The Deadly Triangle of Anemia, Renal Insufficiency, and Cardiovascular Disease: Implications for Prognosis and Treatment

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Recently there has been considerable interest in the associations between blood hemoglobin (Hb) level, renal function, and cardiovascular disease. Anemia is a common feature of end-stage renal disease, but it also accompanies lesser degrees of chronic kidney disease (CKD). The degree of anemia roughly approximates the severity of CKD. Anemia seen in diabetes has been linked to diabetic nephropathy; however, diabetes itself affects the hematologic system in several ways. Anemia is associated with left ventricular hypertrophy, cardiovascular morbidity, progressive loss of kidney function, and poor quality of life. Anemia seems to act as a mortality multiplier; that is, at every decrease in Hb below 12 g/dL, mortality increases in patients with CKD, cardiovascular disease, and those with both. Unlike blood transfusion, treatment of anemia with exogenous erythropoietin in patients with cardiorenal disease has shown promise in reducing morbidity and in improving survival and quality of life. Increasing the Hb level from less than 10 g/dL to 12 g/dL has resulted in favorable changes in left ventricular remodeling, improved ejection fraction, improved functional classification, and higher levels of peak oxygen consumption with exercise testing. Clinical trials are underway to test the role of erythropoietin in patients with CKD and in patients with heart failure.
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Key words: Anemia • Chronic kidney disease • Cardiovascular disease • Diabetes • Erythropoietin

Only recently have we begun to appreciate the implications of renal insufficiency, better termed chronic kidney disease (CKD), as regards adverse outcomes in patients with cardiovascular disease (CVD).[1–3]

Anemia is one of approximately two dozen metabolic/hematologic targets in CKD that might influence resultant CVD.[3] The purpose of this review is to focus on CKD and CVD scenarios in whose natural history anemia is thought to play an important role. In addition, the role of treating the "anemic condition" and moderating the risk associated with this condition will be explored.

In a patient with mild to moderate CKD, there is a greater probability of death due to cardiovascular disease than of development of end-stage renal disease.

Definition and Prevalence of Anemia

The most commonly used definition of anemia is put forth by the World Health Organization and calls for a hemoglobin (Hb) level less than 13 g/dL in men and less than 12 g/dL in women. Approximately 9% of the general adult population meets the definition of anemia at these levels. In general, anemia is present in 30% and 60% of patients with heart failure (HF) and significant CKD, respectively.[4] Hence, anemia is a common and easily identifiable potential therapeutic target.

Risk Factors for Anemia

Reduced Renal Function

Traditional CVD risk factors play a key role in the development of CKD, and vice versa. Particular attention has been paid to both type 1 and type 2 diabetes and their effects on the kidneys. It is now understood that the metabolic syndrome, a prediabetic state, can lead to CVD and CKD in the absence of overt diabetes.[5] It seems that atherosclerosis and all forms of CKD are markedly worsened by hypertension, smoking, and dyslipidemia (high low-density lipoprotein cholesterol and low high-density lipoprotein cholesterol).[6] Among the 8 million Americans with CKD not receiving renal replacement therapy, it is estimated that approximately 80% will succumb to CVD, including sudden death. In fact, there is a greater probability of death due to CVD than of the development of end-stage renal disease (ESRD) in a patient with mild to moderate CKD.[7,8] In a prospective cohort study with 1-year follow-up of 6427 patients with HF and coronary artery disease, the prevalence of CKD, defined as a creatinine clearance of less than 60 mL/min, was 39%.[9] A clear gradient of mortality was observed as renal function worsened, with 1-year mortality increasing by 0.2% for every μmol/L increase in serum creatinine (Figure 1). In an analysis of the Heart and Estrogen/Progestin Replacement Study of 702 patients with HF, renal insufficiency had the highest population-attributable risk for mortality compared with other risk factors, including diabetes, age greater than 70 years, New York Heart Association class, and atrial fibrillation.[10] Thus, CKD and CVD risk factors are inextricably linked in the CKD–CVD–anemia triangle. Among patients with CVD, particularly HF, the prevalence of anemia is approximately 30%.[11] Anemia is a common feature of ESRD, but it also accompanies lesser reductions in kidney function.[11] The degree of anemia roughly approximates the severity of kidney dysfunction and reduction in renal mass. This reduction in renal parenchyma creates a relative deficiency of erythropoietin (EPO), which will be discussed below.[11] Anemia is one of

