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Educational Objectives
After completing this activity, the participant should be better able to:
- Describe the epidemiology and the clinical spectrum of anemia in heart failure
- Review the current hypotheses regarding the underlying pathophysiology and clinical significance of anemia in heart failure
- Describe current treatment options, including the data supporting the clinical trials on erythropoiesis-stimulating agents (ESAs) and iron supplementation

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Anemia in Heart Failure: Current Evidence and Challenges

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Anemia is commonly observed in patients with heart failure, and portends worsening functional capacity and poorer long-term prognosis. Nevertheless, uncertainty remains regarding the underlying pathophysiology and natural history of anemia in the setting of chronic heart failure. The optimal therapeutic targets and treatment options for this "anemia of heart failure" are also uncertain. Careful evaluation of potential underlying reversible causes, particularly renal insufficiency and iron or nutritional deficiencies, may lead to potential treatment options. Recent concerns have focused on the appropriate hemoglobin target and the efficacies of erythropoiesis-stimulating agents (ESAs), such as erythropoietin and darbepoetin alfa, in reducing long-term clinical events. Much work is needed to clarify the safety and efficacy of this drug class. Nevertheless, early unblinded studies and phase II results using ESAs in patients with heart failure have found overall significant improvements in exercise capacity and quality of life, and it is hoped that ongoing pivotal outcome trials and investigations into iron supplementation will clarify their appropriate use.
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Key words: Anemia • Heart failure • Hemoglobin • Erythropoiesis-stimulating agents

Despite important advances in the treatment of heart failure, the overall long-term outcomes and disease burden remain significant. Over the past decade, there has been a surge of academic interest in the pathogenesis and outcomes of anemia in patients with heart failure. The interest is in part due to the increasing recognition of the prevalence and clinical consequences of this comorbidity in the general heart failure population, as well as the availability of specific treatment options to reverse conditions leading to

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anemia. This article provides an overview of the current understanding of anemia in heart failure and considers the promise of treating anemia as a therapeutic strategy in patients with heart failure.

Clinical Spectrum of Anemia in Heart Failure

Emerging Epidemiology of Anemia in Heart Failure

A challenge in this area of research is posed by the lack of a general agreement of the definition of anemia in the heart failure literature. Most reports have adopted the World Health Organization (WHO) criteria (hemoglobin < 13 g/dL for men and < 12 g/dL for women), but some researchers have also considered hemoglobin levels as a continuous variable. In fact, a single cut-off value (eg, < 12 g/dL) can be challenging to interpret. In patients with heart failure, the degree of anemia worsens and erythropoietin levels increase as the severity of heart failure progresses.[1] A retrospective analysis of 142 patients with heart failure found hemoglobin levels of less than 12 g/dL in 79% of New York Heart Association (NYHA) class IV patients as compared with 9.1% of patients in class I.[2] Nevertheless, what is obvious is that mild to moderate anemia is common in patients with heart failure, and the prevalence is higher when the criteria are less stringent and the disease severity is higher. In the Studies of Left Ventricular Dysfunction (SOLVD) database, the prevalence of anemia was estimated to be 22% when defined as hemoglobin less than 13 g/dL, but only about 4% when defined as hemoglobin less than 12 g/dL.[3] These rates are in contrast with those in the Valsartan in Heart Failure Trial (Val-HeFT), which showed an anemia prevalence of 10% (defined as hemoglobin < 12 g/dL),[4] and with a sicker group of patients in the Randomized Etanercept North American Strategy to Study Antagonism of Cytokines (RENAISSANCE) study, in which 12% of patients had hemoglobin less than 12 g/dL.[5] Furthermore, anemia was found in 16% of patients in the Italian IN-CHF registry (defined as < 12 g/dL in men and < 11 g/dL in women),[4] up to 33% of enrollees in the Study of Anemia in a Heart Failure Population (STAMINA-HFP) registry (defined as hemoglobin < 12 g/dL),[6] and as many as 55% of patients in some heart failure registries.[7] The wide range is largely due to the variations in disease severity (of both heart failure and the conditions leading to anemia) and differences in gender and underlying renal function, as well as in the quality of the data collected (documented hemoglobin levels vs administrative coding of anemia).[8] Assessment of prevalence is also complicated by the fact that congestive states of heart failure may produce anemia as a result of hemodilution.

Although women are traditionally more likely than men to develop anemia, the prevalence of anemia in heart failure appears similar in men and women. Recent data from the Carvedilol or Metoprolol European Trial (COMET) demonstrated that in patients with chronic systolic heart failure, 16% of male patients and 15.2% of female patients fulfilled the WHO criteria of anemia at baseline.[9] In addition, severe anemia (defined as hemoglobin < 11.5 g/dL for men and < 10.5 g/dL for women) was observed in 3.6% of male patients and 2.0% of female patients.

