

*Series Editor: Mark A. Perazella, MD, FACP*

## **CKD Series: Evaluation and Treatment of Anemia in Chronic Kidney Disease**

*Ali K. Abu-Alfa, MD, FACP*

**A**nemia is a major consequence of chronic kidney disease (CKD) that develops early in the course of illness and affects most patients who exhibit some degree of reduced renal function. Pooled study data consistently show that lower hemoglobin levels are associated with lower levels of glomerular filtration rate (GFR), that anemia can be seen even at GFR levels as high as 60 mL/min, and that severity of anemia in CKD correlates with duration and extent of renal disease.<sup>1-4</sup>

Anemia appears to have pronounced effects on patient well-being and may ultimately determine overall prognosis both before and after initiation of renal replacement therapy.<sup>5</sup> A particularly important effect of anemia is its potential role in cardiovascular disease in CKD. The relationship between anemia and cardiovascular morbidity and mortality in dialysis patients is well established.<sup>6</sup> Specifically, an independent relationship between cardiovascular disease and anemia has been shown in many studies of end-stage renal disease (ESRD) patients.<sup>7,8</sup> There is a growing body of evidence similarly associating anemia and cardiovascular disease in CKD patients. The effect of anemia on cardiovascular disease appears to start prior to the development of ESRD and many years before renal replacement therapy is actually required.

It is imperative to identify anemia in the CKD population because safe and effective therapies are available to correct this hematologic complication. This article, the fifth in a 6-part series on CKD, summarizes the available evidence supporting a relationship between anemia and important adverse outcomes in CKD patients. It also outlines an approach to evaluation and treatment of anemia in the CKD population.

### **ETIOLOGY OF ANEMIA IN CKD**

The anemia of CKD is characterized by normochromic normocytic red blood cells. Although several factors (eg, decreased red cell production or survival,

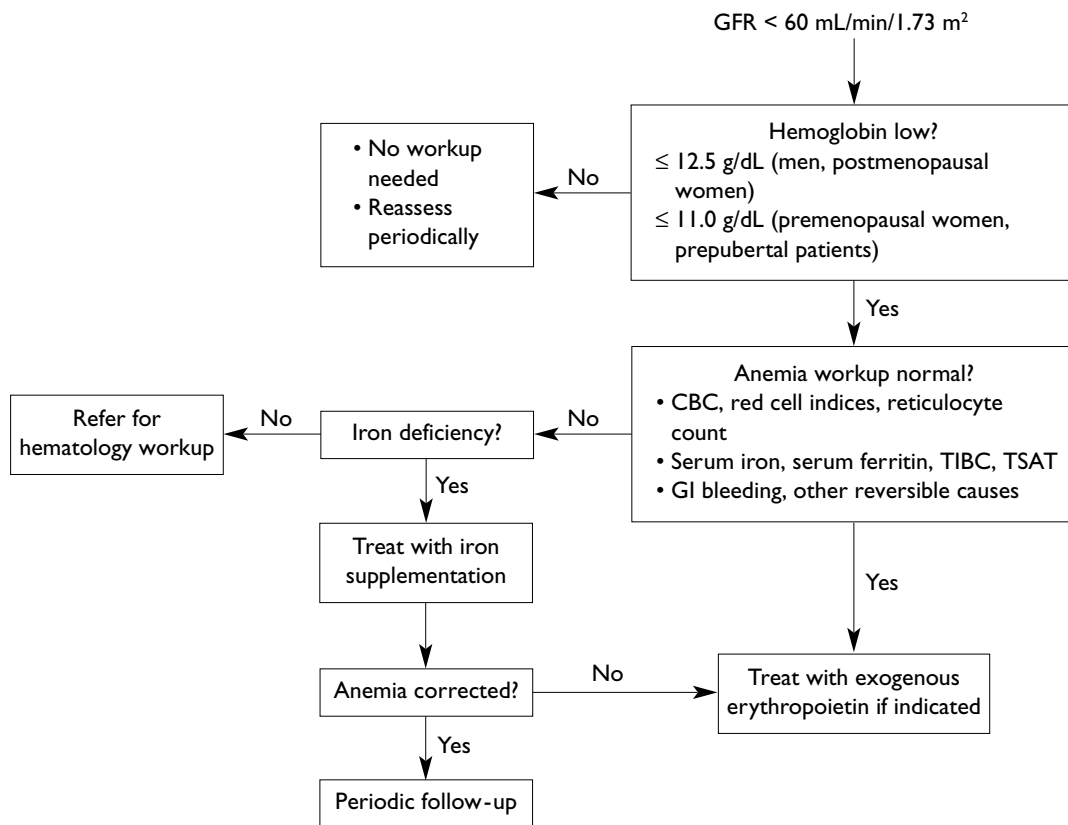
blood loss) may contribute to the development of anemia in patients with CKD, the primary cause is believed to be a deficiency in erythropoietin production by the failing kidneys.<sup>9,10</sup> Support for this belief includes the known presence of severe anemia in anephric patients, the state of "relative" erythropoietin deficiency (ie, inappropriately low erythropoietin levels for the degree of anemia) in CKD patients when compared with normal individuals, and the almost uniform increase in red blood cell mass seen in CKD patients following initiation of exogenous erythropoietic therapy.

