Piecing Together the Evidence on Anemia: The Link Between Chronic Kidney Disease and Cardiovascular Disease

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Chronic kidney disease (CKD) is now accepted as an independent cardiovascular disease (CVD)-risk state, regardless of its underlying cause. Anemia is a common feature of CKD, particularly in end-stage renal disease. Anemia is also independently associated with poorer outcomes in a wide variety of CVD states, including congestive heart failure and coronary artery disease. Anemia appears to act as an independent mortality multiplier when hemoglobin levels drop below 12 g/dL. With the independent and profound contribution of both CKD and anemia to cardiovascular mortality and morbidity, understanding the pathophysiologic links among these disease states is important. In addition, it is hoped that treatments currently under active investigation and geared specifically to attenuate the cardiovascular risk associated with anemia and CKD, such as erythropoietin therapy, will improve outcomes. This article reviews the evidence for an association among CKD, anemia, and CVD.
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Key words: Chronic kidney disease • Hemoglobin • Erythropoietin-α • Anemia

Chronic kidney disease (CKD) is now recognized as an independent and accelerated cardiovascular risk state.[1,2] The relationship between CKD and cardiovascular risk is independent of the etiology of renal insult. Evidence is mounting that cardiovascular risk increases at levels of renal function that were once felt to be normal or borderline deficient. Relying on serum creatinine (Cr) as the standard measure has led to systematic overestimation of renal function and underestimation of the degree of dysfunction, as well as

Table 1
Serum Creatinine Corresponding to an eGFR of 60 mL/min/1.73 m²

Age (y)	European American		African American	
	Men	**Women**	**Men**	**Women**
30	1.47	1.13	1.73	1.34
40	1.39	1.08	1.65	1.27
50	1.34	1.03	1.58	1.22
60	1.30	1.00	1.53	1.18
70	1.26	0.97	1.49	1.15
80	1.23	0.95	1.46	1.12

Calculations in this table assume a weight of 72 kg and body surface area of 1.73 m². Units for serum creatinine are mg/dL (multiply by 88.4 μmol/L = 1 mg/dL).
eGFR, estimated glomerular filtration rate.
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underestimation of cardiovascular risk in these patients (Table 1). The most reliable way to recognize CKD is to estimate glomerular filtration rate (eGFR) from equations that utilize age, gender, race, and serum Cr measures. In addition, the presence of urinary microalbumin, defined as an albumin:creatinine ratio (ACR) greater than 30 mg/g on a random urine specimen, reflects the presence of kidney damage and specifically microvascular dysfunction. Current guidelines define CKD as an eGFR less than 60 mL/min/1.73 m² or ACR greater than 30 mg/g.[3] Stage 1 CKD extends the definition to patients with normal or raised GFR (>/= 90), if any kidney damage is evident. The presence of urinary microalbuminuria seems to add incremental cardiovascular risk to patients with CKD. In the United Kingdom Prospective Diabetes Study (UKPDS), diabetics with no evidence of nephropathy had an annual cardiovascular mortality rate of 0.7%. With the progression to microalbuminuria, macroalbuminuria, and, finally, elevated serum Cr or renal replacement therapy, annual cardiovascular mortality rates increased to 2.0%, 3.5%, and 12.1%, respectively.[4]

We have recently begun to appreciate the ramifications of CKD on adverse outcomes in patients with cardiovascular disease (CVD).[5] Anemia is one of approximately 2 dozen metabolic/hematologic targets, including insulin resistance, dyslipidemia, and platelet dysfunction, that are typical of CKD and may influence resultant CVD risk.[6] Among patients with CKD, diabetes is recognized as a traditional CVD risk factor and anemia is now considered a nontraditional, though modifiable, risk factor (Figure 1).[7] This paper will focus on the link that anemia seems to provide between CKD and CVD risk.