Figure 1. *Risk of death is associated with level of creatinine clearance among women with heart failure and coronary artery disease. Data from the Heart and Estrogen/Progestin Replacement Study. Adapted from Bibbins-Domingo et al.[10]*

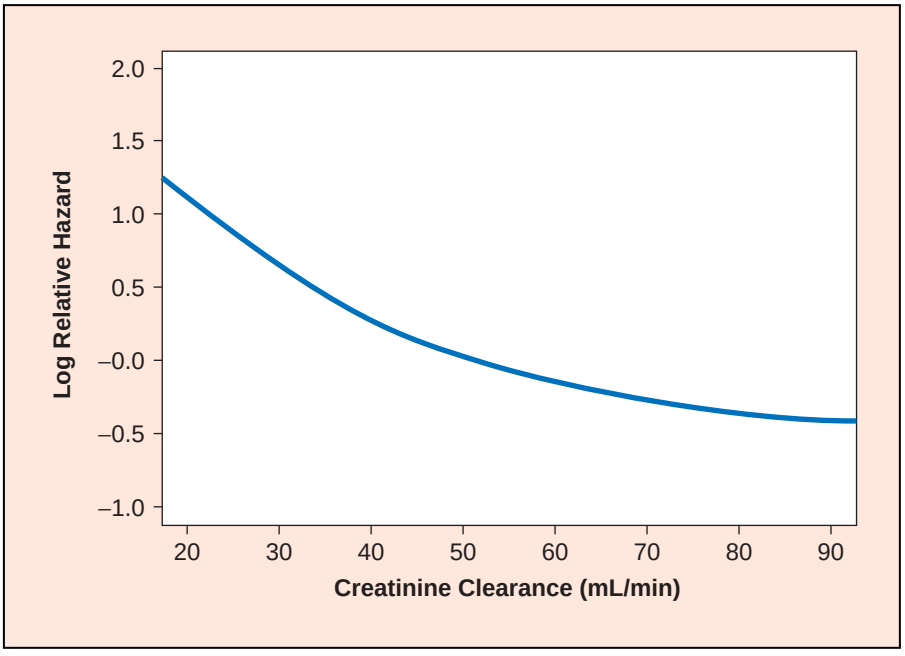


Table 1
All-Cause Mortality in Medicare Recipients Stratified by Anemia, Chronic Kidney Disease, and Heart Failure

Condition	Death (%)
Control	8.0
Anemia	16.6
HF	26.1
HF + anemia	34.6
CKD	16.4
CKD + anemia	27.3
HF + CKD	38.4
HF + CKD + anemia	45.6

HF, heart failure; CKD, chronic kidney disease; Data from Gilbertson DT et al *J Am Soc Nephrol.* 2002;13 suppl. Abstract SA 848.

the most characteristic and visible manifestations of CKD and contributes to multiple adverse outcomes, in part owing to decreased tissue oxygen delivery and utilization.[12,13] A significant correlation between hematocrit (Hct) and creatinine clearance (CrCl) has been found to occur at CrCl rates of less than 45 mL/min/1.73 m^2 in several studies (Figure 2).[14,15] Anemia in the presence of CKD and HF has been associated with graded increases in mortality (Table 1). As the Hb level is reduced, mortality rates rise in a multiplicative fashion (Figure 3).[16] As shown in Figure 4, anemia is part of a complicated cycle involving multiple mechanisms that all work to worsen both heart and kidney function and ultimately increase mortality from both cardiac and noncardiac causes.[17]