Clinical Outcomes of Anemia in Heart Failure

Data in the literature show that the prognostic value of anemia in heart failure is robust. Relatively mild degrees of anemia can be directly associated with worsened symptoms, lower functional status, and poorer survival, as seen in the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) trial database.[10] It can be extrapolated that for each 1 g/dL decrease below 15 g/dL, there was about a 3% to 11% increase in mortality. Lower hemoglobin was often associated with a more impaired hemodynamic profile and higher blood urea nitrogen and creatinine, as well as lower albumin, total cholesterol, and body mass index.[11] After adjusting for known heart failure prognostic factors, low hemoglobin remained an independent predictor of mortality (relative risk 1.131 [confidence interval, 1.05-1.22] for each decrease of 1 g/dL) (Figure 1).[11]

Interestingly, not all studies have the same conclusion. In 552 patients with new-onset heart failure, 18% had hemoglobin levels under 11.5 g/dL, but after adjustments for clinical variables, there was no independent association between baseline hemoglobin and survival.[12] Reports of a lack of prognostic value of hemoglobin levels in the elderly population have also been found.[13] These data challenge the contributions of comorbid conditions and make anemia more likely to be a risk marker than an important risk factor.[14]

Even in stable ambulatory patients with chronic heart failure, development of new onset anemia can be prevalent, and it can be associated with poor outcomes. In the COMET trial, incident (new-onset) anemia occurred at a rate of 14.2% at year 1 to 27.5% at year 5 of follow-up.[9] It was most prevalent in those with advanced age and lower body mass index, higher diuretic dosage, higher creatinine and potassium levels, and lower serum creatinine levels. There is also evidence that the subjective experience of fatigue is associated with anemia even after adjusting for

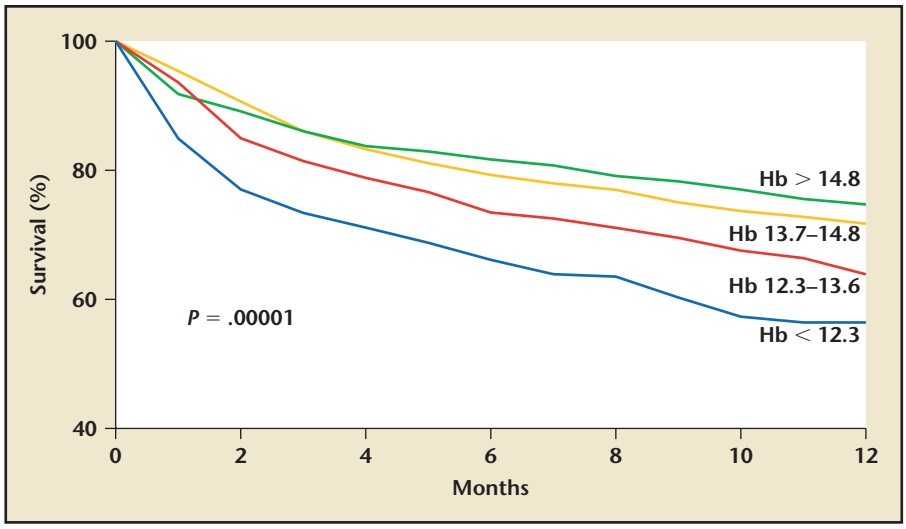

Figure 1. *Kaplan-Meier survival analysis of patients (N = 1061) with advanced heart failure by quartile of hemoglobin (Hb). This figure was published in Horwich TB, Fonarow GC, Hamilton MA, et al. Anemia is associated with worse symptoms, greater impairment in functional capacity and a significant increase in mortality in patients with advanced heart failure.* J Am Coll Cardiol. *2002;39:1780-1786.*[11] *Copyright © 2002 Elsevier.* www.medreviews.com

potential confounding factors, including NYHA class.[15] Higher rates of hospitalizations for heart failure and greater left ventricular mass index have also been associated with lower hemoglobin levels.[5] Furthermore, lower hemoglobin levels have been associated with higher natriuretic peptide levels,[16] as well as the deterioration of renal impairment[17]; resolution of anemia has been associated with improvement in these abnormalities.[18]

Recent data also confirmed that the development of anemia in patients with heart failure was equally common in systolic (25%) or diastolic (27%) heart failure, with over half of the anemic patients having glomerular filtration rates of less than 60 mL/min/1.73 m^2.[19] Both systolic and diastolic heart failure have similar adverse long-term clinical outcomes,[20] and the presence of anemia may be associated with even higher mortality rates in those with diastolic heart failure.[21]

Few studies have evaluated the prognostic impact of changes in hemoglobin levels on the natural history of heart failure, let alone the influence of heart failure treatments on changes in hemoglobin levels and outcomes. In Val-HeFT, those in the quartile that had the biggest decline in hemoglobin over 12 months experienced the greatest increased risk of subsequent hospitalization (hazard ratio 1.47), morbid events (hazard ratio 1.41), and death (hazard ratio 1.6) compared with the quartile that exhibited little change in hemoglobin over 12 months.[22] Furthermore, improvement in hemoglobin levels, regardless of the presence or absence of underlying anemia, was related to lower mortality rates. Beta-blocker therapy has also been associated with improvement in anemia as well as with corresponding improvement in renal function (possible mechanisms are discussed in the following section).[23] Taken together, it can be hypothesized that treatment strategies aimed at correcting anemia may have the potential to improve clinical outcomes in patients with heart failure.