Definition and Prevalence of Anemia

The most commonly used definition of anemia is put forth by the World Health Organization and specifies a hemoglobin (Hb) level lower than 13 g/dL in men and lower than 12 g/dL in women. Approximately 9% of the general adult population meets the definition of anemia at these levels. In patients with CKD, the prevalence of anemia increases as the level of renal function decreases. In patients with heart failure (HF), the prevalence of anemia increases from 9% in patients with New York Heart Association (NYHA) functional class I HF, to 19% in class II patients, and to 79% in class IV HF patients. Nearly 60% of patients with significant CKD also have anemia.[8]

Figure 1. *Traditional and nontraditional cardiovascular disease (CVD) risk factors among patients with chronic kidney disease. HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy. Adapted from Sarnak et al.[7]*

Cardiovascular Risk Factors in Chronic Kidney Disease

Traditional Risk Factors	Nontraditional Risk Factors
• Increasing age	• Albuminuria
• Male sex	• Homocysteine
• Hypertension	• Lipoprotein(a) and apolipoprotein(a) isoforms
• Higher LDL	• Lipoprotein remnants
• Lower HDL	• Anemia
• Diabetes	• Abnormal calcium/phosphate metabolism
• Smoking	• Extracellular fluid volume overload
• Physical inactivity	• Electrolyte imbalance
• Menopause	• Oxidative stress
• Family history of CVD	• Inflammation (C-reactive protein)
• LVH	• Malnutrition
	• Thrombogenic factors
	• Altered nitric oxide/endothelin balance

This prevalence of anemia in patients with CKD and CVD, as well as its ease of diagnosis and association with increased risk, logically makes it a potential therapeutic target.

Risk Factors for Anemia
Reduced Estimated Glomerular Filtration Rate
Anemia is a common feature of end-stage renal disease (ESRD) but it

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Anemia is one of the most characteristic and visible manifestations of CKD, and contributes to multiple adverse outcomes, in part due to decreased tissue oxygen delivery and utilization.

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also accompanies lesser reductions in kidney function.[9] The degree of anemia roughly approximates the severity of kidney dysfunction and reduction in renal mass. The reduction in functional renal parenchyma, the source of erythropoietin synthesis, creates a relative deficiency of erythropoietin-α (EPO), subsequently decreased bone-marrow production of red blood cells, and anemia.[10]

Anemia is one of the most characteristic and visible manifestations of CKD, and contributes to multiple adverse outcomes, in part due to decreased tissue oxygen delivery and utilization.[11,12] A significant correlation between hematocrit (Hct) and Cr clearance (CrCl) has been found to occur in patients with an eGFR below 45 mL/min/1.73 m^2.[10] Anemia is a predictable consequence of progressive renal insufficiency and occurs well before patients progress to ESRD. In patients with serum Cr between 2.1 and 4.0 mg/dL, the prevalence of anemia is 34% and in those with serum Cr greater than 5.0 mg/dL, prevalence is 74%.[13]

Diabetes
Diabetes mellitus is one of the major

risk factors for CKD and is the leading cause of ESRD.[3] As diabetes progresses, the basement membrane of the glomeruli thickens due to the process of glycosylation, causing an increase in intrarenal pressure, with the development of CKD, decreased production of EPO, and anemia. What differentiates diabetic nephropathy from other causes of CKD is the earlier occurrence of anemia at a given stage of renal dysfunction.[14] The anemia seen in diabetics has been thought to relate to uremia in advanced diabetic nephropathy. However, diabetes affects the hematologic system in a variety of ways beyond changes in EPO production, including a reduction in the red-cell life span.[10,11,15,16] The kidney produces 90% of EPO in the body, whereas the liver produces 10%.[8] In subjects with normal renal function, the main stimulus for EPO

production is hypoxia (Figure 2). Normal plasma EPO levels range between 10 and 30 IU/mL. However, during anemic periods, these levels may be elevated as high as 100 IU/mL. There are suggestions that EPO synthesis is impaired in patients with diabetes.[17]

In patients with CKD, there appears to be a relative deficiency in EPO and an inappropriately low EPO level for the corresponding measured blood Hb level.[8] Anemia is increasingly common as eGFR drops below 60 mL/min/1.73 m^2 and, for any particular degree of CKD, diabetics seem to have a higher prevalence of anemia (Figure 3).[18] Kojima and coworkers have reported inappropriately low levels of EPO in persons with diabetes mellitus in the absence of uremia.[15] Yun and associates showed that diabetic patients with anemia and no overt kidney disease had lower levels of EPO than nondiabetic patients with anemia at any given levels of Hb.[19]

It is becoming increasingly clear that a relationship also exists between the development of diabetic neuropathy and anemia. Reports