Iron deficiency is a common secondary cause of anemia in CKD. Several factors may contribute to the development and maintenance of iron deficiency, including blood loss from phlebotomies associated with laboratory testing, occult gastrointestinal bleeding, decreased iron absorption, dietary restrictions, and iron utilization by exogenously stimulated erythropoiesis. The absence of stainable iron in the bone marrow of patients starting dialysis as well as the low transferrin saturation values in anemic CKD patients support a contributory role for iron deficiency in anemia of CKD.<sup>11-15</sup> In an analysis of data from the Third National Health and Nutrition Examination Survey (NHANES), 38.3% of 3453 anemic subjects with GFR levels between 20 and 60 mL/min/1.73 m<sup>2</sup> had transferrin saturation values below 20%.<sup>15</sup> Thus, all potential causes of iron deficiency, in particular gastrointestinal bleeding, should be fully evaluated in CKD patients.

Other secondary causes of anemia in CKD patients include hypothyroidism, severe hyperparathyroidism, acute and chronic inflammatory conditions, aluminum

---

*Dr. Abu-Alfa is an Associate Professor of Medicine, Section of Nephrology, and Director, Peritoneal Dialysis Program, Yale University School of Medicine, New Haven, CT. Dr. Perazella is an Associate Professor of Medicine, Section of Nephrology, and Director, Acute Dialysis Program, Yale University School of Medicine; he is also a member of the Hospital Physician Editorial Board.*



**Figure 1.** Recommended approach to the evaluation of anemia in patients with chronic kidney disease. GFR = glomerular filtration rate; CBC = complete blood count; GI = gastrointestinal; TIBC = total iron-binding capacity; TSAT = transferrin saturation. (Adapted with permission from National Kidney Foundation [NKF] Kidney Disease Outcome Quality Initiative [K/DOQI] Advisory Board. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Kidney Disease Outcome Quality Initiative. *Am J Kidney Dis* 2002;39(2 Suppl 2):S1–246 [Figure 25].)

toxicity, folate and vitamin B<sub>12</sub> deficiencies, shortened red blood cell survival, and hemoglobinopathies. Many of these contributing factors are treatable and, thus, should be considered when anemia is out of proportion to the underlying level of GFR.<sup>16</sup>

### EVALUATION OF ANEMIA IN CKD Recommended Approach to Testing

A working group of the National Kidney Foundation (NKF) recently published the Kidney Disease Outcome Quality Initiative (K/DOQI) guidelines for evaluation and management of CKD.<sup>17</sup> One component of the K/DOQI guidelines specifically addresses the workup of anemia in CKD patients, and a summary of these recommendations is shown in **Figure 1**.<sup>16,17</sup>

The NKF K/DOQI guidelines recommend that all stage 3 and 4 CKD patients (ie, patients with GFR val-

ues < 60 mL/min/1.73 m<sup>2</sup>) be evaluated and treated for anemia. Evaluation should begin with a measurement of hemoglobin level. If hemoglobin is at or below 11 g/dL (in premenopausal women and prepubertal patients) or 12.5 g/dL (in men and postmenopausal women), the workup should proceed as outlined in **Figure 1**. Recommended tests for evaluating anemia in CKD patients are shown in **Table 1**.<sup>16</sup> The NKF recommends hemoglobin testing over hematocrit testing for the evaluation and management of anemia, given the wider variations seen in hematocrit values and instability of samples.<sup>16,17</sup>

Measurement of serum erythropoietin level is of no additional diagnostic value in patients with GFR values less than 60 mL/min/1.73 m<sup>2</sup>. Routine erythropoietin measurement rarely influences clinical decision making in the care of CKD patients, particularly as it relates to

the need to initiate exogenous erythropoietic therapy. In fact, most anemic patients with CKD will have inappropriately low erythropoietin levels, and erythropoietin deficiency can be readily diagnosed upon exclusion of other common causes of anemia. Using GFR values estimated from equations (eg, the Modification of Diet in Renal Disease formula) rather than measuring serum creatinine levels may reduce the need to check erythropoietin levels in some borderline or unclear circumstances.<sup>5</sup> It should be noted, however, that some Medicare fiscal intermediaries and third-party payers may require the documentation of a low erythropoietin level prior to the initiation of exogenous erythropoietic therapy to qualify for reimbursement.