Diabetes

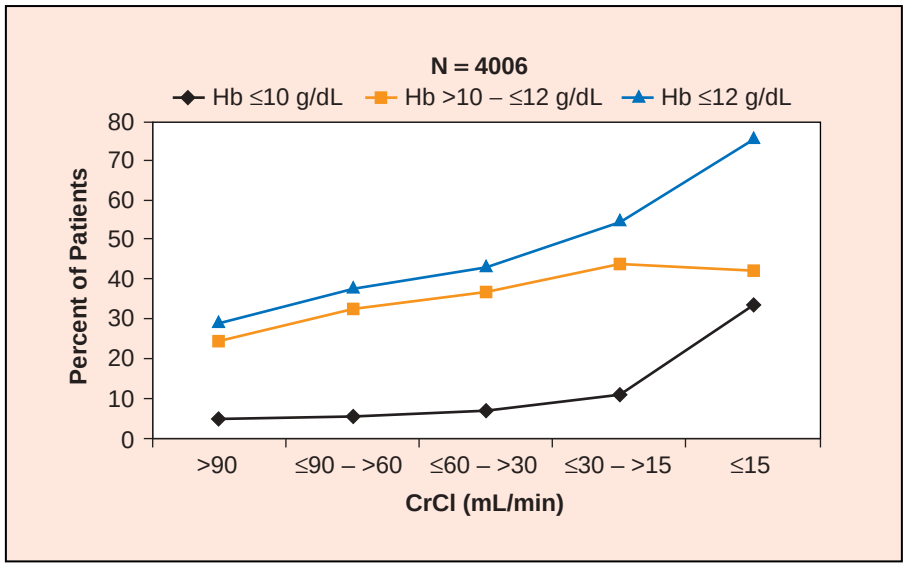
Diabetes mellitus is one of the major risk factors for CKD and is the leading cause of ESRD.[18,19] Anemia seen in diabetes has been thought to relate to advanced uremia in diabetic nephropathy; however, diabetes affects the hematologic system in several ways.[20] Recent studies have linked anemia with relatively low serum EPO in diabetes mellitus, even in persons without advanced renal disease or overt uremia.[21–28] The kidney produces 90% of EPO in the body, whereas the liver produces 10%.[29] The main stimulus for production is hypoxia in those with normal renal function. Normal plasma EPO levels range between 10 IU/mL and 30 IU/mL; however, during anemic periods, these levels might be elevated up to 100 IU/mL. In patients with CKD and HF, there seems to be a relative EPO deficiency, with an inappropriately low EPO level for the measured blood Hb level.[27,28]

In recent studies, investigators have examined anemia among persons with diabetes but without advanced renal disease or overt uremia.[19–27] In most of these studies, inappropriately low levels of EPO in persons with diabetes mellitus have been reported. For example, Bosman and colleagues[23] found that 13 of 27 type 1 diabetics with nephropathy and serum creatinine levels of less than 2 mg/dL had unexplained anemia with relatively low EPO levels, compared with none of 26 nondiabetic patients with glomerulonephritis.

Pathophysiology of Chronic Anemia in Cardiorenal Disease

The exact cause of anemia in patients with cardiorenal disease is not known; however, several factors have been implicated in the development of what seems to be an inadequate response from the bone

Figure 2. *Frequency of anemia by severity, according to estimated glomerular filtration rate. CrCl, creatinine clearance; Hb, hemoglobin. Data from McClellan et al.[14]*



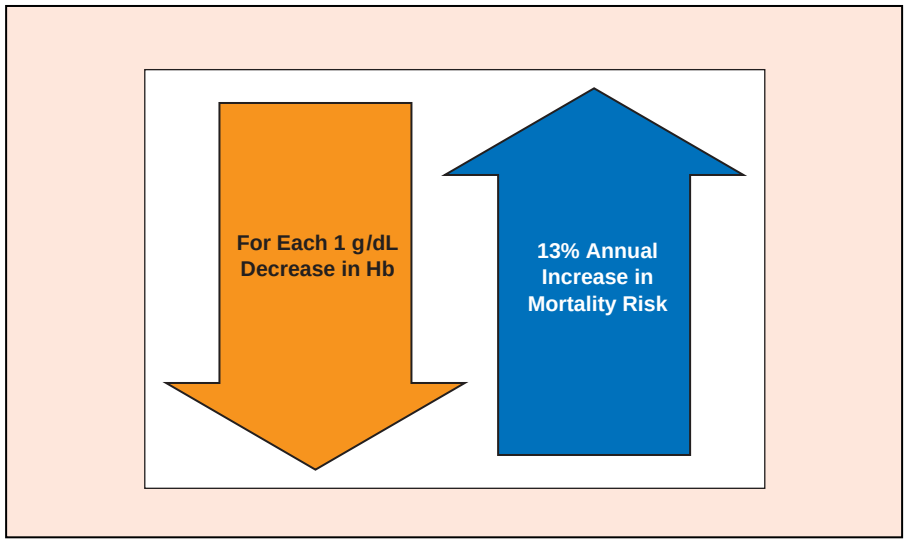


Figure 3. *Relationship between declining hemoglobin (Hb) level and annual all-cause mortality in heart failure patients. Data adapted from Herzog CA et al.[16]* www.medreviews.com

marrow in the production of red blood cells (RBCs) (Table 2).