Figure 2. *Reduced oxygen delivery to the kidney stimulates erythropoietin production. BFU-E, Burst forming units-erythroid; CFU-E, Colony forming units erythroid. Reproduced with permission from Erslev AJ. Erythropoietin. N Engl J Med. 1991;324:1339-1344.*
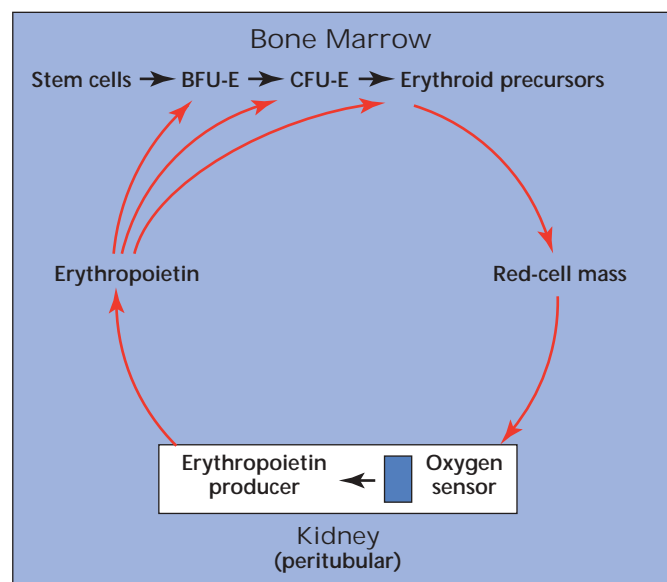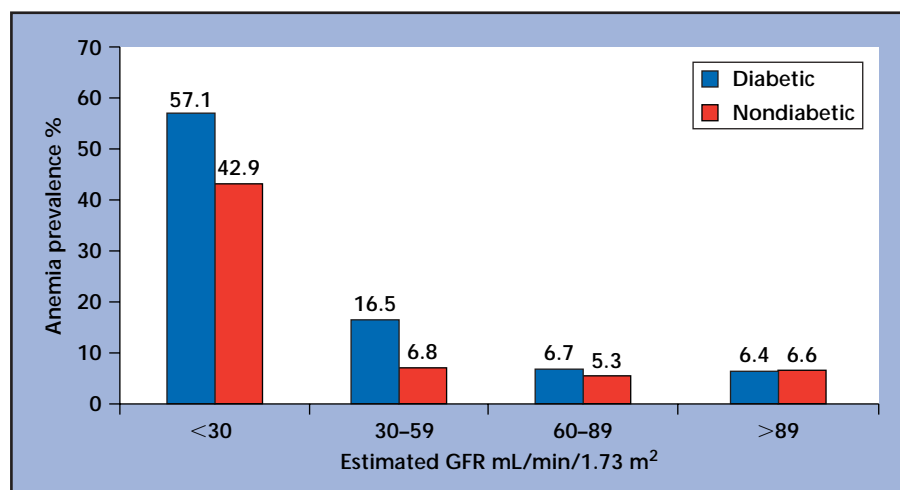
Figure 3. *Frequency of anemia according to estimated glomerular filtration rate (GFR) and diabetes status. Reproduced with permission from El-Achkar et al.[18]*

have shown that the development of autonomic neuropathy with subsequent renal denervation may be a factor in the blunted endogenous response of diabetics and the decreased sensitivity of their oxygen sensors to lower levels of Hb.[12] Thus, a variety of factors seem to influence the development of anemia in diabetics, including the onset of CKD-related decreases in EPO synthesis, blunted EPO response to hypoxia, and decreased erythrocyte survival.

Pathophysiology of Anemia of Chronic Disease

The exact cause of what has been referred to as anemia of chronic disease in patients with CKD and/or CVD is not known. However, there are multiple factors that have been implicated in the development of this problem, in addition to a decrease in EPO production. These include iron deficiency, acute and chronic inflammatory conditions, reduced red cell survival, hyperparathyroidism, folate deficiency, and hypothyroidism. Heart failure itself may contribute to the development of anemia of chronic disease.

