) were the first to report the effect of epoetin alfa and intravenous (IV) iron in 26 patients with anemia and HF. An increase in Hgb was associated with improvements in NYHA functional class and LV ejection fraction and decreases in diuretic dose and hospitalizations. A year later, the same authors reported the result of another study (66) in 32 patients with anemia and HF, randomized to usual care (n = 16) or epoetin alfa and IV iron sucrose (n = 16) that confirmed the findings of the previous study. Although they are difficult to interpret because of the small number of patients studied and the uncontrolled open-label design, these pioneering studies lead to a great interest in the treatment of anemia during HF.

Mancini et al. (67) conducted a patient-blind randomized study in 26 HF patients with anemia and erythropoietin <100 μU/ml. Patients were randomized 2:1 to epoetin alfa plus oral iron and folate, to increased hematocrit (Hct) to >45% or to placebo. After 3 months, Hgb, peak $VO_2$, and 6-min walk distance (6MWD) increased, and Minnesota Living with Heart Failure Questionnaire (MLHFQ) scores improved in treated patients with no changes in the placebo group. Re-

cently, Palazzuoli et al. (68) reported the effects of epoetin beta and oral iron on LV structure and function, pulmonary artery pressure, and BNP in 51 anemic HF patients with CKD (68). Patients were randomized to subcutaneous epoetin beta (n = 26) or saline (n = 25) for 1 year. After 12 months, Hgb increased; LV dimensions, volume, and mass decreased; and EF increased in the epoetin group with no change in the control group. The pulmonary artery pressure and BNP also decreased in the epoetin group.

A randomized, double-blind, placebo-controlled trial on 41 HF patients with anemia and a peak $VO_2$ ≤16 ml/kg/min, assigned subjects to placebo (n = 22) or darbepoetin alfa (n = 19) for 26 weeks (69). Although the mean Hgb increased significantly in the darbepoetin group, the mean changes in peak $VO_2$, exercise duration, Kansas City Cardiomyopathy Questionnaire and MLHFQ scores, BNP, and renal function were not different between treatment groups. A multicenter, double-blind placebo-controlled trial included 165 HF patients who were randomized to placebo (n = 55) or darbepoetin given every 2 weeks for 26 weeks at a weight-adjusted (n = 56) or fixed dose (n = 54) (70). The increase in Hgb in the combined darbepoetin groups was associated with improvement in Kansas City Cardiomyopathy Questionnaire total symptom score, but not in NYHA functional class, EF, MLHFQ score, 6MWD, or Patient's Global Assessment score. There were 6 deaths in the 110 darbepoetin and none in the 55 placebo group. Other adverse events were similar between groups. STAMINA-HeFT (Study of Anemia in Heart Failure-Heart Failure Trial) is the third and largest study in the darbepoetin program (71). In this multicenter, randomized double-blind placebo controlled study, 319 HF patients were randomized to darbepoetin and iron to maintain the Hgb at 14.0 ± 1.0 g/dl (n = 162) or placebo (n = 157) every 2 weeks for a year. At week 27, despite a significant increase in Hgb, the primary end point of change from baseline in treadmill exercise time was not improved, nor was there any improvement in NYHA functional class or MLHFQ score compared with placebo.

A prespecified pooled analysis of the aforementioned 2 trials showed that compared with placebo, treatment with darbepoetin was associated with a trend to lower composite end point of all-cause mortality or first HF-related hospitalization with hazard ratio (95% confidence interval) of 0.67 (0.44 to 1.03), p = 0.06, all-cause mortality 0.76 (0.39 to 1.48), p = 0.42, and hospitalization for HF 0.66 (0.40 to 1.07), p = 0.09 (72). The incidence of other adverse events including development of hypertension and myocardial infarction were similar in the 2 groups.

In summary, analysis of all the published ESA trials in HF reveal that the early small-sized, single center studies that lacked a placebo-controlled arm showed a remarkable improvement in clinical status and LV function when ESA was used to treat anemia. However, the 3 more recent double blind, placebo-controlled, randomized trials with darbepoetin showed less impressive results. Erythropoietin-stimulating agents were generally well tolerated in the HF

| Table 1 | Summary of All Published Studies That Have Tested the Effects of Erythropoietin-Stimulating Agents in Anemic Patients With HF |
|---|---|

