Anemia in Chronic Heart Failure
Prevalence, Etiology, Clinical Correlates, and Treatment Options

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Anemia occurs commonly in patients with chronic heart failure (CHF) and has been proposed as a novel therapeutic target in this patient population. The present review will summarize the current knowledge of the prevalence, causative factors, and pathophysiological correlates of anemia in CHF. Potential risks and benefits of therapy with erythropoietic agents for the treatment of anemia in CHF will also be discussed.

Prevalence of Anemia in CHF

Estimates of the prevalence of anemia in patients with CHF and low ejection fraction range widely from 4% to 61% (median 18%).[1–15] Variability in estimated prevalence is partly attributable to use of inconsistent definitions of anemia in individual reports. The World Health Organization definition of anemia (hemoglobin concentration <13.0 g/dL in men and <12.0 g/dL in women) takes into account known gender differences in distribution of hemoglobin values,[16] whereas the National Kidney Foundation defines anemia as hemoglobin ≤12 g/dL in men and postmenopausal women.[17] These standard definitions of anemia are not based on well-established physiological or population norms. Published reports in CHF populations have used these and other study-specific definitions of anemia (including other arbitrary or statistically defined hemoglobin and hematocrit categories and administrative diagnostic codes from hospital records). Despite these inconsistencies in the definition of anemia cases, most studies indicate that the prevalence of anemia is increased in CHF populations with comorbid kidney disease, advanced age, and more severe symptoms (range, 30% to 61%) when compared with less symptomatic ambulatory populations (range, 4% to 23%). In patients with CHF and preserved ejection fraction, the few published reports indicate that anemia is also highly prevalent in this group.[18–20]

Underlying Cause of Anemia in CHF

Anemia occurs when there is a deficiency in new erythrocyte production relative to the rate of removal of aged erythrocytes. Erythropoietin, a 30.4-kDa glycoprotein growth factor produced primarily by kidney, is the key component of the homeostatic system for regulation of red blood cell mass and tissue oxygen delivery.[21–24] Erythropoietin prevents the programmed cell death of erythrocyte progenitor cells and thereby stimulates their proliferation, maturation, and terminal differentiation.[23] Any abnormality that reduces renal secretion of or bone marrow response to erythropoietin may result in anemia.

Iron deficiency is present in <30% of anemic patients with CHF, so the majority of observed anemia is normocytic, often classified as anemia of chronic disease. Clinical characteristics commonly associated with increased risk of anemia in CHF populations are listed in the Table. Although risk factors for anemia identified in cross-sectional studies do not provide evidence of a causal link, these observations suggest that several distinct mechanisms may commonly contribute to anemia in patients with CHF. Several of the most important potential causal pathways will be discussed briefly below and are summarized in Figure 1.

Chronic kidney disease is a common comorbidity in patients with CHF and is a strong independent predictor of increased risk of anemia in several studies. In chronic kidney disease populations without heart failure, moderate to severe kidney disease (defined as glomerular filtration rate [GFR] <60 mL/min) is associated with diminished erythropoietin production and a progressive decrease in hemoglobin values that is linearly related to reduction in GFR.[25] The estimated prevalence of at least moderate chronic kidney disease (defined as GFR <60 mL/min) in CHF populations is 20% to 40%.[4,9,26,27]

Anemia is frequently associated with decreased body mass index in published reports, a finding that suggests that patients with cachexia are at greater risk for anemia. Serum levels of proinflammatory cytokines are increased in cachectic patients with CHF and may contribute to development of anemia by several mechanisms. Proinflammatory cytokines including tumor necrosis factor-α (TNF-α), interleukin-1, and interleukin-6 have been shown to disrupt multiple aspects of erythropoiesis, including reduction of renal erythropoietin secretion, suppression of erythropoietin activity in red blood cell precursors in the bone marrow level, and reduction of bioavailability of iron stores for hemoglobin synthesis.[28–31] Proinflammatory cytokines also increase levels of the liver-derived peptide hormone, hepcidin.[32,33] Hepcidin interacts with ferroportin and other iron transport proteins in the enterocyte to inhibit gut iron absorption and thereby reduces iron bioavailability for hemoglobin synthesis.[32,33] In a mouse

Clinical Characteristics Associated With Increased Risk of Anemia

Increasing age

Female gender

Chronic kidney disease (increased serum creatinine or decreased GFR)

Decreased body mass index

Use of ACE inhibitors

Increased jugular venous pressure

Lower-extremity edema

model of heart failure induced by myocardial infarction, anemia was linked to activation of the TNF-α/Fas signaling pathway.[34] The number of bone marrow progenitor cells and the proliferative capacity of these cells were reduced by 40% to 50% in heart failure mice when compared with control animals. A 3-fold increase in apoptosis among progenitor cells in heart failure mice was significantly correlated with the increase of TNF-α/Fas expression in bone marrow natural killer and T cells.[34] In patients with CHF, increased levels of proinflammatory cytokines (TNF-α and soluble TNF receptors) or other blood markers of inflammation (C-reactive protein) are inversely related to the hemoglobin level.[35]

The renin-angiotensin system plays an integral role in the normal regulation of plasma volume and red blood cell volume. Increased angiotensin II signaling in the kidney alters peritubular oxygen tension, a key regulatory factor for erythropoietin secretion.[21,24] Reduced oxygen tension in the peritubular fibroblasts of the renal cortex is associated with increased intracellular concentrations of reactive oxygen species, which, in turn, increases activation of hypoxia inducible factor-1 (HIF-1) and erythropoietin gene expression.[36] Angiotensin II increases erythropoietin secretion by reducing renal blood flow and increasing proximal tubular reabsorption.[21] Angiotensin II may also have direct stimulatory effects on bone marrow erythrocyte precursors.[37] Erythropoietin levels are modestly increased in patients with CHF in proportion to measures of activation of the renin-angiotensin system.[38] Inhibition of the renin-angiotensin system with either ACE inhibitors or angiotensin receptor blockers is associated with decreased erythropoietin production and reduced hemoglobin levels.[12,39,40] ACE also catalyzes the breakdown of Ac-SDKP, a tetrapeptide inhibitor of erythropoiesis. In ACE inhibitor–treated anemic CHF subjects with low serum ACE activity, Ac-SDKP levels are increased when compared with nonanemic CHF subjects.[41] Serum taken from anemic patients with CHF with high levels of Ac-SDKP inhibited formation of erythroid precursors in culture when compared with serum from nonanemic CHF or healthy control subjects. The effects of ACE inhibition on hematocrit are complex as ACE inhibition may decrease red cell production and also reduce plasma volume (see discussion on hemodilution below). In clinical trials, pharmacological inhibition of the renin-angiotensin system is associated with small but statistically significant reduction in hemoglobin levels.[12,40,42]