Diagnosis of iron deficiency may not always be straightforward in CKD patients. Functional iron deficiency, which refers to the imbalance between the iron needed to support erythropoiesis and the amount released from storage sites (reticuloendothelial tissue), often is present in these patients.<sup>16</sup> A ferritin level below 100 ng/mL is usually diagnostic of iron deficiency. However, the ferritin level may be elevated secondary to chronic inflammation or infection and, thus, is not always a reliable index of iron deficiency in CKD patients, in contrast to normal individuals without underlying renal disease. Transferrin saturation is considered the best routinely available test of iron deficiency.<sup>16</sup> A transferrin saturation less than 20% usually indicates functional iron deficiency.<sup>16</sup> Newer tests, such as the proportion of hypochromic red blood cells (> 10% with corpuscular hemoglobin < 28 g/dL)<sup>18</sup> and reticulocyte hemoglobin content,<sup>19,20</sup> will likely improve the diagnosis of functional iron deficiency in CKD patients. Ultimately, accurate diagnosis of iron deficiency will optimize iron management in these patients, allowing more efficient use of exogenous erythropoietic therapy.

#### ADVERSE EFFECTS OF ANEMIA IN CKD

Anemia is associated with several important adverse effects in ESRD patients, including decreased quality of life and poorer overall prognosis, and it is likely that anemia has a similar impact on CKD patients. However, most attention currently is focused on the possible role of anemia in cardiovascular disease, given the potential benefit to be gained from anemia correction.

#### Cardiovascular Disease

Cardiovascular disease encompasses a wide spectrum of clinical entities that may be the focus of scientific studies, including left ventricular hypertrophy, left ventricular dilatation, congestive heart failure, ischemic heart disease, peripheral vascular disease, and

**Table I.** Recommended Tests for Evaluation of Anemia in Chronic Kidney Disease

---

Hemoglobin and/or hematocrit level
Red blood cell indices
Reticulocyte count
Fecal occult blood test
Iron parameters
Serum iron
Total iron-binding capacity (TIBC)
Percent transferrin saturation (serum iron × 100 divided by TIBC)
Serum ferritin

---

Data from IV. NKF-K/DOQI Clinical Practice Guidelines for Anemia of Chronic Kidney Disease: update 2000 [published erratum appears in *Am J Kidney Dis* 2000;38:442]. *Am J Kidney Dis* 2000;37(1 Suppl 1):S182–238.

cerebrovascular disease. Evidence supporting a link between anemia of CKD and cardiovascular disease can be examined in 4 questions:

- Is cardiovascular disease more common in CKD patients compared with the general population?
- Do CKD patients have worse outcomes from cardiovascular disease compared with the general population?
- What is the role of anemia in the pathogenesis of cardiovascular disease in CKD patients?
- What is the effect of anemia correction on cardiovascular disease in CKD patients?

**Prevalence.** Several studies show that cardiovascular disease is more prevalent in CKD patients than in the general population. In some studies, an independent effect of CKD as a cardiovascular risk factor has not been clearly established; however, recent large trials have described a significant and independent effect of CKD on cardiovascular risk after adjusting for other risk factors associated with cardiovascular disease.<sup>21–23</sup> Left ventricular hypertrophy and ischemic heart disease are among the most common cardiovascular manifestations in the CKD population.<sup>3,21,22,24,25</sup> This is not surprising, given the shared risk factors of hypertension and diabetes mellitus in both CKD and ischemic heart disease. An analysis of the Framingham study data demonstrated that moderate CKD was associated with twice the prevalence of cardiovascular disease.<sup>21</sup> Left ventricular hypertrophy, as documented by echocardiographic criteria, was present in 74% of CKD patients initiating dialysis in Canada.<sup>26</sup>