| Author, Year (Ref. #) | Study Design | Inclusion Criteria | Patients (n) | Follow-Up Duration (months) | Baseline Hgb (g/dl) | Target Hgb (g/dl) | Achieved Hgb (g/dl) | Agents and Dose Used | Outcomes |
|---|---|---|---|---|---|---|---|---|---|
| Silverberg et al., 2000 (65) | Single-center, uncontrolled, open-label | EF <35, Hgb <12 g/dl | 26 | 7.2 ± 5.5 | 10.2 | 12.0 | 12.1 | S/C epoetin alfa (mean 5,277 IU/week) + IV iron sucrose (mean 185 mg/month) | ↓ NYHA functional class (3.7 ± 0.5 to 2.7 ± 0.7, p < 0.05), ↑ LVEF (28 ± 5% to 35 ± 8%, p < 0.001) Decrease in diuretic dose Decrease in hospitalizations |
| Silverberg et al., 2001 (66) | Single-center, randomized, no placebo, open-label | NYHA functional class III/IV, EF <40%, Hgb 10–11.5 g/dl | 16 usual care, 16 EPO | 8.2 ± 2.6 | 10.3 | 12.5 | 12.9 | S/C epoetin alfa (4,000 IU 1–3× week) IV iron sucrose (200 mg/2× weeks) | ↓ NYHA functional class, ↑ LVEF +5.5% Decrease in diuretic dose Decrease in hospitalizations |
| Mancini et al., 2003 (67) | Single-center, single-blind, randomized, placebo-controlled | NYHA functional class II/IV, Hct <35%, | 9 control, 17 EPO | 3.0 | 11.0 ± 0.6 | Hct >45% | 14.3 ± 1.2 | S/C epoetin alfa 15,000 to 30,000 IU/ week + oral iron 325 mg and folate 1 mg OD | ↑ Peak Vo₂ 11 ± 0.8 to 12.7 ± 2.8 ml/kg/min (p < 0.05), ↑ 6MWD Improvement in MLHFQ |
| Palazzuoli et al., 2007 (68) | Single-center, randomized, double-blind, placebo-controlled | NYHA functional class III/IV, EF <40%, Hgb 9.0–12.0 g/dl, serum creatinine 1.5–3.0 mg/dl | 25 control, 26 beta EPO | 12 | 10.4 ± 0.6 | NA | 12.4 ± 0.8 | S/C epoetin beta 6,000 IU/2× week + oral iron 300 mg for 1 year | ↑ LVEF, ↓ LV volumes, mass ↓ PAP and BNP No change in serum creatinine |
| Ponikowski et al., 2007 (69) | Multicenter, randomized, double-blind, placebo-controlled | Hgb 9.0–12.0 g/dl, peak VO₂ <16 ml/kg/min | 22 placebo, 19 darbepoetin | 27 weeks | 11.8 ± 0.2 | 13.0–15.0 | 13.9 ± 0.4 | Darbepoetin alfa, 0.75 μg/kg Q2W + 200–300 oral iron if serum ferritin <800 ng/ml | Mean change in peak Vo₂ (45 ml/min, p = 0.27) or (0.5 ml/kg/min, p = 0.40) Ex duration 108 s (p = 0.08), ↑ PGA (79% vs. 41%, p = 0.01) No change in KCCQ/MLHFQ No change in BNP or Cr |
| van Veldhuisen et al., 2007 (70) | Multicenter, randomized, double-blind, placebo-controlled | Hgb >9.0 and <12.5 g/dl, NYHA functional class II/III CHF, LVEF <40% | 55 placebo, 56 darbepoetin (weight based), and 54 darbepoetin (fixed dose) | 27 weeks | 11.5 | 14 ± 1.0 | 13.3 | Darbepoetin weight adjusted 0.75 μg/kg vs. fixed dose 50 μg vs. placebo Q2W + oral iron (200 mg OD if serum ferritin <800 ng/ml | Rate of rise Hgb 1.87 vs. 1.64 g/dl in weight-based vs. fixed dose (p = 0.07), improvement in KCCQ (p < 0.03), no significant improvement in 6MWD (p = 0.074), patients global assessment (p = 0.057), NYHA functional class, LVEF, or MLHFQ score |
| Ghali et al., 2008 (STAMINA-HeFT) (71) | Multicenter, randomized, double-blind, placebo-controlled | Hgb >9.0 and <12.5 g/dl, NYHA functional class II/IV CHF, LVEF <40%, | 157 placebo, 162 darbepoetin | 27 weeks for efficacy 55 weeks for safety | 11.4 | 14 ± 1.0 | 13.4 at 27 weeks, 13.4 at 53 weeks | Darbepoetin dose 0.75 μg/kg Q2W vs. placebo + oral iron (200 mg OD if serum ferritin <800 ng/ml) | No significant difference in exercise duration, NYHA functional class or quality of life scores at 27 weeks but trend to a decrease in the combined end point of death and hospitalization for HF |
| van Veldhuisen and McMurray 2007 (72) | Combined safety analysis | Hgb >9.0 and <12.5 g/dl, NYHA functional class II/III CHF, LVEF <40% | 209 placebo, 266 darbepoetin | 55 weeks | 11.4 ± 0.8 | 14 ± 1.0 | 13.4 | Darbepoetin dose 0.75 μg/kg or 50 μg vs. placebo Q2W + oral iron (200 mg OD if serum ferritin <800 ng/ml) | Trend to a decrease in the combined endpoint of death and hospitalization for HF (hazard ratio) and 95% confidence interval) for darbepoetin vs. placebo 0.67 (0.44 to 1.03), p = 0.06 |

CHF = congestive heart failulre; EF = ejection fraction; EPO = epoetin; Hct = hematocrit; HF = heart failure; Hgb = hemoglobulin; IV = intravenous; KCCQ = Kansas City Cardiomyopathy Questionnaire; LV = left ventricular; MLHFQ = Minnesota Living with Heart Failure Questionnaire; NYHA = New York Heart Association; OD = once daily; PAP = systolic pulmonary artery pressure; PGA = Patient's Global Assessment; Q2W = every 2 weeks; S/C = subcutaneous; 6MWD = 6-min walk distance.

patients with no significant increase in cardiovascular or other complications reported in the CKD and cancer population (73).