Anemia is frequently associated with clinical signs and symptoms of congestion, a finding that suggests that plasma volume expansion may contribute to anemia in CHF by a process of hemodilution. In 37 ambulatory nonedematous anemic patients with CHF, a radiolabeled albumin technique for direct measurement of plasma volume demonstrated 46% of the patients with low hematocrit values had normal red blood cell volume such that the anemia was entirely attributable to expanded plasma volume and consequent hemodilution.[3] Patients with hemodilution were clinically similar to patients with reduced red blood cell volume but were at greater risk for mortality during follow-up. The impact of hemodilution on treatment approaches in anemic patients with CHF is uncertain. Administration of erythropoietic agents to increase red blood mass in hemodilution patients could further increase total blood volume with possible adverse clinical consequences. Alternatively, it is possible that more aggressive treatment with diuretics could reduce plasma volume and effectively correct anemia in hemodilution patients.

Pathophysiological Consequences of Anemia

Severe reduction in hemoglobin (to 4 to 5 g/dL) is associated with sodium and water retention, reduction of renal blood flow and glomerular filtration rate, and evidence of neurohormonal activation in the absence of organic heart disease.[43] These cardiorenal responses may be attributable to the effects
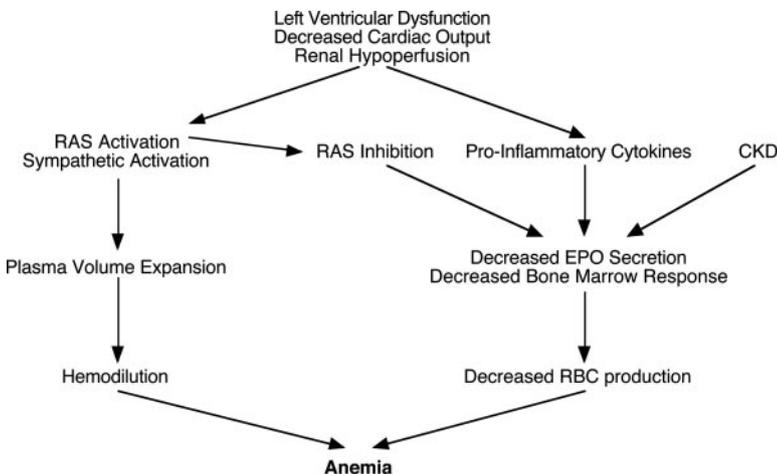

Figure 1. Potential causes of anemia in chronic heart failure.

of severe anemia on blood viscosity, oxygen tension in the microvasculature, and nitric oxide availability.[44,45] Lesser degrees of anemia may contribute to neurohormonal activation and disease progression in patients with CHF.[46] In patients with β-thalassemia syndromes, heart failure is a common complication that is likely mediated by the hemodynamic and neurohormonal effects of severe chronic anemia and iron overload secondary to chronic transfusion requirements.[47] Aggressive iron chelation therapy greatly reduces but does not eliminate the risk of heart failure in these patients.

Hemoglobin content in blood is an important determinant of oxygen delivery to skeletal muscle during exercise. Patients with CHF lack normal physiological reserve to compensate for decreased hemoglobin and may manifest decreased aerobic capacity in response to mild degrees of anemia.[48] Several investigators have reported association between reduced hemoglobin and greater functional impairment as defined by New York Heart Association classification.[3,15,49] Kalra and colleagues[50] reported a linear relation between reduced hemoglobin values and peak oxygen consumption in anemic patients with CHF with hemoglobin <13.0 g/dL.

Cardiac mass increased by 25% in a rat model of chronic anemia.[51] An inverse relation between hemoglobin value or hematocrit value and left ventricular hypertrophy has also described in clinical studies of patients with dialysis-dependent and predialysis chronic kidney disease.[52] In a subgroup of patients with CHF enrolled in the Randomized Etanercept North American Strategy to Study Antagonism of Cytokines (RENAISSANCE) trial with available cardiac MRI data, a 1-g/dL increase in hemoglobin was associated with a 4.1-g/m^2 decrease in left ventricular mass over 24 weeks.[49] This observation was independent of study drug treatment and does not provide evidence of a causal relation between changes in hemoglobin levels and changes in left ventricular mass. In two randomized trials of patients with chronic kidney disease, increased hemoglobin in response to erythropoietic agents was not associated with reduction in left ventricular hypertrophy.[53,54]

Anemia and Clinical Outcomes

Reduced hemoglobin in patients with CHF has been repeatedly shown to be independently associated with increased risk of hospitalization and all-cause mortality.[2–6,8,9,11–13,15,19,42,49] These findings in a diverse array of CHF populations are remarkably concordant and generally suggest a linear association between reduced hemoglobin and increased mortality risk. In studies that analyzed hemoglobin as a continuous variable, a 1-g/dL decrease in hemoglobin was independently associated with significantly increased mortality risk (Figure 2). The potential mechanisms linking anemia to increased mortality risk in CHF have not been characterized but may be related to changes in ventricular loading conditions and cardiac structure, altered neurohormonal activation, or reduced free radical scavenging capacity. It is also possible that anemia is a marker of more severe underlying myocardial disease.
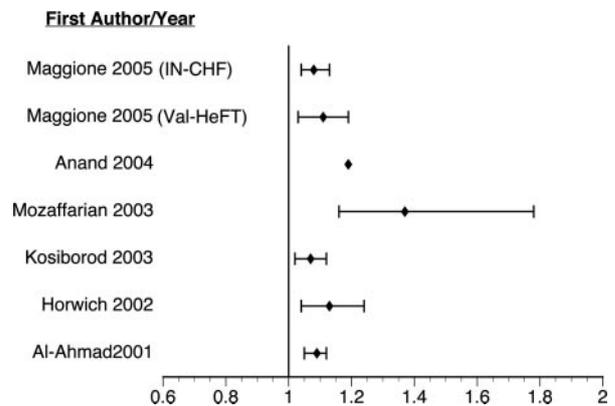