Renal Contribution

There are at least two plausible mechanisms to account for the relatively low EPO level associated with anemia in persons with diabetes and moderate reductions in kidney function. Renal denervation attributable to diabetic autonomic neuropathy can reduce splanchnic sympathetic stimulation of EPO production.[22–27] Also, diabetes might adversely affect peritubular and interstitial structures in the renal cortex, the site of EPO production, even before the development of overt nephropathy. This might attenuate the release of EPO in response to the hypoxic stimuli of anemia.[25,27] These data provide support to the thesis that diabetes, per se, is involved in the pathogenesis of anemia, as discussed above.

The augmentation of anemia risk at levels of moderately reduced kidney function among diabetic men compared with diabetic women might be explained by greater loss of androgen-stimulated RBC production in men. Both diabetes and reduced kidney function have been linked to depressed androgen levels.[30] Androgens stimulate erythropoiesis by increasing EPO production and by direct augmentation of marrow stem cells.[31]

Hussein and colleagues[32] demonstrated in a cohort of 699 patients with HF that 98% of patients had some explanation for anemia, including most commonly renal insufficiency, and iron, folate, or vitamin B12 deficiency. However, a carefully done study[33] in patients with systolic and diastolic HF suggested that the rates of hematinic (iron, vitamin B12, folate) deficiencies were approximately 25% and were no different than in a control population. Despite these other explanations, HF itself creates a unique milieu that could make its own independent contributions to anemia.

Cardiac Contribution

To some degree, CVD probably causes anemia. The best example of this process is HF. As HF worsens, there are increased levels of tumor necrosis factor alpha, interleukins 1 and 6, endothelin, matrix metalloproteinases, and other inflammation-related proteins that are produced by the liver, heart, and vasculature.[34] These factors can work to directly reduce RBC production at the level of the bone marrow. In addition, they act to decrease the renal

Figure 4. *Vicious cycle of worsening heart failure and chronic kidney disease with anemia. EF, left ventricular ejection fraction; GFR, glomerular filtration rate; ADH, antidiuretic hormone, LVH, left ventricular hypertrophy; EPO, erythropoietin; EPC, endothelial progenitor cell. Adapted from Anand et al.[17]*

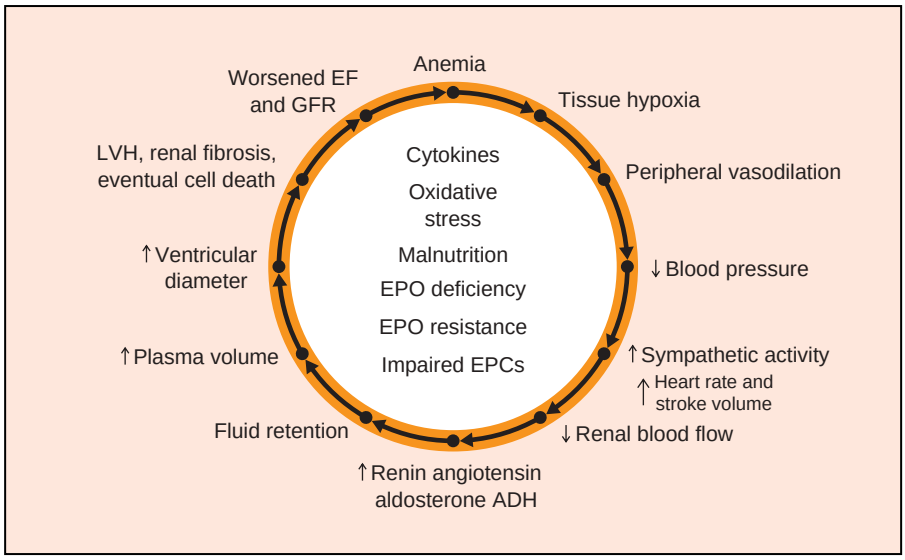


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Table 2
Multiple Factors Related to Anemia in Patients with Chronic Kidney Disease and Heart Failure

- Relative erythropoietin deficiency
- Erythropoietin resistance
- Hemodilution
- Chronic disease
  - ↑ Cytokines
  - ↑ Inflammatory factors
  - ↑ Oxidative stress
- Diabetic renal denervation
  - ↓ Androgen levels
- Shortened RBC lifespan from 120 to 64 days
- Iron losses—iron deficiency
- GI bleeding
- Reduced intake
- Malnutrition and vitamin deficiency
  - ↓ Protein intake
- Vitamin B12 and folate deficiencies
- Anemia related to ACEI and/or ARB
  - ↑ Epoetin alfa consumption
  - ↓ Glomerular stimulus for release
- Inhibition of hemopoietic progenitor cells