## Are There Risks of Increasing Hemoglobin With ESA Therapy?

The second National Kidney Foundation Kidney Disease Outcomes Quality Initiative anemia guidelines recommended use of erythropoietin in CKD patients to a target Hgb of 11 to 13 g/dl to avoid blood transfusions and improve quality of life (74). In the 1990s, several trials were conducted to assess whether complete normalization of Hgb would produce additional benefits. The NHCT (Normal Hematocrit Cardiac Trial) study randomized 1,223 CKD hemodialysis patients to receive epoetin alfa to achieve a Hct of 45% versus 30% (75). The study was terminated early because of a trend to increased risk of the composite of death or nonfatal MI and greater incidence of vascular access thrombosis in the normal Hct group (39% vs. 29%, p = 0.001). More recently, 2 publications—CREATE (Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta) (76) and CHOIR (Correction of Hemoglobin and Outcomes in Renal Insufficiency) (77)—have raised real concerns about the cardiovascular safety of greater Hgb with the use of ESAs in CKD patients. In CREATE, 603 patients (Hgb 11.6 ± 0.6 g/dl) were randomized to epoetin beta to normalize Hgb (13.0 to 15.0 g/dl) or use of epoetin only if Hgb decreased to <10.5 g/dl. There was a trend to increased mortality relative risk of 34% (p = 0.14) with the greater Hgb. In CHOIR, researchers randomized 1,432 patients (Hgb 10.1 ± 0.9 g/dl) to receive epoetin to achieve an Hgb of 13.5 or 11.3 g/dl. The trial was stopped early for presumed futility but showed a 34% (p = 0.03) increase in the composite of death, myocardial infarction, hospitalization for HF, and stroke in the high Hgb group.

There are significant limitations with these trials, particularly CHOIR, regarding imbalance of cardiovascular disease at baseline, issues of dropout, and the use of high doses of erythropoietin (78). Nevertheless, a meta-analysis of 9 randomized trials, including the 3 mentioned previously, that compared different target Hgb concentrations (73), found an increase in all-cause mortality relatively by 17% (p = 0.03), arteriovenous access thrombosis by 34% (p = 0.0001) and poorly controlled BP by 27% (p = 0.004) in the high Hgb group. Therefore, until definitive data are available from well-conducted trials, clinicians should refrain from complete correction of anemia.

Researchers for the TREAT (Trial to Reduce Cardiovascular Events with Aranesp Therapy) study, a 4,000-patient, multicenter, double-blind, placebo-controlled trial in patients with CKD and type 2 diabetes mellitus, have completed enrollment (79). Subjects are randomized to either darbepoetin to a target Hgb of 13 g/dl or placebo and darbepoetin for Hgb <9 g/dl until Hgb is >9 g/dl. The primary end point is the time to mortality and nonfatal cardiovascular events. The accumulated safety database in TREAT already exceeds all previous ESA trials, and the Data Safety Monitoring Board has not recommended any change in its conduct (80). The results of TREAT are likely to provide definitive information regarding the role of ESAs in the management of patients with anemia and CKD.

Meanwhile, on the basis of all the safety data from ESA therapy, the Food and Drug Administration updated the "black box warning" in the prescribing information for all ESAs in November 2007 and revised the dosing recommendations for anemic patients with CKD to maintain Hgb within 10 to 12 g/dl to avoid use of blood transfusion, and removed the previous quality of life claim (81).

## Mechanisms of the Observed Adverse Effects in CKD Patients

The greater risk of developing poorly controlled BP in CKD patients randomized to achieve higher Hgb with ESAs (73) could have contributed to worse cardiovascular events. Increase in BP at higher Hgb is explained on increased viscosity and reduced nitric oxide availability (49,51). Other possible mechanisms include increase in vascular cytosolic calcium (82), and endothelin-1 and tissue-specific renin-angiotensin activity (83,84) associated with erythropoietin use. Greater viscosity and erythropoietin associated antifibrinolytic activity may increase thrombotic risk (85).

Correcting anemia in HF is a tradeoff between the favorable effects of improving oxygen delivery and unfavorable effects of increasing viscosity and SVR on the BP, cardiac output and LV function. An increase in Hgb is associated with reduction in EF and an increase in BP (22,49,51). Hence, correction of anemia is unlikely to have a beneficial effect on LV function or hemodynamics. However, the small uncontrolled trials reported an increase in EF, and no increase in BP or thrombotic events were observed in any trial (65–68). Whether the potential benefit of correcting anemia are outweighed by harm can only be resolved with prospective, double-blind, placebo-controlled randomized controlled trials. Darbepoetin alfa is currently being tested in the RED-HF (Reduction of Events with Darbepoetin alfa in Heart Failure) trial, a large-scale, phase III morbidity and mortality trial (72). The results of this trial are likely to provide important information on the safety and efficacy of ESAs in patients with anemia and HF.

## Nonerythropoietic Effects of ESA

Erythropoietin receptors are also present on the neurons, cardiomyocytes, and endothelial cells (86). Several studies have confirmed that ESAs decrease experimental infarct size, reduce hypoxic injury, prevent myocyte apoptosis, and mobilize endothelial progenitor cells, independent of increases in Hgb (87–89). It is therefore possible that the beneficial effects of ESA are related to their nonhemopoietic effects and not to an increase in Hgb. These findings have

lead to the design of 2 phase II studies, one in the U.S. (90) and another in Europe (91), to examine the effect of an ESA on LV structure and function in post-myocardial infarction patients.