Even in stable ambulatory patients with chronic heart failure, development of new onset anemia can be prevalent, and it can be associated with poor outcomes.

Pathophysiologic Mechanisms of Anemia in Heart Failure

Anemia has been found to be an independent predictor for incident heart failure in the Framingham study[24] as well as in the Medicare population.[25] Early investigations in patients with endstage renal disease have also suggested that anemia contributes to the development of incident or worsening cardiac failure independently of renal deterioration.[26] It has been hypothesized that anemia may trigger compensatory mechanisms, like increased sympathetic activation, that may affect progressive myocardial remodeling and lead to a vicious cycle of further worsening of heart failure and progressive anemia. Other concomitant conditions, such as advanced age, presence of underlying diabetes mellitus, and impaired renal perfusion, can also impact anemia and heart failure (Figure 2). Direct bone marrow suppression or blunted erythropoietin production secretion can result from excessive cytokine production, nutritional deficiencies, autonomic dysfunction, and suppression of endogenous erythropoietin synthesis (with the use of angiotensin-converting enzyme [ACE] inhibitors).[27-29] Recently, levels of the hematopoiesis inhibitor *N*-acetyl-seryl-aspartyl-lysyl-proline, which is degraded by ACE, were found to be significantly higher in anemic patients with heart failure,[30] linking anemia to renin-angiotensin system activity in heart failure.

There are several proposed mechanisms whereby anemia may contribute to worsening heart failure