Figure 2. Estimates of hazard ratio (with 95% CI) for all-cause mortality associated with a decrease in hemoglobin of 1 g/dL. Estimates are derived from Cox proportional hazards models with adjustment for potential confounding variables. For studies with first author Al-Ahmad, Kosiborod and Mozaffarian, estimates of hazard ratio were derived from published data assuming a 1 g/dL decrease in hemoglobin is equivalent to a 3% decrease in hematocrit. The analysis by Mozaffarian included subjects with hematocrit ≤37.5%. Anand and colleagues did not report confidence intervals for their estimate of risk. Maggione and colleagues reported estimates of risk from 2 study populations enrolled in the IN-CHF registry and the Val-HeFT clinical trial.

Treatment Approaches

The clinical utility of blood transfusion in anemic cardiovascular disease populations is controversial. According to the guidelines from the American College of Physicians and the American Society of Anesthesiology, the "transfusion threshold" for patients without known risk factors for cardiac disease is a hemoglobin level in the range of 6 to 8 g/dL.[55] In 78 974 elderly patients hospitalized with acute myocardial infarction, blood transfusion was associated with a significantly lower 30-day mortality rate among patients with a hematocrit ≤30% on admission.[56] In 838 critically ill patients (26% with cardiovascular disease), maintaining hemoglobin at 10 to 12 g/dL did not provide additional benefits on 30-day mortality compared with maintaining hemoglobin at 7 to 9 g/dL.[57] Blood transfusion may be associated with other adverse effects including immunosuppression with increased risk of infection, sensitization to HLA antigens, and iron overload.[58,59] Given this profile of risks and benefits, transfusion may be considered as an acute treatment for severe anemia on an individualized basis but does not appear to be a viable therapeutic strategy for the long-term management of chronic anemia in CHF.

Although erythropoietin levels are modestly elevated in patients with CHF, the increase is less than that observed in other anemic populations.[27,38,60] Accordingly, anemia in CHF may be responsive to exogenous erythropoietin supplementation. The primary mechanism by which erythropoietin stimulates red blood cell production is inhibition of apoptosis of bone marrow erythrocyte progenitors.[23] The erythropoietin receptor is a member of the cytokine class I receptor superfamily.[61] Ligand binding of erythropoietin to the homodimeric erythropoietin receptor activates antiapoptotic signal transduction pathways.[23,62] Bone marrow erythroid progenitor cells escape from apoptosis and proliferate to result in

the growth and maturation of proerythroblasts and normoblasts. Subsequently, reticulocytosis occurs and hemoglobin concentration rises.

There are 3 currently available erythropoietic agents for treatment of anemia: epoetin-α, epoetin-β (both of which are recombinant human erythropoietin [rHuEpo]), and darbepoetin-α.[31] rHuEpo was first synthesized in 1985, 2 years after the erythropoietin gene was cloned, and was approved by the US Food and Drug Administration for clinical use for treatment of anemia in end-stage chronic kidney disease in 1988.[63] Early studies in dialysis-dependent patients with chronic kidney disease showed that intravenous or subcutaneous administration of 150 to 200 IU/kg per week (in 1 to 3 divided doses) increased hemoglobin concentrations to 10 to 12 g/dL in 83% to 90% of anemic patients with chronic kidney disease.[64] Plasma half-life of rHuEpo after intravenous dosing is 6 to 8 hours. Approximately 25% of the administered dose is absorbed after subcutaneous dosing, but the plasma half-life is increased to >24 hours.[65] The amount of subcutaneous rHuEpo needed to achieve hemoglobin targets in patients with chronic kidney disease is approximately 25% less than that needed for intravenous dosing.[65] Darbepoetin-α is a long-acting, N-linked supersialylated analog of human erythropoietin approved by the US Food and Drug Administration for the treatment of anemia in patients with chronic kidney disease in 2001.[30] Compared with both native and recombinant erythropoietin, it has stronger affinity for erythropoietin receptor and longer plasma half-life of approximately 48 hours, with consequent longer dosing intervals of 1 to 2 weeks during maintenance therapy.[66,67]

The effect of rHuEpo treatment on anemic patients with CHF was first reported by Silverberg and his colleagues.[1] In an open-label study design, 26 anemic chronic HF patients (NYHA class III–IV and hemoglobin <12 g/dL) were treated with subcutaneous rHuEpo (mean dose, 5277 IU/wk) and intravenous iron sucrose (mean dose, 185 mg/mo) with 4 to 15 months of follow-up duration (mean, 7 months). rHuEpo therapy increased mean hemoglobin from 10.2 to 12.1 g/dL and was associated with improved NYHA function class (3.7 ± 0.5 at baseline to 2.7 ± 0.7, $P<0.05$), increased left ventricular ejection fraction ($28\pm5\%$ at baseline to $35\pm8\%$, $P<0.001$), and reduced need for oral and intravenous furosemide.[1] The same investigators subsequently reported a randomized open-label trial with a mean follow-up duration of 8 months to compare the effects of partial correction of anemia with subcutaneous rHuEpo and intravenous iron sucrose therapy versus usual care in 32 patients with severe CHF and anemia (NYHA class III–IV and hemoglobin <11.5 g/dL).[68] When compared with usual care, the rHuEpo therapy (4000 IU 1 to 3 times weekly subcutaneously plus intravenous iron sucrose 200 mg every 2 weeks) significantly increased the hemoglobin level (10.3 to 12.9 g/dL versus 10.9 to 10.8 g/dL, $P<0.0001$), improved NYHA functional class (rHuEpo 3.8 ± 0.4 to 2.2 ± 0.7 versus usual care 3.5 ± 0.7 to 3.9 ± 0.3, $P<0.0001$), and decreased hospitalization days (rHuEpo 13.8 ± 7.2 to 2.9 ± 6.6 days versus usual care 9.9 ± 4.8 versus 15.5 ± 9.8 days, $P<0.0001$).[68] An uncontrolled clinical series from the same investigators demonstrated comparable clinical benefits of rHuEpo in 179 patients