RBC, red blood cell; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers.

production of EPO. For this reason, multivariate analyses have consistently shown an independent relationship between HF severity and anemia, even when controlling for renal function.[35–37] An additional cardiac contribution to anemia might be in the use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, which can reduce the renal responsiveness to EPO.[38]

Malnutrition

Cachexia related both to cardiac and renal failure has been attributed to elevated levels of cytokines, anorexia, and decreased caloric intake.[39,40] In addition, there seem to be measurable levels of protein–calorie malnutrition and skeletal myopathy in patients with cardiorenal disease.[37,38] Degrees of iron, folate, and vitamin B12 deficiency might further worsen the anemia, as discussed above. Entangled in the relationships between renal function, anemia, and HF is the issue of malnutrition and reduced levels of serum albumin.[41,42] It is clear that of all the targets in this clinical web, anemia is the most easily understood and treated.

An additional cardiac contribution to anemia might be in the use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers.

Hemodilution

It has been postulated that chronic volume expansion due to salt and water retention in patients with CKD and HF results to some degree in hemodilution and lower measured Hb levels. Studies of total body blood volume in HF patients support, to some degree, the notion that hemodilution contributes to the measured Hb from the complete blood count test.[43] However, it is unlikely that hemodilution alone accounts for all of the Hb reduction observed. The data supporting the effects of uremia, diabetes, relative EPO deficiency, and other factors need to be accounted for in the explanation for a given patient's anemia.

Oxidative Stress: Anemia Begetting More Anemia

Under normal conditions there is a steady-state balance in the body between the production of free radicals and their destruction by antioxidant systems.[44] RBCs are mobile scavengers of reactive oxygen species (ROS).[45–49] They provide protection to tissues and organs by their antioxidant enzymes, including RBC glutathione peroxidase, RBC glutathione reductase, and RBC superoxide dismutase. Oxidative stress can arise from deficiencies of antioxidants and/or increased formation of ROS. Therefore, measurements of oxidant/antioxidant levels might be useful tests to evaluate ROS. An increase in ROS is manifested by an increase in oxidant markers and/or a decrease in antioxidant markers.[43–46] Oxidative stress is increased in HF and CKD,[47–49] and it might be an important contributor to the severity of these conditions.[44–50] Correcting anemia with EPO has been shown to reduce ROS in dialysis patients.[46–49] Hence, it is possible that the anemia in patients with cardiorenal disease, through the mechanisms of oxidative stress, not only worsens the anemia but also worsens the target organ function of both the heart and the kidneys.

Anemia as a Mortality Multiplier in Cardiorenal Disease

In patients with CKD, anemia is a straightforward multiplier of

mortality. In a recent review, 28 of 29 large prospective studies of HF have found anemia to be an independent predictor of mortality.[51] On average, among those patients with HF, for each 1 g/dL decrement in Hb, there is a 13% increase in risk for all-cause mortality.[16]

We have long appreciated the role of anemia predisposing to acute and subacute decompensation in patients with congestive HF. Anemia has also been associated with increased hospitalizations in patients with congestive HF in several studies.[35–37] How the anemic condition leads to a more malignant course of HF is not clear. The effects of anemia on left ventricular geometry, which might explain at least a part of the connection between anemia and HF, were observed in The Framingham Heart Study. In 1376 men and 1769 women without hypertension and cardiovascular disease, each 3% lower Hct was associated with a 2.6 g/m higher mean left ventricular mass index in men and a 1.8 g/m higher index in postmenopausal women after adjustment for confounders.[52] Lower Hcts were also associated with left ventricular hypertrophy. Regression of left ventricular hypertrophy has also been observed in patients with CKD after correction of anemia with EPO.[53] This positive effect on ventricular geometry might be related to either a direct effect of EPO or mediated through the increase in Hb levels due to EPO treatment.