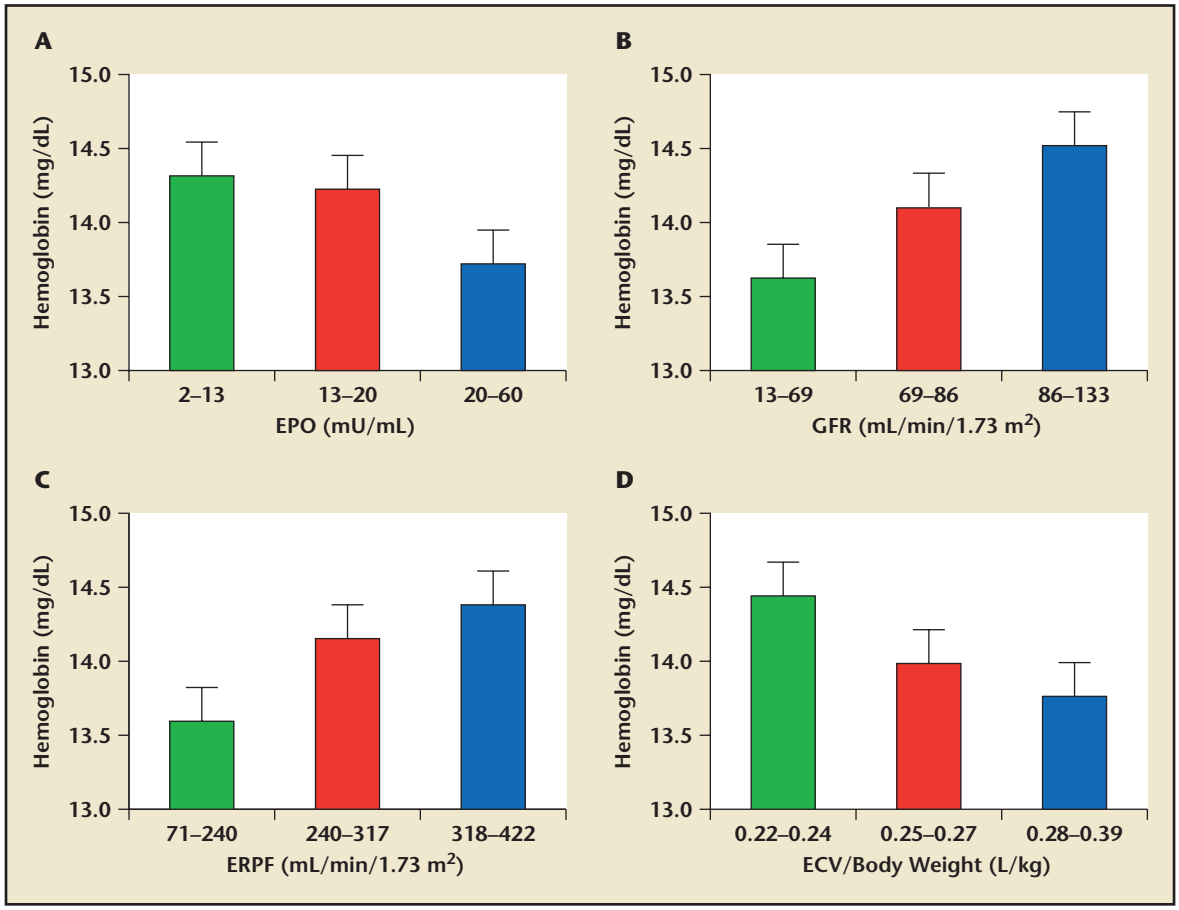

Figure 2. *Relation between hemoglobin levels and erythropoietin levels (EPO), glomerular filtration rates (GFR), effective renal plasma flow (ERPF), and extracellular volume (ECV). From Westenbrink BD, Visser FW, Voors AA, et al. Anaemia in chronic heart failure is not only related to impaired renal perfusion and blunted erythropoietin production, but to fluid retention as well.* Eur Heart J. *2007;28:166-171.[28] Reprinted with permission of Oxford University Press.* www.medreviews.com

pathophysiology. Lower systemic oxygen delivery may result from a reduction in the oxygen-carrying capacity of erythrocytes,[31] and patients with heart failure may lack the contractile reserve to compensate for a reduced hemoglobin level.[32] Acute anemia may lead to lower blood viscosity, hypoxia-induced vasodilatation, enhanced nitric oxide activity, and compensatory angiogenesis as normal adaptive responses; chronic anemia is associated with arterial remodeling and ventricular hypertrophy.[33] Reduction in circulating erythrocytes may also lead to an increase in circulating hemoglobin, which scavenges nitric oxide and thus contributes to impaired nitric oxide bioavailability and endothelial dysfunction as seen in the sickle cell population[34] or in ischemic heart disease.[35] Data supporting this theory in the heart failure population are still limited.

Interestingly, worsening clinical outcomes in the setting of anemia appear to be independent of the extent of coronary artery disease. In fact, patients with nonischemic cardiomyopathy were considered to be more affected by the presence of anemia,[36] suggesting that anemia may exert its effect on heart failure outcomes through mechanisms beyond simply the exacerbation of myocardial ischemia.

Current Controversies in Managing Anemia in Heart Failure

The so-called *anemia hypothesis* assumed that the presence of anemia in the setting of heart failure contributes to worsening prognosis and symptomatology, and that treatment strategies that directly target the improvement of anemia in patients with heart failure may be associated with improved symptoms and exercise capacity, better health-related quality of life, improved cardiac function, and better clinical outcomes. However, this notion has been highly debated, and investigations are needed to better define

appropriate evaluation, appropriate treatment targets, and appropriate treatment modalities for anemia in heart failure.

Appropriate Evaluation of Anemia in Heart Failure

Evaluation of anemia in the heart failure population follows the same approach used in other patient populations. The "anemia of heart failure" has long been considered as part of the cohort of anemia of chronic diseases. Commonly, anemia in heart failure is presented as a normocytic anemia. Determination of reversible etiologies is paramount. A careful review of medical history should include the potential of bleeding or other iatrogenic causes (recent surgeries, pregnancies, cancer treatments, etc), and/or underlying acquired or inherited hematologic abnormalities. Laboratory evaluation may reflect the classification of anemia (macrocytic, normocytic, microcytic), and specific testing may indicate conditions such as nutritional deficiencies (iron, B_{12}, or folate deficiency) or renal insufficiency. Examination of peripheral smear and bone marrow biopsy may be indicated when evidence of accelerated red cell destruction or impaired erythropoiesis is evident. In addition, many of these patients are on antiplatelet or anticoagulation therapies, so one must always bear in mind the possibility of a gastrointestinal source of chronic blood loss.

Few studies have carefully examined the underlying etiologies leading to the development of anemia in patients with heart failure. A retrospective series has suggested that 98% of subjects have an identified cause, including renal insufficiency (glomerular filtration rate < 60 mL/min/m^2), malnutrition, and malabsorption of iron, folate, or B_{12}.[37] In another series of patients with advanced heart failure, iron deficiency was the most common cause of anemia.[38] Nevertheless, there are still reports of a large proportion of unexplained anemia in patients with heart failure,[39] which is evident from ongoing clinical trial enrollment.