with CHF and concomitant predialysis chronic kidney disease.[69] Mancini and colleagues[70] conducted a single-blinded, randomized, placebo-controlled trial of rHuEpo therapy in 26 patients with advanced CHF and anemia (hematocrit <35%). Patients received subcutaneous rHuEpo 5000 IU 3 times per week adjusted to raise hematocrit to >45% for up to 3 months or a single subcutaneous injection of saline. Supplemental oral iron and folate were also given to the patients who received rHuEpo therapy. Compared with the placebo group, rHuEpo therapy was associated with significant increases in hemoglobin (11.0 ± 0.5 to 14.3 ± 1.0 g/dL, $P<0.05$), peak oxygen uptake (11.0 ± 1.8 to 12.7 ± 2.8 mL/min per kilogram, $P<0.05$), and treadmill exercise duration (590 ± 107 to 657 ± 119 seconds, $P<0.004$). The increases in hemoglobin levels were linearly associated with the increase in peak oxygen uptake ($r=0.53$, $P<0.02$).[70] Subjects with both hemodilution anemia and true anemia with reduced red blood cell volume appeared to derive comparable improvement in exercise capacity in response to rHuEpo therapy. In the hemodilution subgroup with expanded plasma volume, the rise in measured hematocrit in response to rHuEPO treatment was primarily due to a decrease in plasma volume. As diuretic dosing did not change during the study, this finding suggests that erythropoietin has direct or indirect effects on renal regulation of plasma volume.

The pharmacokinetic and pharmacodynamic profile of darbepoetin-α was compared in 33 anemic CHF patients (hemoglobin ≤12.5 g/dL) versus 30 healthy subjects.[71] Darbepoetin-α administered once monthly at doses of 2.0 μg/kg or higher produced a sustained increase in hemoglobin concentration in anemic patients with CHF without severe drug-related adverse events.[71] The effect of treatment with darbepoetin-α (0.7 μg/kg subcutaneously every 2 weeks for 26 weeks) on exercise tolerance in 41 anemic patients with CHF (hemoglobin 9 to 12 g/dL) was evaluated in a randomized placebo controlled trial.[72] An abstract report of the study findings indicates favorable effects of darbepoetin-α on exercise duration and quality of life when compared with placebo.[72] A larger double-blinded, placebo-controlled, randomized trial, Studies of Anemia in Heart Failure Trial (STAMINA HeFT), was undertaken to determine whether increased hemoglobin in response to darbepoetin-α can improve exercise capacity and quality of life in 300 anemic patients with CHF.[73] The study has completed enrollment, but results have not yet been published.

Potential Risks of Erythropoietic Therapy

Erythropoietic agents are associated with increased risk of thrombosis. Increased thrombotic risk may be partly attributable to effects of increased hemoglobin levels on blood viscosity or platelet–erythrocyte interactions or to direct effects of erythropoietin in platelets or vascular endothelial cells.[74–76] Clinical studies on the incidence of thrombotic events associated with chronic rHuEpo therapy in anemic patients with end-stage renal disease on dialysis have reported mixed findings.[77–79] In the largest randomized clinical trial to date, Besarab and colleagues[77] compared the effects of treatment with rHuEpo to a low target hematocrit of 30% versus a normal range target hemoglobin of 42% in 1233

patients with hemodialysis-dependent end-stage chronic kidney disease and comorbid heart disease. This study was terminated prematurely because of a trend toward increased relative risk of death or nonfatal myocardial infarction in the group assigned to the normal hemoglobin target when compared with group assigned to the target hematocrit of 30% (relative risk, 1.3, 95% CI, 0.9 to 1.9). The mechanisms underlying this observation are uncertain, as within each treatment group, higher hemoglobin values were associated with reduced risk. In a retrospective study of anemic patients with cervical cancer, chronic rHuEpo therapy was associated with increased risk of deep vein thrombosis that was independent of hematocrit.[80] rHuEPO therapy has also been associated with increased risk of all-cause mortality in 2 randomized, placebo-controlled trials of patients with breast cancer and head and neck cancer.[81,82] Thrombotic events were not common causes of death in these studies. Although the findings in chronic kidney disease and cancer populations may not be directly pertinent to patients with CHF, these findings raise concerns and emphasize the need for additional trials to determine the long-term safety and efficacy of erythropoietic agents in the CHF population. In the small clinical trials of anemic patients with CHF summarized above, no thrombotic events or other adverse effects of erythropoietic agents have been reported in approximately 300 patients.[1,68–70,72] Antiplatelet and anticoagulant medications commonly prescribed in patients with CHF may mitigate prothrombotic effects of erythropoietic agents.

Chronic rHuEPO therapy is frequently associated with increased blood pressure.[83,84] Increased blood pressure during chronic erythropoietic therapy may be attributable to increased blood viscosity due to increased red cell mass, altered neurohormonal milieu, and direct effects on microvascular structure and function.[84,85] In patients with chronic kidney disease, risk factors for hypertension include rapid increase in hematocrit during therapy, a low baseline hematocrit before rHuEpo administration, high doses and intravenous route of rHuEPO administration, the presence of native kidneys, and a genetic predisposition to hypertension.[85] In the study of anemic subjects with CHF by Mancini and colleagues,[70] treatment with rHuEPO did not change blood pressure at rest or during exercise and did not change forearm vascular resistance as measured with venous occlusion plethysmography.

Other rare serious side effects reported with rHuEPO therapy include seizures and pure red cell aplasia caused by antibody formation against erythropoietin.