Recently, a second receptor for erythropoietin that mediates tissue protection has been identified consisting of the common $\beta$ receptor subunits, also known as CD 131, that is not within the erythropoietin receptor-binding domain and is present in the myocardium (92). Modification of erythropoietin by carbamylation of all its lysines to homocitrulline carbamylated erythropoietin caused the compound to completely lack erythropoietic activity but retain tissue protection (93). Carbamylated erythropoietin has been shown to prevent ischemia/reperfusion related apoptosis after myocardial infarction in vivo and in isolated cardiomyocytes in vitro (94). These agents could potentially provide myocardial protection in HF without the undesirable effects of erythropoietin. At present, there are no clinical data in HF.

## Treatment of Anemia Using Iron Alone

As discussed previously, either relative or absolute iron deficiency is frequently found in anemic HF patients. Iron is essential not only for erythropoiesis but also for several enzyme-linked bioenergetic processes in the skeletal muscle and in the Krebs cycle (95). Chronic iron deficiency may, by itself, reduce exercise capacity (96) and cause ultrastructural alterations in the cardiac myocytes (97). Therefore, IV iron alone may be beneficial in iron-deficient, anemic or non-anemic HF patients. Three studies have tested this hypothesis in patients with iron deficiency defined by transferrin saturation and ferritin levels. In an uncontrolled open-label study in 16 anemic (Hgb ≤12 g/dl) HF patients with iron deficiency in 44% of patients, IV iron sucrose was given for 12 to 17 days, and patients were followed for 92 ± 6 days (98). Iron treatment increased Hgb from 11.2 ± 0.7 g/dl to 12.6 ± 1.2 g/dl (p = 0.0007) and improved NYHA functional class, MLHFQ score, and 6MWD. The second study was a randomized, double-blind, placebo-controlled trial in 40 anemic HF patients (99). Control subjects (n = 20) received IV saline whereas the treatment group was given 200 mg of IV iron sucrose weekly for 5 weeks. After 6 months, Hgb increased by a mean of 1.4 g/dl (p < 0.01), and there was an improvement in creatinine clearance and MLHFQ score, decrease in CRP and N-terminal-proBNP, and increase in EF and 6MWD in the IV iron but not placebo group. The FERRIC-HF (Ferric iron sucrose in Heart Failure) (100) trial evaluated exercise capacity in iron-deficient anemic and nonanemic, HF patients with peak VO$_2$ ≤18 ml/kg/min. Eighteen anemic (Hgb <12.5 g/dl) and 17 nonanemic (Hgb 12.5 to 14.5 g/dl) patients were randomized to open-label, observer-blinded treatment with placebo or intravenous iron sucrose 200 mg/week for 4 weeks and then 200 mg/month for 3 months. Iron therapy increased serum ferritin and improved NYHA functional

class but, unlike the previous 2 studies, Hgb did not increase. Peak VO$_2$ increased significantly in the anemic but not in the nonanemic group. Although these 3 small underpowered studies raise the possibility that iron therapy alone may have a role in anemic patients with HF, large randomized placebo-controlled trials are required to confirm these intriguing findings. One such trial, IRON-HF (Iron Supplementation in Heart Failure Patients With Anemia), is in progress (101).

It must be emphasized that iron therapy is not without risks and has been associated with the risk of developing bacteremia (102). Moreover, iron therapy in the setting of immune activation may promote highly toxic hydroxyl radicals that can cause tissue damage and endothelial dysfunction, and increase the risk of adverse cardiovascular outcomes (103).

## Implication for Clinicians

None of the HF clinical practice guidelines from the U.S. or Europe currently discuss the assessment and management of anemia in HF. Given current evidence, the use of ESA and supplemental iron should only be considered in patients with concomitant CKD. The National Kidney Foundation KDOQI clinical practice guideline were updated in 2007 after publication of CREATE and CHOIR trials and recommend use of ESA to achieve a Hgb target in the range of only 11.0 to 12.0 g/dl (104). With the removal of the quality of life claim by the Food and Drug Administration, the only claim for the use of ESA is to improve exercise tolerance and functional ability of CKD patients (81). In HF patients, even these have not been convincingly shown to improve. Therefore, until long-term clinical outcomes data are available in HF patients with anemia, the use of ESA is not recommended in anemic patients with HF who do not have a CKD indication for its use.

## Conclusions

Anemia is a common comorbidity in patients with HF and is associated with worse long-term outcomes. Although the cause of anemia in HF is unclear, the weight of evidence suggests that renal dysfunction and neurohormonal and proinflammatory cytokine activation in HF favor the development of anemia of chronic disease. Similarly, the mechanisms by which anemia worsens HF outcomes are unknown but may be related to increased myocardial workload. Although anemia is a rational therapeutic target to improve outcomes, there are as yet no convincing data regarding the efficacy and long-term safety of ESA. Further studies are required to understand the basis of the remarkable association of anemia with HF outcomes, to prospectively assess the potential benefit of correcting anemia, to evaluate the ideal threshold at which therapy should be initiated, and the extent of correction considered safe and desirable. Two large mortality morbidity trials, TREAT in

CKD (79) and RED-HF (72) in HF, are in progress and may be able to provide answers to some of these questions.