Volume status is an important determinant of anemia, particularly in the setting of acute decompensated heart failure, in which hemodilution can be operative. It appears that 1 in 4 patients admitted for decompensated heart failure may experience transient anemia.[40] Clearly, occult hypervolemia may contribute to the clinical picture of anemia and may lead to poorer prognosis.[41] In the Acute Decompensated Heart Failure Registry (ADHERE), up to 40% of enrollees met a diagnosis of anemia (hemoglobin $<$ 12 g/dL).[42] In the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbation of Chronic Heart Failure (OPTIME-CHF) trial, anemia was associated with a greater number of comorbid conditions, and lower baseline hemoglobin was associated with risk of short-term adverse clinical outcomes, even after adjustment for other baseline differences.[43]

Appropriate Target of Treatment for Anemia in Heart Failure

Observations from a symptomatic heart failure clinical trial population have suggested that the mortality risk of anemia follows a U-shaped curve, with the lowest risk cohort having hemoglobin levels of 14.5 g/dL to 15.4 g/dL, and increased mortality in hemoglobin ranges that are either higher or lower.[44] Epidemiologic evidence suggested that anemia falling below the range of 12 g/dL to 12.5 g/dL could be considered the "threshold" of when clinical event rates begin to rise. However, information regarding the appropriate target of therapy is lacking, since there are still limited data regarding the risks of raising hemoglobin in the heart failure population. This is perhaps most relevant when erythropoiesis-stimulating agents (ESAs) are used to raise hemoglobin levels, and small mechanistic studies have targeted levels up to 12.5 g/dL to 13 g/dL.

The controversy has been raised following recent reports of a prospective study examining 2 different therapeutic targets of recombinant human erythropoietin (epoetin alfa) therapy in the setting of chronic renal insufficiency. The investigators found significantly higher risk in the higher hemoglobin target group (hemoglobin rise up to 13.5 g/dL) than in the lower group (hemoglobin rise up to 11.3 g/dL), with no incremental improvement in quality of life.[45] These data were further supported by a meta-analysis of 9 trials, indicating that the use of recombinant human erythropoietin in the setting of chronic kidney disease is associated with increased mortality risk when higher hemoglobin concentrations are targeted.[46] Another study in patients with chronic renal insufficiency, Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE), found that hypertensive events and headaches were more common in the treatment group (epoetin beta, target hemoglobin 13 g/dL to 15 g/dL) compared with placebo, although overall there was no significant reduction of cardiovascular events despite better health status.[47] Furthermore, correcting underlying anemia may not directly translate into improvement in clinical outcomes. In the case of anemia in patients undergoing chemotherapy to treat head and neck cancer, administration of human recombinant erythropoietin

(rHuEPO) improved hemoglobin levels but did not affect survival or cancer control.[48] All these studies casted some doubt as to whether the risks of an erythropoietin-based strategy may outweigh the benefits. The current target level for Food and Drug Administration-approved indications for ESA therapy is 12 g/dL.

Appropriate Treatment Modality for Anemia in Heart Failure

Treatment options under consideration have included iron supplementation, erythropoiesis-stimulating agents, and red-cell transfusion.

Iron supplementation. Patients with heart failure can be deficient in iron stores due to poor nutrition, poor absorption, underlying inflammation and other comorbid conditions, and/or occult bleeding. Functional iron deficiency may also occur due to ESAs that shift iron uptake to meet the demands of increased erythrocyte production. Often, transferrin saturation (a surrogate for circulating iron pool, defined as the ratio of serum iron and total iron binding capacity) and serum ferritin (surrogate for storage iron) can be low in the setting of iron deficiency. In fact, both surrogates can be affected by acute phase responses. In general, transferrin saturation should be maintained above 20%, and serum ferritin should be maintained above 100 ng/mL and rechecked periodically (every 3 to 6 months) to ensure adequate iron stores in the setting of anemia management. Although oral iron supplementation has been the primary therapeutic strategy, side effects (eg, constipation) and excessive pill burden may limit adoption in the heart failure population, even though generic ferrous sulfate can be relatively affordable. Some studies have advocated the use of intravenous iron preparations, and have suggested the potential benefits of restoring iron stores even in the absence of ESAs.[49] However, excess iron may have deleterious side effects (including the potential for increasing oxidant load, potential anaphylactic reactions, and excessive iron deposition in organs), and can be expensive. Ongoing clinical trials will aim to address these uncertainties.[50]

ESAs. The use of ESAs to increase hemoglobin in patients with heart failure has been investigated in a series of clinical studies in advanced symptomatic heart failure by Silverberg and colleagues[51] targeting hemoglobin levels between 12 g/dL to 13 g/dL and serum ferritin levels greater than 400 ng/mL to 700 ng/mL. Mean baseline hemoglobin for the majority of studies was about 10 g/dL. rHuEPO was given at 10,000 to 30,000 IU/week dosing with concomitant intravenous iron administration (200 mg IV every 1 to 2 weeks). Long-term follow-up has suggested that resolution of anemia may be associated with reduction in diuretic use and fewer hospitalizations,[2,51,52] and even improved survival.[53] These responses were similar between patients with or without diabetes mellitus.[54] However, these early studies were nonblinded and have relatively small sample sizes and short follow-up durations, and hence they can be subject to significant selection bias and confounding. In a carefully conducted, single-blind study by Mancini and colleagues,[55] 3-month administration of rHuEPO and oral ferrous gluconate/folate was associated with significant increases in peak oxygen consumption and exercise duration.