Role of Iron Supplementation

Although frank iron deficiency is apparent in only a minority of anemic patients with CHF, functional iron deficiency, which is characterized by reduced availability of tissue iron stores for erythropoiesis, may be a common problem in the CHF population.[86] Available small studies in anemic patients with CHF demonstrated significant increases in hemoglobin values in response to rHuEpo with intravenous or oral iron supplementation.[69,70] Current guidelines from the National Kidney Foundation recommend use of intravenous iron to maintain serum ferritin level of 100 to 800 ng/mL and a transferrin saturation 20% to 50% to optimize the clinical response to erythropoietic agents.[17] Although intravenous iron sucrose and iron gluconate preparations are not associated with anaphylaxis and are generally well tolerated in chronic kidney disease populations, there are concerns that excess iron stores may be associated with increased risk of infection and cardiovascular events.[17,87,88] Additional work is needed to determine the safety and efficacy of intravenous iron supplementation in anemic patients with CHF with functional iron deficiency.

Recommendations for Current Practice

There is little discussion of assessment and treatment options for anemia in recent CHF clinical guidelines.[89,90] On the basis of available data, we recommend serial measurement of hemoglobin in patients with CHF at 6-month intervals in order to identify the subset of patients with anemia who may benefit from further assessment and treatment. In patients with anemia (defined by World Health Organization criteria), further assessment including evaluation for iron or other nutritional deficiencies and estimation of glomerular filtration rate should be performed. For the subpopulation of patients with CHF with moderate-to-severe anemia (hemoglobin <11 g/dL) and concomitant moderate to severe chronic kidney disease (estimated glomerular filtration rate ≤60 mL/min), current guidelines of the National Kidney Foundation recommend treatment with erythropoietic agents and supplemental iron to a target hemoglobin of 12 g/dL.[17,27] The primary goal of treatment is to improve quality of life; there are no clinical outcome trials in predialysis patients with chronic kidney disease that support use of erythropoietic agents. Given the absence of data on long-term clinical outcomes in patients with CHF and the concerns raised by the finding of increased mortality rates in other anemic populations, treatment with erythropoietic agents in patients with CHF with less severe degrees of anemia and preserved renal function is not recommended until more data on safety and efficacy is available.[91]

Future Directions

The erythropoietin receptor is present in a variety of cells not directly involved in erythropoiesis, including endothelial cells, vascular smooth muscle cells, neuronal cells, and myocardium.[92,93] Cytoprotective antiapoptotic effects of erythropoietin have been reported in animal models of central nervous system injury and in experimental models of myocardial hypoxia or ischemia-reperfusion injury.[93–96] Because ongoing apoptosis has been postulated to be an important mechanism of myocyte loss in CHF, the antiapoptotic effects of rHuEpo in cardiovascular tissues suggest a potential therapeutic role beyond the treatment of anemia.[97] Certain derivatives of naturally occurring erythropoietin (carbamylated erythropoietin and erythropoietin mutants) do not bind to the classical erythropoietin receptor nor promote erythropoiesis and yet have been shown to confer neuroprotection in experimental models of stroke, spinal cord compression, and diabetic neuropathy.[98] These derivatives appear to mediate cytoprotective effects via specific binding to a heterodimeric receptor complex consisting of the erythropoietin receptor and common β-receptor.[99,100] Derivatives designed to target

this heteroreceptor could potentially provide therapeutic cytoprotection without stimulating erythropoiesis in nonanemic CHF or other cardiovascular disease populations.

Conclusions

Preliminary studies suggest potential beneficial effects of treatment of anemia with erythropoietic agents on exercise capacity and quality of life. Further studies are needed to determine the optimal threshold for initiation of treatment and target hemoglobin during therapy, optimum dosing regimen and choice of erythropoietic agent, the role of intravenous or oral iron supplementation, and long-term safety of erythropoietic agents in anemic patients with CHF.

Disclosures

References

1. Silverberg DS, Wexler D, Blum M, Keren G, Sheps D, Leibovitch E, Brosh D, Laniado S, Schwartz D, Yachnin T, Shapira I, Gavish D, Baruch R, Koifman B, Kaplan C, Steinbruch S, Iaina A. 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.

2. Al-Ahmad A, Rand WM, Manjunath G, Konstam MA, Salem DN, Levey AS, Sarnak MJ. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. *J Am Coll Cardiol*. 2001;38:955–962.

3. Androne AS, Katz SD, Lund L, LaManca J, Hudaihed A, Hryniewicz K, Mancini DM. Hemodilution is common in patients with advanced heart failure. *Circulation*. 2003;107:226–229.

4. 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.

5. 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.

6. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Borenstein 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;39:1780–1786.

7. Cromie N, Lee C, Struthers AD. Anaemia in chronic heart failure: what is its frequency in the UK and its underlying causes? *Heart*. 2002;87:377–378.

8. Kosiborod M, Smith GL, Radford MJ, Foody JM, Krumholz HM. The prognostic importance of anemia in patients with heart failure. *Am J Med*. 2003;114:112–119.

9. 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;13:1928–1936.

10. Tanner H, Moschovitis G, Kuster GM, Hullin R, Pfiiffner D, Hess OM, Mohacsi P. The prevalence of anemia in chronic heart failure. *Int J Cardiol*. 2002;86:115–121.

11. Felker GM, Gattis WA, Leimberger JD, Adams KF, Cuffe MS, Gheorghiade M, O'Connor CM. Usefulness of anemia as a predictor of death and rehospitalization in patients with decompensated heart failure. *Am J Cardiol*. 2003;92:625–628.

12. Anand IS, Kuskowski MA, Rector TS, Florea VG, Glazer RD, Hester A, Chiang YT, Aknay N, Maggioni AP, Opasich C, Latini R, Cohn JN. 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.

13. Szachniewicz J, Petruk-Kowalczyk J, Majda J, Kaczmarek A, Reczuch K, Kalra PR, Piepoli MF, Anker SD, Banasiak W, Ponikowski P.
Anaemia is an independent predictor of poor outcome in patients with chronic heart failure. *Int J Cardiol*. 2003;90:303–308.

14. Wexler D, Silverberg D, Sheps D, Blum M, Keren G, Iaina A, Schwartz D. Prevalence of anemia in patients admitted to hospital with a primary diagnosis of congestive heart failure. *Int J Cardiol*. 2004;96:79–87.