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## REFERENCES

1. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225–37.
2. Rosamond W, Flegal K, Friday G, et al. Heart disease and stroke statistics—2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2007;115:e69–171.
3. Dallman PR. Iron Nutrition in Health and Disease. Eastleigh, UK: John Libbey & Co., 1996.
4. Sarnak MJ, Tighiouart H, Manjunath G, et al. Anemia as a risk factor for cardiovascular disease in The Atherosclerosis Risk in Communities (ARIC) study. J Am Coll Cardiol 2002;40:27–33.
5. Beutler E, Waalen J. The definition of anemia: what is the lower limit of normal of the blood hemoglobin concentration? Blood 2006;107:1747–50.
6. Komajda M. Prevalence of anemia in patients with chronic heart failure and their clinical characteristics. J Card Fail 2004;10:S1–4.
7. Anand IS. Pathogenesis of anemia in cardiorenal disease. Rev Cardiovasc Med 2005;6 Suppl 3:S13–21.
8. Tang Y-D, Katz SD. The prevalence of anemia in chronic heart failure and its impact on clinical outcomes. Heart Fail Rev 2008;13:387–92.
9. Ishani A, Weinhandl E, Zhao Z, et al. Angiotensin-converting enzyme inhibitor as a risk factor for the development of anemia, and the impact of incident anemia on mortality in patients with left ventricular dysfunction. J Am Coll Cardiol 2005;45:391–9.
10. Anand IS, Kuskowski MA, Rector TS, et al. Anemia and change in hemoglobin over time related to mortality and morbidity in patients with chronic heart failure: results from Val-HeFT. Circulation 2005;112:1121–7.
11. Komajda M, Anker SD, Charlesworth A, et al. The impact of new onset anaemia on morbidity and mortality in chronic heart failure: results from COMET. Eur Heart J 2006;27:1440–6.
12. Nair D, Shlipak MG, Angeja B, Liu HH, Schiller NB, Whooley MA. Association of anemia with diastolic dysfunction among patients with coronary artery disease in the Heart and Soul Study. Am J Cardiol 2005;95:332–6.
13. Felker GM, Shaw LK, Stough WG, O'Connor CM. Anemia in patients with heart failure and preserved systolic function. Am Heart J 2006;151:457–62.
14. Berry C, Norrie J, Hogg K, Brett M, Stevenson K, McMurray JJ. The prevalence, nature, and importance of hematologic abnormalities in heart failure. Am Heart J 2006;151:1313–21.
15. O'Meara E, Clayton T, McEntegart MB, et al. Clinical correlates and consequences of anemia in a broad spectrum of patients with heart failure: results of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Program. Circulation 2006;113:986–94.
16. Ezekowitz JA, McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated with poor outcomes: insights from a cohort of 12,065 patients with new-onset heart failure. Circulation 2003;107:223–5.
17. Opasich C, Cazzola M, Scelsi L, et al. Blunted erythropoietin production and defective iron supply for erythropoiesis as major causes of anaemia in patients with chronic heart failure. Eur Heart J 2005;26:2232–7.
18. Anand IS, Rector T, Deswal A, et al. Relationship between proinflammatory cytokines and anemia in heart failure Eur Heart J 2006;27 Suppl 1:485.
19. Anand I, McMurray JJ, Whitmore J, et al. Anemia and its relationship to clinical outcome in heart failure. Circulation 2004;110:149–54.
20. Al-Ahmad A, Rand WM, Manjunath G, et al. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. J Am Coll Cardiol 2001;38:955–62.
21. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, zjaBorenstein J. Anemia is associated with worse symptoms, greater impairment in functional capacity and a significant increase in mortality in patients with advanced heart failure. J Am Coll Cardiol 2002;39:1780–6.
22. McMahon LP, Mason K, Skinner SL, Burge CM, Grigg LE, Becker GJ. Effects of haemoglobin normalization on quality of life and cardiovascular parameters in end-stage renal failure. Nephrol Dial Transplant 2000;15:1425–30.
23. Witte KK, Desilva R, Chattopadhyay S, Ghosh J, Cleland JG, Clark AL. Are hematinic deficiencies the cause of anemia in chronic heart failure? Am Heart J 2004;147:924–30.
24. Cromie N, Lee C, Struthers AD. Anaemia in chronic heart failure: what is its frequency in the UK and its underlying causes? Heart 2002;87:377–8.
25. Westenbrink BD, Visser FW, Voors AA, et al. Anaemia in chronic heart failure is not only related to impaired renal perfusion and blunted erythropoietin production, but to fluid retention as well. Eur Heart J 2007;28:166–71.
26. Felker GM, Gattis WA, Leimberger JD, et al. Usefulness of anemia as a predictor of death and rehospitalization in patients with decompensated heart failure. Am J Cardiol 2003;92:625–8.
27. de Silva R, Rigby AS, Witte KK, et al. Anemia, renal dysfunction, and their interaction in patients with chronic heart failure. Am J Cardiol 2006;98:391–8.
28. Nanas JN, Matsouka C, Karageorgopoulos D, et al. Etiology of anemia in patients with advanced heart failure. J Am Coll Cardiol 2006;48:2485–9.
29. Weiss G, Goodnough LT. Anemia of chronic disease. N Engl J Med 2005;352:1011–23.
30. Bauer C, Kurtz A. Oxygen sensing in the kidney and its relation to erythropoietin production. Annu Rev Physiol 1989;51:845–56.
31. Anand IS, Ferrari R, Kalra GS, Wahi PL, Poole-Wilson PA, Harris PC. Edema of cardiac origin. Studies of body water and sodium, renal function, hemodynamic indexes, and plasma hormones in untreated congestive cardiac failure. Circulation 1989;80:299–305.
32. McClellan WM, Flanders WD, Langston RD, Jurkovitz C, Presley R. Anemia and renal insufficiency are independent risk factors for death among patients with congestive heart failure admitted to community hospitals: a population-based study. J Am Soc Nephrol 2002;13:1928–36.
33. Volpe M, Tritto C, Testa U, et al. Blood levels of erythropoietin in congestive heart failure and correlation with clinical, hemodynamic, and hormonal profiles. Am J Cardiol 1994;74:468–73.
34. van der Meer P, Voors AA, Lipsic E, Smilde TD, van Gilst WH, van Veldhuisen DJ. Prognostic value of plasma erythropoietin on mortality in patients with chronic heart failure. J Am Coll Cardiol 2004;44:63–7.
35. Jensen JD, Eiskjaer H, Bagger JP, Pedersen EB. Elevated level of erythropoietin in congestive heart failure relationship to renal perfusion and plasma renin. J Intern Med 1993;233:125–30.
36. Pham I, Andrivet P, Sediame S, et al. Increased erythropoietin synthesis in patients with COLD or left heart failure is related to alterations in renal haemodynamics. Eur J Clin Invest 2001;31:103–9.
37. Mrug M, Stopka T, Julian BA, Prchal JF, Prchal JT. Angiotensin II stimulates proliferation of normal early erythroid progenitors. J Clin Invest 1997;100:2310–4.
38. Albitar S, Genin R, Fen-Chong M, Serveaux MO, Bourgeon B. High dose enalapril impairs the response to erythropoietin treatment in haemodialysis patients. Nephrol Dial Transplant 1998;13:1206–10.
39. Fyhrquist F, Karppinen K, Honkanen T, Saijonmaa O, Rosenlof K. High serum erythropoietin levels are normalized during treatment of congestive heart failure with enalapril. J Intern Med 1989;226:257–60.
40. van der Meer P, Lipsic E, Westenbrink BD, et al. Levels of hematopoiesis inhibitor N-acetyl-seryl-aspartyl-lysyl-proline partially explain the occurrence of anemia in heart failure. Circulation 2005;112:1743–7.
41. Deswal A, Petersen NJ, Feldman AM, Young JB, White BG, Mann DL. Cytokines and cytokine receptors in advanced heart failure: an