Recently, the availability of darbepoetin alfa, a longer-acting analog of erythropoietin (so-called *erythropoiesis-stimulating protein*), has been examined in a multicenter, randomized, double-blind, placebo-controlled study of patients with symptomatic heart failure and anemia (hemoglobin 9 g/dL to 12 g/dL). Twenty-seven–week administration of darbepoetin alfa was associated with raised (+ 1.5 g/dL) and maintained hemoglobin concentrations, as well as self-reported clinical improvements. A trend toward increased exercise time was also observed (Figure 3), although peak oxygen consumption and quality of life instrument scores showed no correlation.[56]

These data have been validated in a few multicenter, double-blind, randomized control trials using darbepoetin alfa, and preliminary results indicated benefits in exercise capacity and quality of life, with a trend toward reducing long-term mortality and outcomes. These studies differed from previous intervention studies for ESAs in the following aspects—the study population had relatively preserved renal function, and a therapeutic hemoglobin target of 13 g/dL was used instead of higher targets. These promising phase II studies led to the ongoing Reduction of Events with Darbepoetin alfa in Heart Failure (RED-HF) trial, which is designed and powered to definitively determine whether treating anemia with darbepoetin alfa can improve outcomes.

Red-cell transfusion. Red-cell transfusions are often performed in response to an acute decline in hemoglobin levels (often due to increased blood loss or destruction) to immediately restore oxygen-carrying capacity and improve tissue oxygenation. Apart from standard indications for anemic hospitalized patients, there is no published study to support any specific benefits for red-cell transfusions in the setting of chronic heart failure, especially with

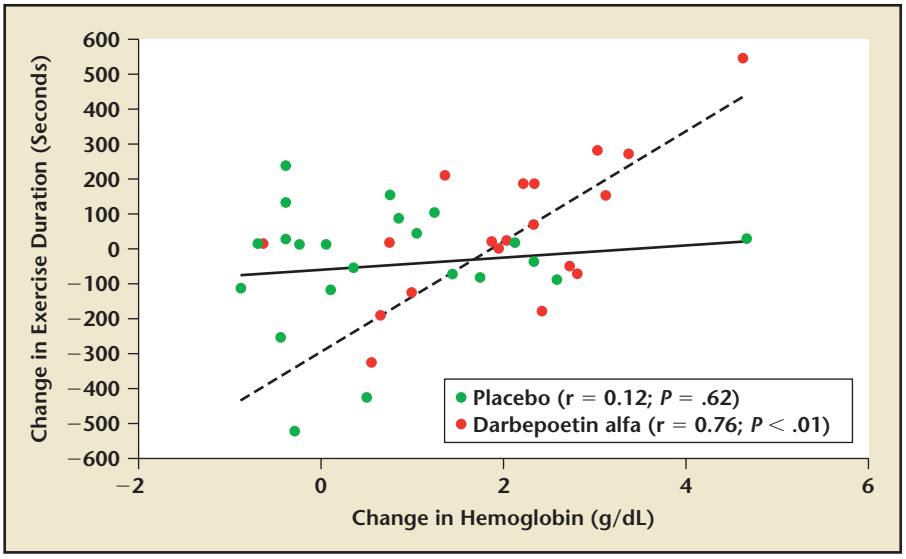

Figure 3. *Individual changes from baseline to week 27 in hemoglobin concentration relative to the change from baseline in exercise duration: comparison between darbepoetin alfa and placebo. This figure was published in Ponikowski P, Anker SD, Szachniewicz J, et al. Effect of darbepoetin alfa on exercise tolerance in anemic patients with symptomatic chronic heart failure: a randomized, double-blind, placebo-controlled trial.* J Am Coll Cardiol. *2007;49:753-762.*[56] *Copyright © 2007 Elsevier.* www.medreviews.com

the increased risks of contracting bloodborne infections, the high cost, and the stress reactions associated with the transfusion. Given the transitory nature of the increase in oxygen-carrying capacity accomplished by blood transfusions, the cost, and the increasing complication rate with recurrent transfusions, transfusion does not represent a reasonable approach to the average patient with some intrinsic hematopoietic function and chronic anemia.