15. Maggioni AP, Opasich C, Anand I, Barlera S, Carbonieri E, Gonzini L, Tavazzi L, Latini R, Cohn J. 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.

16. McCullough PA, Lepor NE Anemia: a modifiable risk factor for heart disease. Introduction. *Rev Cardiovasc Med*. 2005;6(Suppl 3):S1–S3.

17. IV. NKF-K/DOQI Clinical Practice Guidelines for Anemia of Chronic Kidney Disease: update 2000. *Am J Kidney Dis*. 2001;37:S182–S238.

18. Berry C, Hogg K, Norrie J, Stevenson K, Brett M, McMurray J. Heart failure with preserved left ventricular systolic function: a hospital cohort study. *Heart*. 2005;91:907–913.

19. Brucks S, Little WC, Chao T, Rideman RL, Upadhya B, Wesley-Farrington D, Sane DC. Relation of anemia to diastolic heart failure and the effect on outcome. *Am J Cardiol*. 2004;93:1055–1057.

20. Klapholz M, Maurer M, Lowe AM, Messineo F, Meisner JS, Mitchell J, Kalman J, Phillips RA, Steingart R, Brown EJ Jr, Berkowitz R, Moskowitz R, Soni A, Mancini D, Bijou R, Sehhat K, Varshneya N, Kukin M, Katz SD, Sleeper LA, Le Jemtel TH. Hospitalization for heart failure in the presence of a normal left ventricular ejection fraction: results of the New York Heart Failure Registry. *J Am Coll Cardiol*. 2004;43:1432–1438.

21. Katz SD. Mechanisms and treatment of anemia in chronic heart failure. *Congest Heart Fail*. 2004;10:243–247.

22. Bauer C, Kurtz A. Oxygen sensing in the kidney and its relation to erythropoietin production. *Annu Rev Physiol*. 1989;51:845–856.

23. Jelkmann W. Molecular biology of erythropoietin. *Intern Med*. 2004;43:649–659.

24. Donnelly S. Why is erythropoietin made in the kidney? The kidney functions as a critmeter. *Am J Kidney Dis*. 2001;38:415–425.

25. McCullough PA, Lepor NE. Piecing together the evidence on anemia: the link between chronic kidney disease and cardiovascular disease. *Rev Cardiovasc Med*. 2005;6(suppl 3):S4–S12.

26. Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. *J Am Coll Cardiol*. 2000;35:681–689.

27. Foley RN. Myocardial disease, anemia, and erythrocyte-stimulating proteins in chronic kidney disease. *Rev Cardiovasc Med*. 2005;6(Suppl 3):S27–S34.

28. 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;103:2055–2059.

29. Torre-Amione G, Bozkurt B, Deswal A, Mann DL. An overview of tumor necrosis factor alpha and the failing human heart. *Curr Opin Cardiol*. 1999;14:206–210.

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

31. Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med*. 2005;352:1011–1023.

32. Nemeth E, Tuttle MS, Powelson J, Vaughn MB, Donovan A, Ward DM, Ganz T, Kaplan J. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. *Science*. 2004;306:2090–2093.

33. Ganz T. Hepcidin, a key regulator of iron metabolism and mediator of anemia of inflammation. *Blood*. 2003;102:783–788.

34. 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:R166–172.

35. Rauchhaus M, Doehner W, Francis DP, Davos C, Kemp M, Liebenthal C, Niebauer J, Hooper J, Volk HD, Coats AJ, Anker SD. Plasma cytokine parameters and mortality in patients with chronic heart failure. *Circulation*. 2000;102:3060–3067.

36. Ebert BL, Bunn HF. Regulation of the erythropoietin gene. *Blood*. 1999;94:1864–1877.

37. Mrug M, Stopka T, Julian BA, Prchal JF, Prchal JT. Angiotensin II stimulates proliferation of normal early erythroid progenitors. *J Clin Invest*. 1997;100:2310–2314.

38. 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;233:125–130.

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;226:257–260.

40. Ishani A, Weinhandl E, Zhao Z, Gilbertson DT, Collins AJ, Yusuf S, Herzog CA. 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;45:391–399.

41. van der Meer P, Lipsic E, Westenbrink BD, van de Wal RM, Schoemaker RG, Vellenga E, van Veldhuisen DJ, Voors AA, van Gilst WH. Levels of hematopoiesis inhibitor N-acetyl-seryl-aspartyl-lysyl-proline partially explain the occurrence of anemia in heart failure. *Circulation*. 2005;112:1743–1747.

42. 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;25:1021–1028.

43. 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;70:357–362.

44. 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;25:1402–1407.

45. 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.

46. Anand IS. Pathogenesis of anemia in cardiorenal disease. *Rev Cardiovasc Med*. 2005;6(Suppl 3):S13–S21.

47. Hahalis G, Alexopoulos D, Kremastinos DT, Zoumbos NC. Heart failure in beta-thalassemia syndromes: a decade of progress. *Am J Med*. 2005;118:957–967.

48. Katz SD, Maskin C, Jondeau G, Cocke T, Berkowitz R, LeJemtel T. Near-maximal fractional oxygen extraction by active skeletal muscle in patients with chronic heart failure. *J Appl Physiol*. 2000;88:2138–2142.

49. Anand I, McMurray JJ, Whitmore J, Warren M, Pham A, McCamish MA, Burton PB. Anemia and its relationship to clinical outcome in heart failure. *Circulation*. 2004;110:149–154.

50. Kalra PR, Bolger AP, Francis DP, Genth-Zotz S, Sharma R, Ponikowski PP, Poole-Wilson PA, Coats AJ, Anker SD. Effect of anemia on exercise tolerance in chronic heart failure in men. *Am J Cardiol*. 2003;91:888–891.

51. Rakusan K, Cicutti N, Kolar F. Effect of anemia on cardiac function, microvascular structure, and capillary hematocrit in rat hearts. *Am J Physiol Heart Circ Physiol*. 2001;280:H1407–H1414.

52. Levin A. Anemia and left ventricular hypertrophy in chronic kidney disease populations: a review of the current state of knowledge. *Kidney Int Suppl*. 2002:35–38.