analysis of the cytokine database from the Vesnarinone trial (VEST). Circulation 2001;103:2055–9.

42. Anand IS, Latini R, Florea VG, et al. C-reactive protein in heart failure: prognostic value and the effect of valsartan. Circulation 2005;112:1428–34.

43. Jelkmann W. Proinflammatory cytokines lowering erythropoietin production. J Interferon Cytokine Res 1998;18:555–9.

44. Macdougall IC, Cooper AC. Erythropoietin resistance: the role of inflammation and pro-inflammatory cytokines. Nephrol Dial Transplant 2002;17 Suppl 11:39–43.

45. Iversen PO, Woldbaek PR, Tonnessen T, Christensen G. Decreased hematopoiesis in bone marrow of mice with congestive heart failure. Am J Physiol Regul Integr Comp Physiol 2002;282:R166–72.

46. Androne AS, Katz SD, Lund L, et al. Hemodilution is common in patients with advanced heart failure. Circulation 2003;107:226–9.

47. Anand IS, Veall N, Kalra GS, et al. Treatment of heart failure with diuretics: body compartments, renal function and plasma hormones. Eur Heart J 1989;10:445–50.

48. Metivier F, Marchais SJ, Guerin AP, Pannier B, London GM. Pathophysiology of anaemia: focus on the heart and blood vessels. Nephrol Dial Transplant 2000;15:14–8.

49. Anand IS, Chandrashekhar Y, Ferrari R, Poole-Wilson PA, Harris PC. Pathogenesis of oedema in chronic severe anaemia: studies of body water and sodium, renal function, haemodynamic variables, and plasma hormones. Br Heart J 1993;70:357–62.

50. Ni Z, Morcos S, Vaziri ND. Up-regulation of renal and vascular nitric oxide synthase in iron-deficiency anemia. Kidney Int 1997;52: 195–201.

51. Anand IS, Chandrashekhar Y, Wander GS, Chawla LS. Endothelium-derived relaxing factor is important in mediating the high output state in chronic severe anemia. J Am Coll Cardiol 1995;25:1402–7.

52. Anand IS, Ferrari R, Kalra GS, Wahi PL, Poole-Wilson PA, Harris PC. Pathogenesis of edema in constrictive pericarditis. Studies of body water and sodium, renal function, hemodynamics, and plasma hormones before and after pericardiectomy. Circulation 1991;83: 1880–7.