The Importance of Worsening Anemia

Not only has baseline Hb been consistently found to be important, as discussed above, but the relative change in blood Hb levels in CVD patients is also important. As Hb drops over time, there is a graded increase in HF hospitalizations and death. Conversely, those patients who have had a rise in Hb, whether it be due to improved nutrition, reduced neurohormonal factors, or other unknown factors, enjoy a significant reduction in endpoints over the next several years. In the Randomized Etanercept North American Strategy to Study Antagonism of Cytokines (RENAISSANCE) Trial, patients with class 2-4 congestive HF had serial Hb and cardiac magnetic resonance imaging studies performed in a subgroup.[37] Those who experienced an increase in Hb over time (not given exogenous EPO) had a significant reduction in left ventricular mass index, suggesting a favorable change in left ventricular remodeling (Figure 5). These observational data suggest that movement or changes in Hb, either up or down, are associated with clinical consequences. Hence, there is a rationale for intervention on Hb level to change the natural history of HF and possibly CKD.

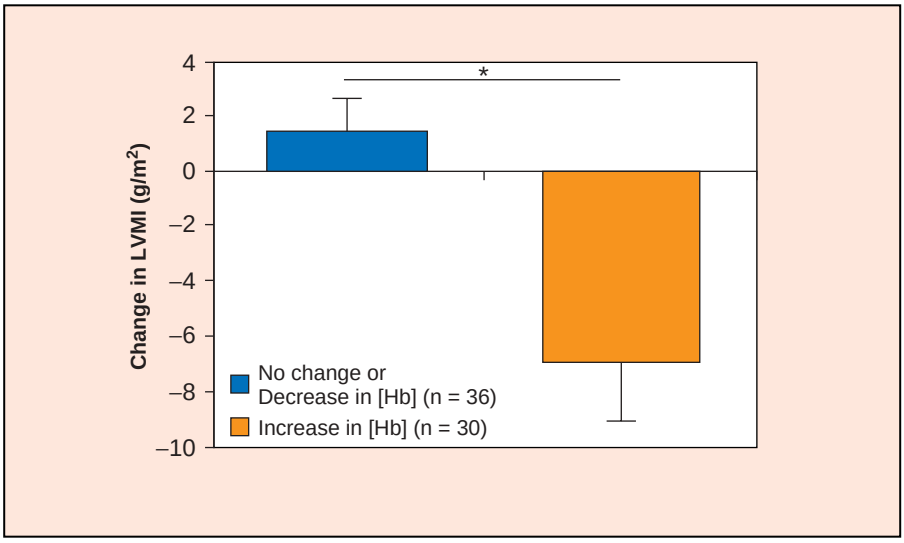
In the RENAISSANCE trial, heart failure patients who experienced an increase in Hb over time had a significant reduction in left ventricular mass index, suggesting a favorable change in left ventricular remodeling.

Anemia Correction With EPO

Heart Failure

In addition to the effect on Hb levels, the pleiotropic effects of EPO include positive effects on coronary endothelium, resulting in an increase in coronary flow reserve.[54] This effect might be mediated through the activation of endothelial nitric oxide synthase via protein kinase B phosphorylation and through the prevention of endothelial cell apoptosis.[54] Erythropoietin might also have the potential for enhancing myocardial repair in patients with acute injury. This might minimize the progression of left ventricular dysfunction by recruiting vascular progenitor cells,

Figure 5. *Relationship between changes in hemoglobin (Hb) level over time and left ventricular mass index (LVMI) in a subset of 66 patients with chronic congestive heart failure from the Randomized Etanercept North American Strategy to Study Antagonism of Cytokines Trial. *P < .0009. Adapted from Anand et al.[37]*



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which can become functional myocardial cells and thereby increase the contractile function.[55] The molecular targets for EPO include the EPO receptors expressed on cardiac myocytes, endothelial cells, and endothelial progenitor cells, as well as hematopoietic stem cells.[56]

In the EPO-treated group, mean functional class improved by 42.1%, LVEF increased by 5.5%, and the need for oral and intravenous furosemide decreased by 51.3% and 91.3%, respectively.