53. Parfrey PS, Foley RN, Wittreich BH, Sullivan DJ, Zagari MJ, Frei D. Double-blind comparison of full and partial anemia correction in incident hemodialysis patients without symptomatic heart disease. *J Am Soc Nephrol*. 2005;16:2180–2189.

54. Roger SD, McMahon LP, Clarkson A, Disney A, Harris D, Hawley C, Healy H, Kerr P, Lynn K, Parnham A, Pascoe R, Voss D, Walker R, Levin A. Effects of early and late intervention with epoetin alpha on left ventricular mass among patients with chronic kidney disease (stage 3 or 4): results of a randomized clinical trial. *J Am Soc Nephrol*. 2004;15:148–156.

55. Practice Guidelines for blood component therapy: A report by the Am Society of Anesthesiologists Task Force on Blood Component Therapy. *Anesthesiology*. 1996;84:732–747.

56. Wu WC, Rathore SS, Wang Y, Radford MJ, Krumholz HM. Blood transfusion in elderly patients with acute myocardial infarction. *N Engl J Med*. 2001;345:1230–1236.

57. Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care: Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med*. 1999;340:409–417.

58. Vincent JL, Baron JF, Reinhart K, Gattinoni L, Thijs L, Webb A, Meier-Hellmann A, Nollet G, Peres-Bota D. Anemia and blood transfusion in critically ill patients. *JAMA*. 2002;288:1499–1507.

59. Goodnough LT, Brecher ME, Kanter MH, AuBuchon JP. Transfusion medicine: first of two parts–blood transfusion. *N Engl J Med*. 1999;340:438–447.

60. 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;44:63–67.

61. Youssoufian H, Longmore G, Neumann D, Yoshimura A, Lodish HF. Structure, function, and activation of the erythropoietin receptor. *Blood*. 1993;81:2223–2236.

62. Cheung JY, Miller BA. Molecular mechanisms of erythropoietin signaling. *Nephron*. 2001;87:215–222.

63. Winearls CG. Recombinant human erythropoietin: 10 years of clinical experience. *Nephrol Dial Transplant*. 1998;13(Suppl 2):3–8.

64. Eschbach JW, Abdulhadi MH, Browne JK, Delano BG, Downing MR, Egrie JC, Evans RW, Friedman EA, Graber SE, Haley NR, Korbet S, Krantz SB, Lundin AP, Nissenson AR, Ogden DA, Paganini ED, Rader B, Rutsky EA, Stivelman J, Stone WJ, Teschan P, van Stone JC, van Wyck DB, Zuckerman K, Adamson JW. Recombinant human erythropoietin in anemic patients with end-stage renal disease: results of a phase III multicenter clinical trial. *Ann Intern Med*. 1989;111:992–1000.

65. Fisher JW. Erythropoietin: physiology and pharmacology update. *Exp Biol Med (Maywood)*. 2003;228:1–14.

66. Locatelli F, Canaud B, Giacardy F, Martin-Malo A, Baker N, Wilson J. Treatment of anaemia in dialysis patients with unit dosing of darbepoetin alfa at a reduced dose frequency relative to recombinant human erythropoietin (rHuEpo). *Nephrol Dial Transplant*. 2003;18:362–369.

67. Macdougall IC, Matcham J, Gray SJ. Correction of anaemia with darbepoetin alfa in patients with chronic kidney disease receiving dialysis. *Nephrol Dial Transplant*. 2003;18:576–581.

68. Silverberg DS, Wexler D, Sheps D, Blum M, Keren G, Baruch R, Schwartz D, Yachnin T, Steinbruch S, Shapira I, Laniado S, Iaina A. 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;37:1775–1780.

69. Silverberg DS, Wexler D, Blum M, Tchebiner JZ, Sheps D, Keren G, Schwartz D, Baruch R, Yachnin T, Shaked M, Schwartz I, Steinbruch S, Iaina A. 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.

70. 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;107:294–299.

71. Cleland JG, Sullivan JT, Ball S, Horowitz JD, Agoram B, Rosser D, Yates W, Tin L, Fuentealba P, Burton PB. Once-monthly administration of darbepoetin alfa for the treatment of patients with chronic heart failure and anemia: a pharmacokinetic and pharmacodynamic investigation. *J Cardiovasc Pharmacol*. 2005;46:155–161.

72. Cleland JG, Coletta AP, Clark AL, Velavan P, Ingle L. Clinical trials update from the European Society of Cardiology Heart Failure meeting and the Am College of Cardiology: darbepoetin alfa study, ECHOS, and ASCOT-BPLA. *Eur J Heart Fail*. 2005;7:937–939.

73. Mitka M. Researchers probe anemia-heart failure link. *JAMA*. 2003;290:1835–1838.

74. Valles J, Santos MT, Aznar J, Martinez M, Moscardo A, Pinon M, Broekman MJ, Marcus AJ. Platelet-erythrocyte interactions enhance alpha(IIb)beta(3) integrin receptor activation and P-selectin expression during platelet recruitment: down-regulation by aspirin ex vivo. *Blood*. 2002;99:3978–3984.

75. Diaz-Ricart M, Etebanell E, Cases A, Lopez-Pedret J, Castillo R, Ordinas A, Escolar G. Erythropoietin improves signaling through tyrosine phosphorylation in platelets from uremic patients. *Thromb Haemost*. 1999;82:1312–1317.

76. Fuste B, Serradell M, Escolar G, Cases A, Mazzara R, Castillo R, Ordinas A, Diaz-Ricart M. Erythropoietin triggers a signaling pathway in endothelial cells and increases the thrombogenicity of their extracellular matrices in vitro. *Thromb Haemost*. 2002;88:678–685.

77. Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, Schwab SJ, Goodkin DA. 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;339:584–590.

78. Foley RN, Parfrey PS, Morgan J, Barre PE, Campbell P, Cartier P, Coyle D, Fine A, Handa P, Kingma I, Lau CY, Levin A, Mendelssohn

D, Muirhead N, Murphy B, Plante RK, Posen G, Wells GA. Effect of hemoglobin levels in hemodialysis patients with asymptomatic cardiomyopathy. *Kidney Int.* 2000;58:1325–1335.