53. Varat MA, Adolph RJ, Fowler NO. Cardiovascular effects of anemia. Am Heart J 1972;83:415–26.

54. Go AS, Yang J, Ackerson LM, et al. Hemoglobin level, chronic kidney disease, and the risks of death and hospitalization in adults with chronic heart failure: the Anemia in Chronic Heart Failure: Outcomes and Resource Utilization (ANCHOR) Study. Circulation 2006;113:2713–23.

55. Sharma R, Francis DP, Pitt B, Poole-Wilson PA, Coats AJ, Anker SD. Haemoglobin predicts survival in patients with chronic heart failure: a substudy of the ELITE II trial. Eur Heart J 2004;25: 1021–8.

56. Gagnon DR, Zhang TJ, Brand FN, Kannel WB. Hematocrit and the risk of cardiovascular disease—the Framingham study: a 34-year follow-up. Am Heart J 1994;127:674–82.

57. Brown DW, Giles WH, Croft JB. Hematocrit and the risk of coronary heart disease mortality. Am Heart J 2001;142:657–63.

58. Sabatine MS, Morrow DA, Giugliano RP, et al. Association of hemoglobin levels with clinical outcomes in acute coronary syndromes. Circulation 2005;111:2042–9.

59. Datta BN, Silver MD. Cardiomegaly in chronic anemia in rats and man experimental study including ultrastructural, histometric, and stereologic observations. Lab Invest 1975;32:503–14.

60. Olivetti G, Quaini F, Lagrasta C, et al. Myocyte cellular hypertrophy and hyperplasia contribute to ventricular wall remodeling in anemia-induced cardiac hypertrophy in rats. Am J Pathol 1992;141:227–39.

61. Levin A. The treatment of anemia in chronic kidney disease: understandings in 2006. Curr Opin Nephrol Hypertens 2007;16: 267–71.

62. Collins AJ. The hemoglobin link to adverse outcomes. Adv Stud Med 2003;3:S194–7.

63. Anker SD, Coats AJ. Cardiac cachexia: a syndrome with impaired survival and immune and neuroendocrine activation. Chest 1999;115: 836–47.

64. Demetri GD. Anaemia and its functional consequences in cancer patients: current challenges in management and prospects for improving therapy. Br J Cancer 2001;84 Suppl 1:31–7.

65. Silverberg DS, Wexler D, Blum M, et al. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. J Am Coll Cardiol 2000;35:1737–44.

66. Silverberg DS, Wexler D, Sheps D, et al. The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study. J Am Coll Cardiol 2001;37:1775–80.

67. Mancini DM, Katz SD, Lang CC, LaManca J, Hudaihed A, Androne AS. Effect of erythropoietin on exercise capacity in patients with moderate to severe chronic heart failure. Circulation 2003;107: 294–9.

68. Palazzuoli A, Silverberg DS, Iovine F, et al. Effects of beta-erythropoietin treatment on left ventricular remodeling, systolic function, and B-type natriuretic peptide levels in patients with the cardiorenal anemia syndrome. Am Heart J 2007;154:645e9–15.

69. Ponikowski P, Anker SD, Szachniewicz J, et al. Effect of darbepoetin alfa on exercise tolerance in anemic patients with symptomatic chronic heart failure: a randomized, double-blind, placebo-controlled trial. J Am Coll Cardiol 2007;49:753–62.

70. van Veldhuisen DJ, Dickstein K, Cohen-Solal A, et al. Randomized, double-blind, placebo-controlled study to evaluate the effect of two dosing regimens of darbepoetin alfa in patients with heart failure and anaemia. Eur Heart J 2007;28:2208–16.

71. Ghali JK, Anand IS, Abraham WT, et al. Randomized double-blind trial of darbepoetin alfa in patients with symptomatic heart failure and anemia. Circulation 2008;117:526–35.

72. van Veldhuisen DJ, McMurray JJ. Are erythropoietin stimulating proteins safe and efficacious in heart failure? Why we need an adequately powered randomised outcome trial. Eur J Heart Fail 2007;9:110–2.

73. Phrommintikul A, Haas SJ, Elsik M, Krum H. Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis. Lancet 2007; 369:381–8.

74. Fishbane S, Ragolia L, Palaia T, Johnson B, Elzein H, Maesaka JK. Cytoprotection by darbepoetin/epoetin alfa in pig tubular and mouse mesangial cells. Kidney Int 2004;65:452–8.

75. Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med 1998; 339:584–90.

76. Drueke TB, Locatelli F, Clyne N, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. N Engl J Med 2006;355:2071–84.

77. Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med 2006;355:2085–98.

78. Levin A. Understanding recent haemoglobin trials in CKD: methods and lesson learned from CREATE and CHOIR. Nephrol Dial Transplant 2007;22:309–12.

79. Mix TC, Brenner RM, Cooper ME, et al. Rationale—Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT): evolving the management of cardiovascular risk in patients with chronic kidney disease. Am Heart J 2005;149:408–13.

80. Pfeffer MA. An ongoing study of anemia correction in chronic kidney disease. N Engl J Med 2007;356:959–61.

81. Food and Drug Administration. Information for Healthcare Professionals Erythropoiesis Stimulating Agents (ESA) [Aranesp (darbepoetin), Epogen (epoealfa)], November 8, 2007. Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/RHE200711HCP.htm. Accessed June 9, 2008.