Renal Failure

There are at least 2 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.[8] Also, diabetes may adversely affect peritubular and interstitial structures in the renal cortex, the site of EPO production, even prior to the development of overt nephropathy. This might attenuate the release of EPO in response to the hypoxic stimuli of anemia.[8] Both diabetes and reduced kidney function have been linked to depressed androgen levels.[20] Androgens stimulate erythropoiesis by increasing EPO production and by directly influencing the function of marrow stem cells.[20]

Heart Failure

Heart failure, which shares many of the neurohormonal and inflammatory systemic features of CKD, is also related to anemia.[8] As HF worsens, there are increased levels of tumor necrosis factor-α, interleukins 1 and

6, endothelin, matrix matalloproteinases, and other inflammation-related proteins that are produced by the liver, heart, and vasculature.[21] These factors can work to directly reduce red blood cell production at the level of the bone marrow. In addition, they act to decrease the renal production of EPO. For this reason, multivariate analyses have consistently shown an independent relation between HF severity and anemia, even when controlling for renal function.[8]

Chronic volume expansion due to salt and water retention in patients with CKD and HF may result 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 measured Hb in a complete blood count test.[22] However, it is unlikely that hemodilution alone accounts for all of the Hb reduction observed.

Malnutrition, Catabolism, and Oxidative Stress

Malnutrition associated with both cardiac and renal failure has been attributed to elevated levels of cytokines, anorexia, and decreased caloric intake.[8] In addition, there appear to be measurable levels of protein-calorie malnutrition and skeletal myopathy in patients with cardiorenal disease.[8] Degrees of iron, folate, and vitamin B_{12} deficiency may further worsen anemia.[23] In patients with reduced renal function, anemia, and HF, a catabolic state and malnutrition can lead to reduced levels of serum albumin.[24]

There is a normal, steady-state balance in the body between the production of free radicals and their destruction by antioxidant systems.[25] Red blood cells are mobile scavengers of reactive oxygen species (ROS).[26] They provide protection to
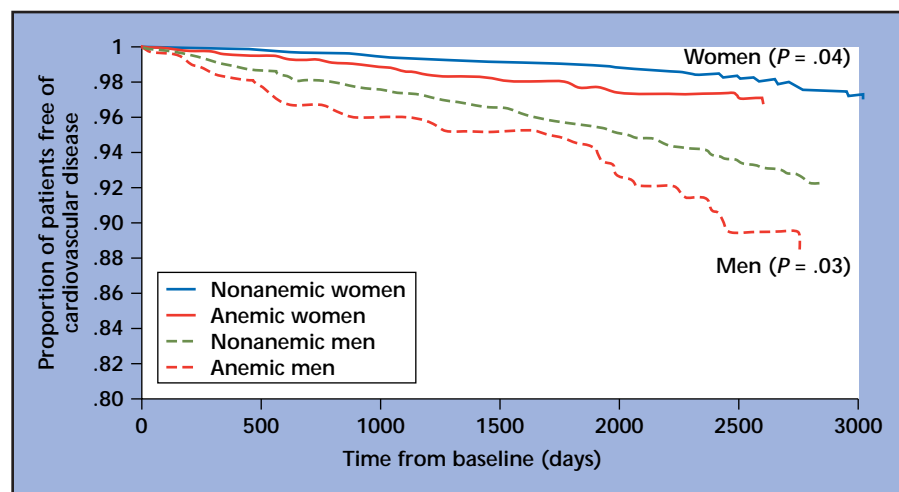
Figure 4. *Impact of anemia on gender-related incidence of cardiovascular disease from the Atherosclerosis in Communities at Risk Study. Reproduced with permission from Sarnak et al.[28]*

tissues and organs through their antioxidant enzymes, including RBC glutathione peroxidase, RBC glutathione reductase, and RBC superoxide dismutase. Thus, increased oxidative stress can arise as a consequence of anemia. The increase in ROS is manifested by an increase in oxidant markers and/or a decrease in antioxidant markers.[25-27] Oxidative stress is increased in HF and CKD[25,27] and it may be an important contributor to the severity of these conditions. Further, oxidative stress can work in a feedback loop to worsen anemia.[8]

Anemia and Progression of Heart and Kidney Disease

A reduced blood Hb level has been linked to higher rates of incident CVD in the Atherosclerosis in Communities at Risk (ARIC) Study (Figure 4).[28] Part of this increased rate may be attributable to increases in left ventricular mass. In the Framingham Study, among 1376 men and 1769 women without hypertension and CVD, every 3% reduction of hematocrit was associated with a 2.6 g/m higher

mean left ventricular mass index in men and a 1.8 g/m higher mean left ventricular mass in postmenopausal women, after adjustment for confounders.[29] Among patients with CKD, for every 1 g/dL reduction in Hb, there is a 6% increased risk of left ventricular hypertrophy (LVH).[30] In fact, at the time of dialysis initiation, 74% of patients with ESRD have measurable LVH.[31]