79. Churchill DN, Muirhead N, Goldstein M, Posen G, Fay W, Beecroft ML, Gorman J, Taylor DW. Probability of thrombosis of vascular access among hemodialysis patients treated with recombinant human erythropoietin. *J Am Soc Nephrol.* 1994;4:1809–1813.

80. Wun T, Law L, Harvey D, Sieracki B, Scudder SA, Ryu JK. Increased incidence of symptomatic venous thrombosis in patients with cervical carcinoma treated with concurrent chemotherapy, radiation, and erythropoietin. *Cancer.* 2003;98:1514–1520.

81. Henke M, Laszig R, Rube C, Schafer U, Haase KD, Schilcher B, Mose S, Beer KT, Burger U, Dougherty C, Frommhold H. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. *Lancet.* 2003;362:1255–1260.

82. Leyland-Jones B, Semiglazov V, Pawlicki M, Pienkowski T, Tjulandin S, Manikhas G, Makhson A, Roth A, Dodwell D, Baselga J, Biakhov M, Valuckas K, Voznyi E, Liu X, Vercammen E. Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study. *J Clin Oncol.* 2005;23:5960–5972.

83. Mann JF. Hypertension and cardiovascular effects–long-term safety and potential long-term benefits of r-HuEPO. *Nephrol Dial Transplant.* 1995;10(Suppl 2):80–84.

84. Vaziri ND. Mechanism of erythropoietin-induced hypertension. *Am J Kidney Dis.* 1999;33:821–828.

85. Maschio G. Erythropoietin and systemic hypertension. *Nephrol Dial Transplant.* 1995;10(Suppl 2):74–79.

86. Cavill I. Intravenous iron as adjuvant therapy: a two-edged sword? *Nephrol Dial Transplant.* 2003;18(Suppl 8):viii24–viii28.

87. Day SM, Duquaine D, Mundada LV, Menon RG, Khan BV, Rajagopalan S, Fay WP. Chronic iron administration increases vascular oxidative stress and accelerates arterial thrombosis. *Circulation.* 2003; 107:2601–2606.

88. Sullivan JL. Iron therapy and cardiovascular disease. *Kidney Int Suppl.* 1999;69:S135–S137.

89. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, Tavazzi L, Smiseth OA, Gavazzi A, Haverich A, Hoes A, Jaarsma T, Korewicki J, Levy S, Linde C, Lopez-Sendon JL, Nieminen MS, Pierard L, Remme WJ. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. *Eur Heart J.* 2005;26:1115–1140.

90. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW, Antman EM, Smith SC Jr, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult–Summary Article: A Report of the Am College of Cardiology/Am Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): Developed in Collaboration With the Am College of Chest Physicians and the International Society for Heart and Lung Transplantation: Endorsed by the Heart Rhythm Society. *Circulation.* 2005;112:1825–1852.

91. Pfeffer MA, Solomon SD, Singh AK, Ivanovich P, McMurray JJ. Uncertainty in the treatment of anemia in chronic kidney disease. *Rev Cardiovasc Med.* 2005;6 Suppl 3:S35–41.

92. Wu H, Lee SH, Gao J, Liu X, Iruela-Arispe ML. Inactivation of erythropoietin leads to defects in cardiac morphogenesis. *Development.* 1999; 126:3597–3605.

93. Cerami A, Brines M, Ghezzi P, Cerami C, Itri LM. Neuroprotective properties of epoetin alfa. *Nephrol Dial Transplant.* 2002;17(Suppl 1):8–12.

94. Calvillo L, Latini R, Kajstura J, Leri A, Anversa P, Ghezzi P, Salio M, Cerami A, Brines M. Recombinant human erythropoietin protects the myocardium from ischemia-reperfusion injury and promotes beneficial remodeling. *Proc Natl Acad Sci U S A.* 2003;100:4802–4806.

95. Parsa CJ, Matsumoto A, Kim J, Riel RU, Pascal LS, Walton GB, Thompson RB, Petrofski JA, Annex BH, Stamler JS, Koch WJ. A novel protective effect of erythropoietin in the infarcted heart. *J Clin Invest.* 2003;112:999–1007.

96. Moon C, Krawczyk M, Ahn D, Ahmet I, Paik D, Lakatta EG, Talan MI. Erythropoietin reduces myocardial infarction and left ventricular functional decline after coronary artery ligation in rats. *Proc Natl Acad Sci U S A.* 2003;100:11612–11617.

97. Wencker D, Chandra M, Nguyen K, Miao W, Garantziotis S, Factor SM, Shirani J, Armstrong RC, Kitsis RN. A mechanistic role for cardiac myocyte apoptosis in heart failure. *J Clin Invest.* 2003;111:1497–1504.

98. Leist M, Ghezzi P, Grasso G, Bianchi R, Villa P, Fratelli M, Savino C, Bianchi M, Nielsen J, Gerwien J, Kallunki P, Larsen AK, Helboe L, Christensen S, Pedersen LO, Nielsen M, Torup L, Sager T, Sfacteria A, Erbayraktar S, Erbayraktar Z, Gokmen N, Yilmaz O, Cerami-Hand C, Xie QW, Coleman T, Cerami A, Brines M. Derivatives of erythropoietin that are tissue protective but not erythropoietic. *Science.* 2004;305: 239–242.

99. Brines M, Grasso G, Fiordaliso F, Sfacteria A, Ghezzi P, Fratelli M, Latini R, Xie QW, Smart J, Su-Rick CJ, Pobre E, Diaz D, Gomez D, Hand C, Coleman T, Cerami A. Erythropoietin mediates tissue protection through an erythropoietin and common beta-subunit heteroreceptor. *Proc Natl Acad Sci U S A.* 2004;101:14907–14912.

100. Fiordaliso F, Chimenti S, Staszewsky L, Bai A, Carlo E, Cuccovillo I, Doni M, Mengozzi M, Tonelli R, Ghezzi P, Coleman T, Brines M, Cerami A, Latini R. A nonerythropoietic derivative of erythropoietin protects the myocardium from ischemia-reperfusion injury. *Proc Natl Acad Sci U S A.* 2005;102:2046–2051.