Treatment of anemia with exogenous EPO in CKD has shown promise in reducing CVD morbidity and in improving survival and quality of life. Increasing the Hb level from less than 10 g/dL to 12 g/dL has been linked to favorable changes in left ventricular remodeling, improved left ventricular ejection fraction (LVEF), improved functional classification, and higher levels of peak oxygen consumption with exercise testing.[57–60]

In a study by Silverberg and colleagues,[57] the records of 142 patients treated in a special HF clinic were evaluated retrospectively; the findings included a relationship between functional classification, the prevalence of anemia (Hb $<$ 12g/dL), and serum creatinine. From this group of patients, 26 who remained refractory to maximal medical therapy were selected for treatment with subcutaneous EPO and intravenous iron for a mean of 7 months. At baseline and after therapy the mean Hb, LVEF, and functional class were 10.2 g/dL vs 12.1 g/dL, 27.7% vs 35.4%, and 3.6 vs 2.6, respectively. In addition, the finding of a significant reduction in rehospitalization rates compared with pretreatment rates was also noted. Although this uncontrolled study showed that treating patients with severe HF and anemia with iron and EPO had very positive clinical effects, separating the effects of treating the anemia from the effect of EPO alone is not possible and needs to be addressed by randomized clinical trials. One such trial has been completed by the same group led by Silverberg.[59] This trial recruited 32 class III to IV patients with systolic dysfunction, whose Hb levels were persistently between 10.0 g/dL and 11.5 g/dL. They were randomized to subcutaneous EPO and intravenous iron to increase the level of Hb to at least 12.5 g/dL, or usual care. Over a mean of 8 months, the mean functional class improved by 42.1%, LVEF increased by 5.5%, and the need for oral and intravenous furosemide decreased by 51.3% and 91.3%, respectively, in the EPO-treated group. The number of days spent in hospital compared with the same period of time before entering the study decreased by 79.0% in the EPO group, whereas it rose in the usual-care group. These data are promising preliminary results that are the basis for several ongoing clinical trials attempting to prevent CVD in patients with CKD and anemia and to treat active HF in patients with anemia (Table 3).

Ischemic Heart Disease

There are significant implications of anemia in patients with ischemic heart disease. As discussed above, anemia has been related to coronary ischemia, owing to both a lack of oxygen delivery and increased myocardial oxygen demands. Thus, in the setting of fixed coronary disease, it is postulated that anemia might contribute to outcomes in both the chronic and acute phases of the illness.

Low Hb has been found to be an independent predictor of adverse cardiovascular outcomes in women presenting with suspected ischemia-related chest discomfort.[61] As part of the National Heart, Lung and Blood Institute–sponsored Women's Ischemia Syndrome Evaluation, 936 consecutive women referred for coronary angiography were prospectively studied. The prevalence of anemia, defined as Hg less than 12 g/dL,

Table 3
Ongoing Multicenter Trials of EPO or Other Bone Marrow–Stimulating Proteins in the Prevention or Treatment of Heart Failure in Patients with CKD

Trial	Target Population	Intervention
Canada-Europe Normalization of Hemoglobin Study	ESRD early on dialysis without HF (n = 554)	EPO with target Hb ~14 g/dL vs 10–11 g/dL
CREATE	CKD with CrCl 15–35 mL/min (n = 600)	EPO target Hb 13–15 vs 10.5–11.5 g/dL
CHOIR	CKD with CrCl 15–50 mL/min	EPO target Hb 13.5 vs usual care ~12.3 g/dl
TREAT	Type 2 Diabetes- and CKD-induced anemia	Darbepoetin alfa

EPO, erythropoietin; CKD, chronic kidney disease; ESRD, end-stage renal disease; Hb, hemoglobin; CrCl, creatinine clearance.

was 21%. Anemic women had significantly higher serum creatinine levels compared with nonanemic women (1.1 mg/dL vs 0.8 mg/dL, $P <$ .001) and higher levels of inflammatory markers. Despite there being no difference in LVEF in these two groups, women with anemia had greater rates of CVD mortality (6% vs 2.6%) and all-cause mortality (10.3% vs 5.4%) compared with nonanemic women. In a retrospective cohort study[62] of 689 male patients admitted for elective percutaneous coronary intervention (PCI), 1-year mortality was 22.2% in the quintile of patients with the lowest Hb levels (≤12.9 g/dL), compared with 3.7% in patients in the normal Hb (14.6–15.2 g/dL) quintile. A partial explanation for the risk posed by anemia in PCI is an observed association between anemia and contrast-induced nephropathy.[63] The kidneys are very sensitive to hypoxia. In the setting of anemia and other potential factors, including hypotension superimposed on CKD, patients can have very high rates of contrast-induced nephropathy, which itself is related to short- and long-term mortality.[64,65] In the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial, of 2082 patients with acute ST-segment elevation myocardial infarction undergoing primary PCI, 12.8% had anemia at baseline (Hct <39% for men and <36% for women).[66] Patients with anemia were more likely to develop worsened anemia while in hospital (6.2% vs 2.4%) and to have more transfusions (13.1% vs 3.1%). This resulted in longer lengths of stay and higher costs. Importantly, mortality while in hospital (4.6% vs 1.1%), at 30 days (5.8% vs 1.5%), and at 1 year (9.4% vs 3.5%) was higher in those with baseline anemia. Multivariate analysis found anemia to be an independent predictor of in-hospital and 1-year mortality.