Among diabetics, anemia has been associated with an overall higher prevalence of existing CVD.[32] In a recently presented study of patients screened for CKD, those patients with microalbuminuria, anemia, and eGFR < 30 mL/min/1.73 m^2, there was a greater than 70% prevalence of CVD (Figure 5).[33] In addition to hypertension, myocardial infarction, LVH, and HF, stroke has been found to be more common among those with an eGFR lower than 60 mL/min/1.73 m^2 and anemia.[34]

Anemia and kidney function are inextricably linked as discussed above, given the kidney's important role in EPO production.[8] However, there are data to suggest that anemia itself leads to worsening renal function. In the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial, diabetic nephropathy patients with anemia (Hb < 11.3 g/dL) had a 2-fold adjusted increased risk of progressing to ESRD during the follow-up period (Figure 6).[35] Thus, it appears that anemia is both a cause and result of progressive kidney disease.

Figure 5. *Prevalence of cardiovascular disease in patients with microalbuminuria and anemia stratified by baseline estimated glomerular filtration rate (eGFR). CVD, cardiovascular disease. Adapted from McCullough et al.[33]*
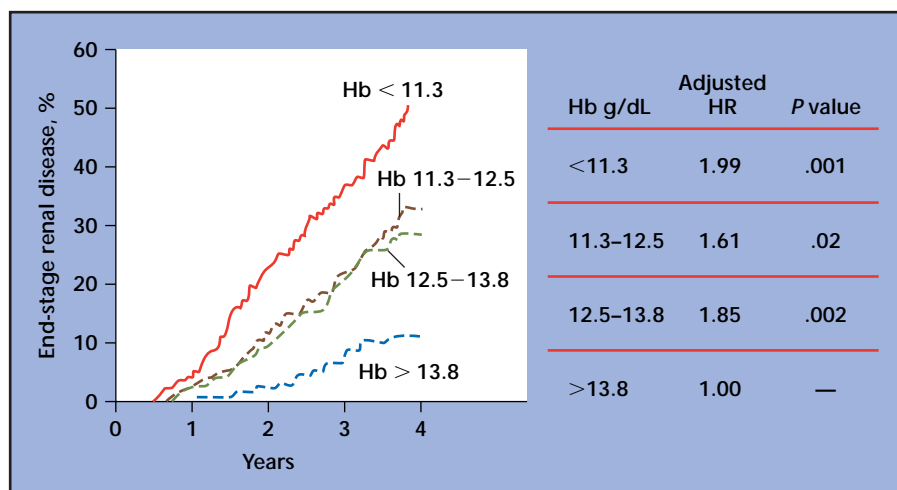
Hb g/dL	Adjusted HR	*P* value
<11.3	1.99	.001
11.3–12.5	1.61	.02
12.5–13.8	1.85	.002
>13.8	1.00	—
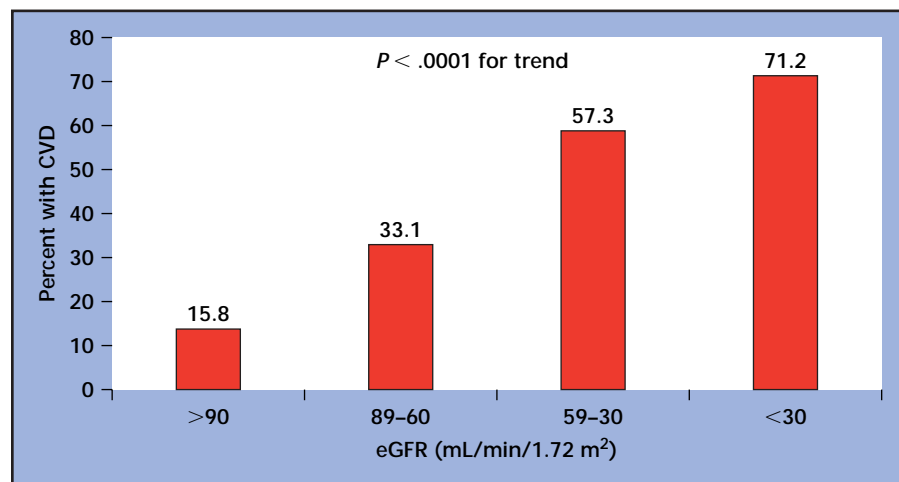
Figure 6. *Baseline hemoglobin (Hb) and adjusted risk of developing end-stage renal disease in patients with diabetic nephropathy in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study. HR, hazard ratio. Reproduced with permission from Mohanram et al.[35]*