82. Vaziri ND. Cardiovascular effects of erythropoietin and anemia correction. Curr Opin Nephrol Hypertens 2001;10:633–7.

83. Rodrigue ME, Moreau C, Lariviere R, Lebel M. Relationship between eicosanoids and endothelin-1 in the pathogenesis of erythropoietin-induced hypertension in uremic rats. J Cardiovasc Pharmacol 2003;41:388–95.

84. Eggena P, Willsey P, Jamgotchian N, et al. Influence of recombinant human erythropoietin on blood pressure and tissue renin-angiotensin systems. Am J Physiol 1991;261:E642–6.

85. Tobu M, Iqbal O, Fareed D, et al. Erythropoietin-induced thrombosis as a result of increased inflammation and thrombin activatable fibrinolytic inhibitor. Clin Appl Thromb Hemost 2004;10:225–32.

86. Brines M, Cerami A. Emerging biological roles for erythropoietin in the nervous system. Nat Rev Neurosci 2005;6:484–94.
87. Parsa CJ, Matsumoto A, Kim J, et al. A novel protective effect of erythropoietin in the infarcted heart. J Clin Invest 2003;112:999–1007.
88. Calvillo L, Latini R, Kajstura J, et al. Recombinant human erythropoietin protects the myocardium from ischemia-reperfusion injury and promotes beneficial remodeling. Proc Natl Acad Sci U S A 2003;100:4802–6.
89. Westenbrink BD, Lipsic E, van der Meer P, et al. Erythropoietin improves cardiac function through endothelial progenitor cell and vascular endothelial growth factor mediated neovascularization. Eur Heart J 2007;28:2018–27.
90. REVEAL. Reduction of Infarct Expansion and Ventricular Remodeling With Erythropoietin After Large Myocardial Infarction. (ClinicalTrials.gov Identifier: NCT00378352). Available at: http://clinicaltrials.gov/show/NCT00378352. Accessed June 9, 2008.
91. HEBEIII. Clinical Study to Examine the Effects of Erythropoietin on Left Ventricular Function After Acute Myocardial Infarction (ClinicalTrials.gov Identifier: NCT00449488). Available at: http://clinicaltrials.gov/ct2/show/NCT00449488. Accessed June 9, 2008.
92. Brines M, Grasso G, Fiordaliso F, et al. Erythropoietin mediates tissue protection through an erythropoietin and common beta-subunit heteroreceptor. Proc Natl Acad Sci U S A 2004;101:14907–12.
93. Leist M, Ghezzi P, Grasso G, et al. Derivatives of erythropoietin that are tissue protective but not erythropoietic. Science 2004;305:239–42.
94. Fiordaliso F, Chimenti S, Staszewsky L, et al. A nonerythropoietic derivative of erythropoietin protects the myocardium from ischemia-reperfusion injury. Proc Natl Acad Sci U S A 2005;102:2046–51.
95. Dunn LL, Rahmanto YS, Richardson DR. Iron uptake and metabolism in the new millennium. Trends Cell Biol 2007;17:93–100.
96. Brownlie Tt, Utermohlen V, Hinton PS, Haas JD. Tissue iron deficiency without anemia impairs adaptation in endurance capacity after aerobic training in previously untrained women. Am J Clin Nutr 2004;79:437–43.
97. Dong F, Zhang X, Culver B, Chew HG Jr., Kelley RO, Ren J. Dietary iron deficiency induces ventricular dilation, mitochondrial ultrastructural aberrations and cytochrome c release: involvement of nitric oxide synthase and protein tyrosine nitration. Clin Sci (Lond) 2005;109:277–86.
98. Bolger AP, Bartlett FR, Penston HS, et al. Intravenous iron alone for the treatment of anemia in patients with chronic heart failure. J Am Coll Cardiol 2006;48:1225–7.
99. Toblli JE, Lombrana A, Duarte P, Di Gennaro F. Intravenous iron reduces NT-pro-brain natriuretic peptide in anemic patients with chronic heart failure and renal insufficiency. J Am Coll Cardiol 2007;50:1657–65.
100. Okonko DO, Grzeslo A, Witkowski T, et al. Effect of intravenous iron sucrose on exercise tolerance in anemic and nonanemic patients with symptomatic chronic heart failure and iron deficiency FERRIC-HF: a randomized, controlled, observer-blinded trial. J Am Coll Cardiol 2008;51:103–12.
101. Beck-da-Silva L, Luís Eduardo Rohde L, Pereira-Barretto AC, et al. Rationale and Design of the IRON-HF Study: A Randomized Trial to Assess the Effects of Iron Supplementation in Heart Failure Patients With Anemia. J Card Fail 2007;13.
102. Weinberg ED. Iron loading and disease surveillance. Emerg Infect Dis 1999;5:346–52.
103. Sullivan JL. Long-term risks of increased use of intravenous iron. Lancet 2007;370:481–2, author reply 482–3.
104. National Kidney Foundation Kidney Disease Outcomes Quality Initiative. KDOQI clinical practice guideline and clinical practice recommendations for anemia in chronic kidney disease: 2007 update of hemoglobin target. Available at: http://www.kidney.org/professionals/KDOQI/. Accessed June 9, 2008.