In ischemic heart disease, whether it is chronic, undergoing PCI, or in the setting of an acute myocardial infarction, it seems that there is an independent relationship between anemia and mortality. The relationship has held up in multivariate analyses that control for confounders, including age and CKD. This has led to an interest in short-term correction of anemia with blood transfusion.

Anemia Correction With Blood Transfusion

Many of the principles of anemia correction could be applied on a short-term basis with blood transfusion. In this area, multiple retrospective studies are not supportive of aggressive blood transfusion. In a study by Wu and colleagues,[67] among 78,974 Medicare beneficiaries aged 65 years or older, those with severe to moderate anemia (Hct 5%–33%) seemed to have a mortality benefit with blood transfusion. At a Hct of 33%, there was no observed benefit. In a recent analysis of 24,112 patients with acute coronary syndromes from three large trials,[68] blood transfusion was associated with an overall higher mortality rate, even after adjustment of baseline

Main Points

- In general, anemia is present in 30% and 60% of patients with heart failure (HF) and significant chronic kidney disease (CKD), respectively; hence, anemia is a common and easily identifiable potential therapeutic target.
- In patients with CKD, anemia is a straightforward multiplier of mortality; among patients with HF, on average, for each 1 g/dL decrement in hemoglobin (Hb) there is a 13% increase in risk for all-cause mortality.
- Several factors have been implicated in the development of anemia in patients with cardiorenal disease: these include relative erythropoietin alpha (EPO) deficiency, EPO resistance, hemodilution, diabetic renal denervation, iron losses/deficiency, and malnutrition.
- In patients with cardiovascular disease, as Hb drops over time, there is a graded increase in HF hospitalizations and death, whereas patients who have a rise in Hb enjoy a significant reduction in endpoints. Hence, there is a rationale for intervention on Hb level to change the natural history of HF and possibly CKD.
- Treatment of anemia with exogenous EPO in CKD has shown promise in reducing cardiovascular morbidity and in improving survival and quality of life. In addition to the effect on Hb levels, the pleiotropic effects of EPO include positive effects on coronary endothelium, resulting in an increase in coronary flow reserve.
- Many of the principles of anemia correction could be applied on a short-term basis with blood transfusion. Current recommendations are to use blood transfusions on a short-term basis in symptomatic cardiovascular patients with Hb levels less than 8.0 g/dL to a target Hb level of approximately 10 g/dL and to avoid overly aggressive transfusion.

confounders and the propensity to receive transfused blood. In this study, 10.0% underwent at least one blood transfusion during their hospitalization, and, similar to the CADILLAC trial, they had a higher 30-day mortality rate, 8.0% vs 3.1%. The predicted probability of 30-day death was greater with transfusion at nadir Hct values above 25%, consistent with the Medicare data, suggesting that transfusing patients with Hb levels greater than 8–10 g/dL is not of any benefit and might potentially cause harm. There is always the concern that nonrandomized studies are influenced by "confounding by indication." This means that those who received the most transfusions were likely the sickest patients and hence had the worst outcomes. This being understood, the current recommendations are to use blood transfusions on a short-term basis in symptomatic cardiovascular patients with Hb levels less than 8.0 g/dL to a target Hb level of approximately 10 g/dL and to avoid overly aggressive transfusion.

Conclusions

We are just beginning to understand the relationships among the cardiovascular, renal, and hematopoietic systems. The more we study the implications of anemia as regards cardiovascular events in patients with coronary artery disease and HF, the more we are appreciating the role of EPO in endothelial function and cardiovascular repair, independent of its effect in increasing Hb levels. At present, it would seem reasonable for cardiologists to take an assertive approach with their patients with CKD and CVD who are anemic. Raising Hb levels with EPO (and supplemental iron) might be part of a future optimal medical regimen for patients with cardiorenal disease, with anemia being added to the list of "modifiable" risk factors. We look forward to the results of prospective randomized trials to learn more about optimizing the treatment of patients with anemia and cardiovascular disease. ■

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