Anemia and All-Cause Mortality

In patients with CKD, anemia is a straightforward multiplier of mortality. In a recent review, 28 of 29 large prospective studies of HF determined anemia to be an independent predictor of mortality.[36] On average, among those patients with HF, for each 1 g/dL decrement in Hb, there is a 13% increased risk for all-cause mortality.[37]

Anemia has also been associated with reduced functional capacity and increased hospitalizations in patients with HF.[38] How the anemic condition leads to a more malignant course of HF is not clear. It may be related to increased cardiac work and neurohormonal activation resulting from tissue hypoxia, leading to worsening of HF, and to the exacerbation of underlying ischemic heart disease, arrhythmias, and, ultimately, acute coronary syndromes. The effects of anemia on left ventricular geometry

In patients with CKD, anemia is a straightforward multiplier of mortality.

may explain at least part of the connection between anemia and HF. Regression of LVH has been observed in patients with CKD after correction of anemia with EPO and may be a key mechanism for the observed improvement in HF symptoms.[39] This

positive effect on ventricular geometry may be related to either a direct effect of EPO, improved tissue oxygen delivery, reduced cytokines/oxidative stress, or a yet to be discovered metabolic effect mediated by red blood cells, or their progenitors, on the myocardium.[40,41]

Worsening Anemia—A Dynamic Signal in Heart Failure

The relative change in blood Hb levels in patients with CVD is a dynamic signal of disease severity. As Hb drops over time, there are gradations of increase in HF hospitalizations and death.[42] Conversely, those patients who have had a rise in Hb, whether due to improved nutrition, reduced neurohormonal activation, or other, unknown factors, enjoy a significant reduction in adverse endpoints over the ensuing several years. In the Randomized Etanercept North American Strategy to Study Antagonism of Cytokines (RENAISSANCE) Trial, a subgroup of patients with NYHA class II-IV chronic HF underwent serial Hb and cardiac magnetic resonance imaging studies (Figure 7).[42] Those who experienced an increase in Hb

Figure 7. *Changes in hemoglobin (Hb) level over time in 66 patients with chronic heart failure, who had serial Hb and left ventricular mass index (LVMI), as measured by cardiac magnetic resonance imaging, recorded in the Randomized Etanercept North American Strategy to Study Antagonism of Cytokines Trial. Adapted from Anand et al.[42]*
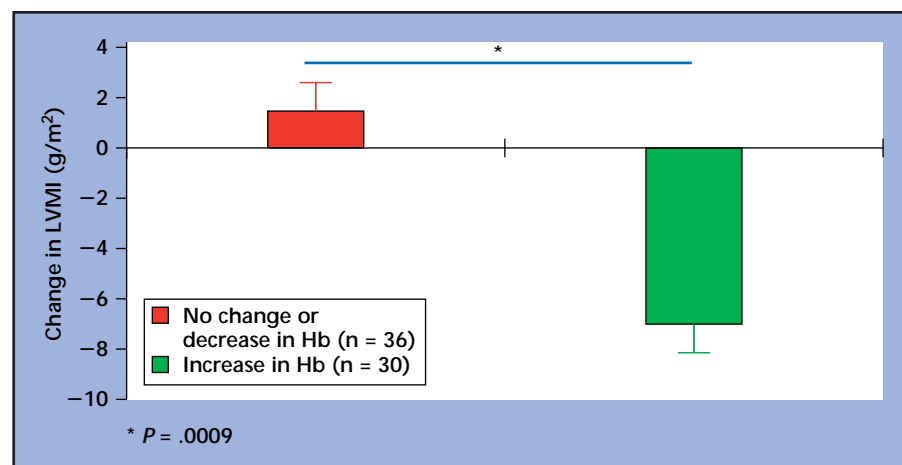
over time (not given exogenous EPO) had a significant reduction in left ventricular mass index, suggesting a favorable change in left ventricular remodeling. These observational data suggest that movement or change in Hb, either up or down, is associated with clinical consequences. Hence, there is a rationale for clinical intervention to control Hb level in order to alter the natural history of HF, and possibly CKD.