Clinical Perspectives

The emerging attention focused on anemia as a potential therapeutic target, as with many other comorbid conditions, has engendered much enthusiasm and skepticism over what the best management strategies should be. What has definitely been the most important development in this area is the recognition by cardiologists that more attention is needed to evaluate and manage anemia, because of its common occurrence and also the adverse consequences if left untreated. The question of whether ESAs may provide a therapeutic option to improve morbidity and mortality in anemia patients with advanced heart failure remains to be defined by large-scale clinical trials. The knowledge base currently acquired from mechanistic studies will likely provide important insights into the balance of the cardiorenal axis in the setting of heart failure, leading to the discovery and clinical applications of novel mechanisms and new compounds.[57] ■

References

1. 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;74:468-473.
2. 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;35:1737-1744.
3. Al-Ahmad A, Rand WM, Manjunath G, et al. Reduced kidney function and anemia as risk factors for mortality in patients with left

Main Points

- In patients with heart failure, a single hemoglobin cut-off value (eg, < 12 g/dL) can be challenging to interpret. In these patients, the degree of anemia worsens and erythropoietin levels increase as the severity of heart failure progresses.
- Relatively mild degrees of anemia can be directly associated with worsened symptoms, lower functional status, and poorer survival.
- Some data have suggested that there is no independent association between baseline hemoglobin and survival and that anemia is more likely to be a risk marker than an important risk factor.
- Commonly, anemia in heart failure is presented as a normocytic anemia. Determination of reversible etiologies is paramount.
- Correcting underlying anemia may or may not directly translate into improvement in clinical outcomes.

ventricular dysfunction. *J Am Coll Cardiol*. 2001;38:955-962.
4. Maggioni AP, Opasich C, Anand I, et al. Anemia in patients with heart failure: prevalence and prognostic role in a controlled trial and in clinical practice. *J Card Fail*. 2005;11:91-98.
5. Anand I, McMurray JJ, Whitmore J, et al. Anemia and its relationship to clinical outcome in heart failure. *Circulation*. 2004;110:149-154.
6. Wagoner LE, Butler J, Oren R, et al. Anemia is common in patients with heart failure seen in speciality and community cardiology clinics: results from the STAMINA-HFP Registry (Study of Anemia in a Heart Failure Population) [abstract]. *J Am Coll Cardiol*. 2004;43:217A.
7. 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;107:223-225.
8. Lindenfeld J. Prevalence of anemia and effects on mortality in patients with heart failure. *Am Heart J*. 2005;149:391-401.
9. 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;27:1440-1446.
10. Mozaffarian D, Nye R, Levy WC. Anemia predicts mortality in severe heart failure: the prospective randomized amlodipine survival evaluation (PRAISE). *J Am Coll Cardiol*. 2003; 41:1933-1939.
11. Horwich TB, Fonarow GC, Hamilton MA, et al. 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;39:1780-1786.
12. Kalra PR, Collier T, Cowie MR, et al. Haemoglobin concentration and prognosis in new cases of heart failure. *Lancet*. 2003;362:211-212.
13. Kerzner R, Gage BF, Rich MW. Anemia does not predict mortality in elderly patients with heart failure. *Am J Geriatr Cardiol*. 2007;16:92-96.
14. Kosiborod M, Curtis JP, Wang Y, et al. Anemia and outcomes in patients with heart failure: a study from the National Heart Care Project. *Arch Intern Med*. 2005;165:2237-2244.
15. Falk K, Swedberg K, Gaston-Johansson F, Ekman I. Fatigue and anaemia in patients with chronic heart failure. *Eur J Heart Fail*. 2006; 8:744-749.
16. Baggish AL, van Kimmenade R, Bayes-Genis A, et al. Hemoglobin and N-terminal pro-brain natriuretic peptide: independent and synergistic predictors of mortality in patients with acute heart failure. Results from the International Collaborative of NT-proBNP (ICON) Study. *Clin Chim Acta*. 2007;381:145-150.
17. Bansal N, Tighiouart H, Weiner D, et al. Anemia as a risk factor for kidney function decline in individuals with heart failure. *Am J Cardiol*. 2007;99:1137-1142.
18. Palazzuoli A, Silverberg D, Iovine F, et al. Erythropoietin improves anemia exercise tolerance and renal function and reduces B-type natriuretic peptide and hospitalization in patients with heart failure and anemia. *Am Heart J*. 2006;152:1096.e9-15.
19. 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;113:986-994.
20. Felker GM, Shaw LK, Stough WG, O'Connor CM. Anemia in patients with heart failure and preserved systolic function. *Am Heart J*. 2006; 151:457-462.
21. Grigorian Shamagian L, Varela Roman A, Garcia-Acuna JM, et al. Anaemia is associated with higher mortality among patients with heart failure with preserved systolic function. *Heart*. 2006;92:780-784.
22. 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;112:1121-1127.
23. Khan W, Deepak SM, Coppinger T, et al. Beta blocker treatment is associated with improvement in renal function and anaemia in patients with heart failure. *Heart*. 2006;92:1856-1857.
24. Kannel WB. Epidemiology and prevention of cardiac failure: Framingham Study insights. *Eur Heart J*. 1987;8(suppl F):23-26.
25. Sandgren PE, Murray AM, Herzog CA, et al. Anemia and new-onset congestive heart failure in the general Medicare population. *J Card Fail*. 2005;11:99-105.
26. Foley RN, Parfrey PS, Harnett JD, et al. The impact of anemia on cardiomyopathy, morbidity, and mortality in end-stage renal disease. *Am J Kidney Dis*. 1996;28:53-61.
27. Chatterjee B, Nydegger UE, Mohacsi P. Serum erythropoietin in heart failure patients treated with ACE-inhibitors or AT(1) antagonists. *Eur J Heart Fail*. 2000;2:393-398.
28. 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;28:166-171.
29. 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;26:2232-2237.
30. 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;112:1743-1747.
31. Rady M, Jafry S, Rivers E, Alexander M. Characterization of systemic oxygen transport in end-stage chronic congestive heart failure. *Am Heart J*. 1994;128:774-781.
32. Weiskopf RB, Viele MK, Feiner J, et al. Human cardiovascular and metabolic response to acute, severe isovolemic anemia. *JAMA*. 1998; 279:217-221.
33. Metivier F, Marchais SJ, Guerin AP, et al. Pathophysiology of anaemia: focus on the heart and blood vessels. *Nephrol Dial Transplant*. 2000; 15(suppl 3):14-18.
34. Morris CR, Kato GJ, Poljakovic M, et al. Dysregulated arginine metabolism, hemolysis-associated pulmonary hypertension, and mortality in sickle cell disease. *JAMA*. 2005;294: 81-90.
35. Andreotti F, Coluzzi G, Lavorgna A, et al. Relation between nitric oxide metabolites and haemoglobin concentrations in patients with ischaemic heart disease. *Heart*. 2007;93:255-257.
36. Felker GM, Stough WG, Shaw LK, O'Connor CM. Anaemia and coronary artery disease severity in patients with heart failure. *Eur J Heart Fail*. 2006;8:54-57.
37. Hussein SJ, Jain R, Shlipak MG, et al. Chronic heart failure is not an independent cause of anemia [abstract]. *J Card Fail*. 2003;9:19.
38. Nanas JN, Matsouka C, Karageorgopoulos D, et al. Etiology of anemia in patients with advanced heart failure. *J Am Coll Cardiol*. 2006; 48:2485-2489.
39. Witte KK, Desilva R, Chattopadhyay S, et al. Are hematinic deficiencies the cause of anemia in chronic heart failure? *Am Heart J*. 2004;147: 924-930.
40. Formiga F, Chivite D, Castaner O, et al. Anemia in new-onset congestive heart failure inpatients admitted for acute decompensation. *Eur J Intern Med*. 2006;17:179-184.
41. Androne AS, Hryniewicz K, Hudaihed A, et al. Relation of unrecognized hypervolemia in chronic heart failure to clinical status, hemodynamics, and patient outcomes. *Am J Cardiol*. 2004;93:1254-1259.
42. Fonarow GC. The Acute Decompensated Heart Failure National Registry (ADHERE): opportunities to improve care of patients hospitalized with acute decompensated heart failure. *Rev Cardiovasc Med*. 2003;4(suppl 7):S21-S30.
43. 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: 625-628.
44. Sharma R, Francis DP, Pitt B, et al. Haemoglobin predicts survival in patients with chronic heart failure: a substudy of the ELITE II trial. *Eur Heart J*. 2004;25:1021-1028.
45. Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med*. 2006;355:2085-2098.
46. 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;369:381-388.
47. 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;355:2071-2084.
48. Henke M, Laszig R, Rube C, et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. *Lancet*. 2003;362:1255-1260.
49. 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;48:1225-1227.
50. Beck-da-Silva L, Rohde LE, 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;13:14-17.