Beyond Heart Failure

Anemia has been related to coronary ischemia, due to both a lack of oxygen delivery and increased myocardial oxygen demands. Therefore, in the setting of fixed coronary disease, anemia may contribute to outcomes both in 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.[43] 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 overall prevalence of anemia defined as Hb less than 12 g/dL was 21%. Anemic women had significantly higher serum Cr levels compared to women who were not anemic (1.1 vs 0.8 mg/dL, $P = .001$) as well as higher levels of inflammatory markers. Women with anemia had a greater rate of cardiovascular mortality compared to non-anemic women (6.0% vs 2.6%) and all-cause mortality (10.3% vs 5.4%).

In a retrospective cohort 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 to 3.7% in patients in the normal
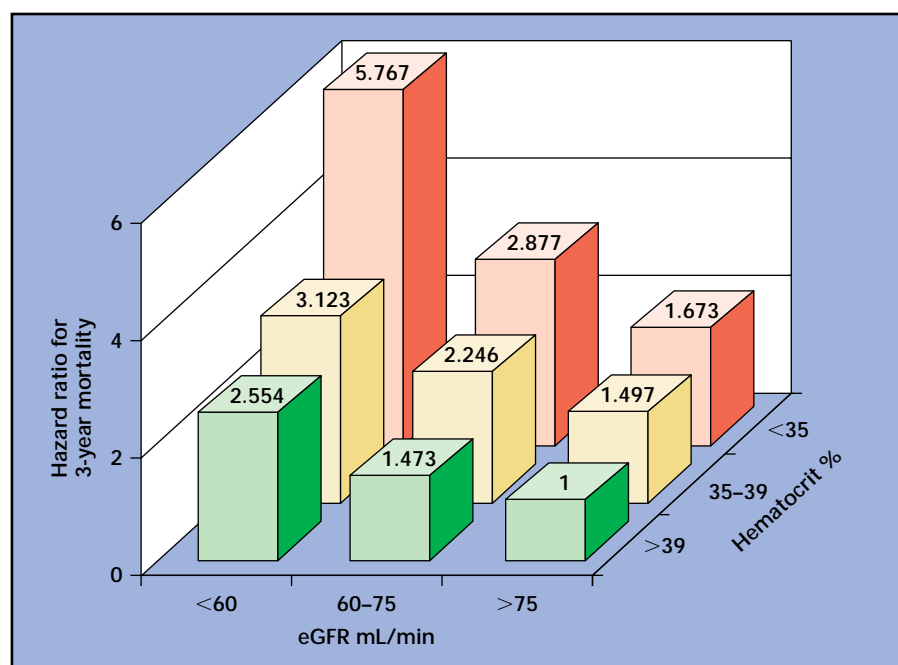

Figure 8. *Pooled data from 3 randomized controlled trials of platelet IIb/IIIa inhibition in patients who underwent percutaneous coronary intervention (EPIC, EPILOG, and EPISTENT trials) with adjusted hazard ratios for all-cause mortality at 3 years according to estimated glomerular filtration rate (eGFR) and hematocrit, N = 6,408. Reproduced with permission from Gurm et al.[45]*

Hb (14.6-15.2 g/dL) quintile.[44] Importantly, the impact of anemia and reduced eGFR are synergistic in increasing the relative risk of death after PCI, as shown in Figure 8.[45] A partial explanation for the risk posed by anemia in PCI is an observed association between anemia and contrast-induced nephropathy (CIN).[46]

As kidney function and renal tubular viability are very sensitive to hypoxia, the impact of contrast-induced reduction of renal blood flow may be further enhanced by the presence of anemia. In the setting of anemia, and other potential factors, including hypotension superimposed on CKD, patients can have very high rates of CIN, which has a profound impact on short- and long-term mortality.[47,48] In the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial, of the 2,082 patients with acute ST-segment ele-

vation myocardial infarction undergoing primary PCI, 12.8% were anemic at baseline (Hct < 39% for men and < 36% for women).[49] Patients with anemia were more likely to develop hemorrhagic complications while in hospital, (6.2% vs 2.4%), and have more transfusions (13.1% vs 3.1%). This resulted in anemic patients having longer lengths of stay and incurring higher hospital-related costs. Importantly, the in-hospital mortality (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 than in those who were not anemic. Multivariate analysis found anemia to be an independent predictor of in-hospital and 1-year mortality. These results have been largely supported in an analysis by Sabatine and colleagues that showed a 2-fold increased risk of mortality in those patients with Hb less than 13 g/dL, up to 12 months
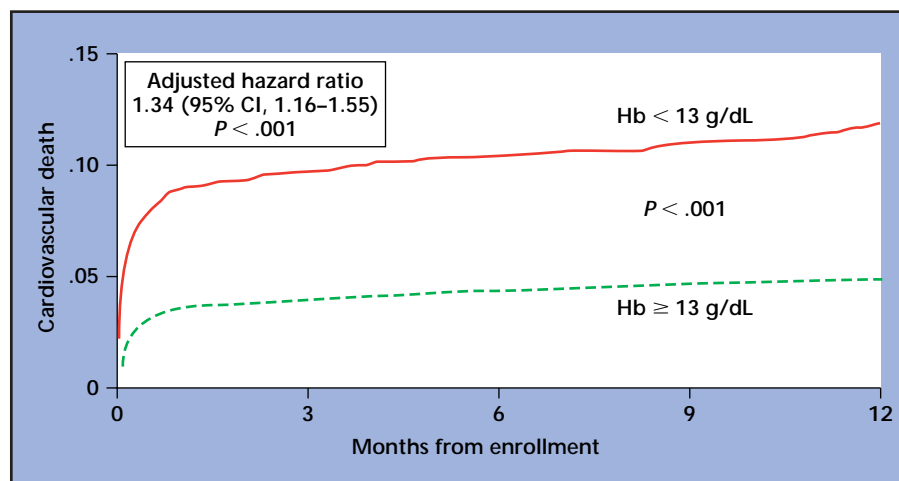
Figure 9. *Cardiovascular death after ST-segment elevation myocardial infarction is related to baseline blood hemoglobin (Hb) level. Reproduced with permission from Sabatine et al.*[50]

after the initial STEMI event (Figure 9).[50]

In ischemic heart disease, whether chronic, related to treatment with PCI, or in the setting of an acute myocardial infarction, there appears to be an independent relationship between anemia and outcomes, including mortality. Whether the interaction of anemia is related to an associated reduction of EPO levels and subsequent reductions in circulating hematopoietic progenitor cells that may play an important role in vascular repair, or to a direct effect of anemia, is not clear. This has led to an interest in evaluating the impact of treating the anemic condition on development and progression of heart and kidney disease, with EPO, blood transfusions, and iron replacement therapy.

Conclusion

There is a complicated and important pathophysiological relationship (Figure 10) among the cardiovascular, renal, and hematopoietic systems. Because anemia is easy to recognize and is readily treatable with erythrocyte stimulating proteins, it is a promising diagnostic and therapeutic target in patients with CKD and/or CVD. ∎
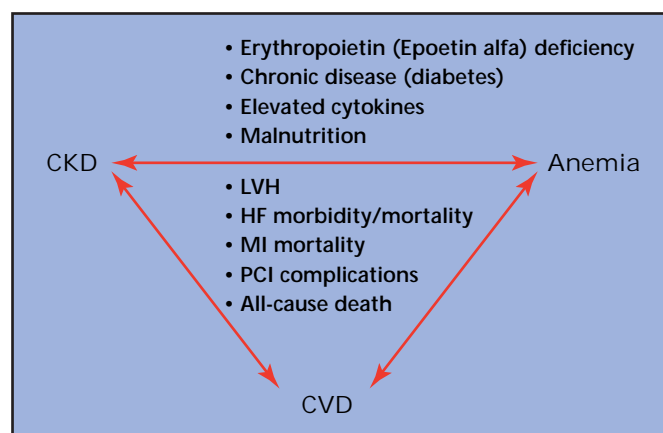

Figure 10. *Triangular relationship among chronic kidney disease (CKD), anemia, and cardiovascular disease (CVD) outcomes. LVH, left ventricular hypertrophy; HF, heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention.*

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Main Points

- The World Health Organization defines anemia as a hemoglobin level lower than 13 g/dL in men and 12 g/dL in women.

- Any condition that leads to chronic kidney disease (CKD) and diabetes mellitus should be considered a risk factor for anemia.

- Anemia of chronic diseases, including CKD, cardiovascular disease, and heart failure, develops primarily through the decreased production of erythropoietin.

- Anemia is a straightforward multiplier of mortality in patients with CKD and acts as a dynamic signal of heart failure through relative changes in hemoglobin levels in heart failure patients.

- Because anemia is easily recognized and easily treated with erythrocyte stimulating proteins, it is a promising diagnostic and therapeutic target in patients with either CKD or chronic cardiovascular disease.