51. Silverberg DS, Wexler D, Blum M, et al. Aggressive therapy of congestive heart failure and associated chronic renal failure with medications and correction of anemia stops or slows the progression of both diseases. *Perit Dial Int*. 2001;21(suppl 3):S236-S240.
52. Silverberg DS, Wexler D, Blum M, et al. Effects of treatment with epoetin beta on outcomes in patients with anaemia and chronic heart failure. *Kidney Blood Press Res*. 2005;28: 41-47.
53. Mishra TK, Mishra SK, Mohanty NK, Rath PK. Prevalence, prognostic importance and therapeutic implications of anemia in heart failure. *Indian Heart J*. 2005;57:670-674.
54. Silverberg DS, Wexler D, Blum M, et al. The effect of correction of anaemia in diabetics and non-diabetics with severe resistant congestive heart failure and chronic renal failure by subcutaneous erythropoietin and intravenous iron. *Nephrol Dial Transplant*. 2003;18:141-146.
55. Mancini DM, Katz SD, Lang CC, et al. Effect of erythropoietin on exercise capacity in patients with moderate to severe chronic heart failure. *Circulation*. 2003;107:294-299.
56. 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;49:753-762.
57. Macdougall IC, Eckardt KU. Novel strategies for stimulating erythropoiesis and potential new treatments for anaemia. *Lancet*. 2006;368: 947-953.