Indirect evidence from other studies conducted in Canada supports this high prevalence and suggests that left ventricular hypertrophy develops progressively in these patients over the years preceding the start of dialysis. The prevalence averaged 34% to 39% in 2 studies of CKD patients; higher rates were noted in patients with lower GFR values.<sup>3,24</sup> In addition, eccentric rather than concentric left ventricular hypertrophy was found to be twice as prevalent, suggesting a prominent role for anemia in the genesis of hypertrophied left ventricles in CKD patients.<sup>3</sup> Of interest, limited data generated in two 1-year studies indicated that the incidence of overall cardiovascular disease and left ventricular hypertrophy in CKD was 20% and 10%, respectively.<sup>3,24</sup>

**Outcomes.** Studies also show that CKD patients have a higher mortality risk from cardiovascular disease. In ESRD patients commencing dialysis, the presence of left ventricular hypertrophy appears to be independently associated with increased mortality.<sup>26</sup> In addition, the risk of death during the first year following a myocardial infarction (MI) was almost twice that of the general population.<sup>27</sup> Similar findings are seen in CKD patients. One recent study from the Netherlands found a strong association between mild to moderate renal insufficiency and increased risk of overall cardiovascular mortality.<sup>28</sup> Several additional studies have documented worse outcomes after MI in CKD patients.<sup>29–31</sup> A possible explanation may be undertreatment with state-of-the-art cardiovascular therapies (eg, inhibitors of the renin-angiotensin system, contrast material, aspirin) out of fear of exacerbating underlying CKD. The risk of bleeding complications from thrombolytics employed for acute coronary syndromes in CKD patients with dysfunctional platelets reduces the use of this potentially life-saving therapy.<sup>29–31</sup> CKD also is associated with an increased risk for death after coronary revascularization surgery and valvular surgery.<sup>29,32–34</sup>

**Pathogenetic role of anemia.** Anemia has been documented to be independently associated with the presence of left ventricular hypertrophy in CKD patients and to play a significant role in its evolution. Evidence supporting a connection between anemia and left ventricular hypertrophy includes data from a cross-sectional study of 175 patients with mean creatinine clearance of 25.5 mL/min.<sup>24</sup> A decline in hemoglobin of 1 g/dL was independently associated with a 6-fold increased risk for left ventricular hypertrophy.<sup>24</sup> Similarly, a 0.5 g/dL decrease in hemoglobin was independently associated with a 1.32 odds ratio for left ventricular hypertrophy in a prospective 1-year study.<sup>3</sup> More severe left ventricular hypertrophy also was seen with lower hemoglobin levels despite these values being close to

normal. Of interest, the absence of left ventricular hypertrophy at baseline was found to be a risk factor for left ventricular growth, highlighting the need to address reversible causes (eg, anemia) at an early stage.<sup>3</sup>

At this time, a clear role for anemia in initiating or accelerating atherogenesis in CKD patients has not been shown. However, there are concerns regarding the negative role anemia might play in oxidative stress. In addition, other factors peculiar to CKD (eg, the uremic milieu, calcification, hypertension, volume expansion) contribute to the maladaptive cardiac response to anemia; cardiac fibrosis and potentially irreversible LVH may result from these factors.<sup>35,36</sup>

**Cardiovascular benefits of anemia correction.** Correction of anemia in ESRD patients has been shown to reduce left ventricular mass index, improve ejection fraction, and mitigate ischemic changes that develop during stress tests.<sup>37–41</sup> Similar data are available in CKD patients, although studies have included only a small number of patients with severe left ventricular hypertrophy and significantly reduced GFR values.<sup>42–44</sup> Prospective studies, such as the CREATE trial, are underway to further elucidate the long-term benefits of anemia correction in earlier stages of CKD and less severe left ventricular hypertrophy.<sup>45</sup> Earlier intervention raises the interesting question of whether primary prevention of anemia in CKD might serve to modulate development of irreversible cardiac changes.

#### **TREATMENT OF ANEMIA IN CKD**

Correction of anemia in CKD patients has benefits beyond solely improving cardiac status. A reduction in mortality during the first 24 months after initiating hemodialysis was noted in patients treated with erythropoietin in the predialysis phase of care.<sup>46</sup> Additional benefits of anemia correction in CKD that have been reported in the literature include (1) improved sense of well-being, quality of life,<sup>47</sup> neurocognitive function,<sup>48</sup> and work capacity<sup>49</sup>; (2) reduced need for packed red blood cell transfusions; (3) reduced allo-sensitization prior to renal transplantation<sup>50</sup>; and (4) reduced hospitalization.<sup>51</sup>

#### **Approach to Anemia Correction**

Exogenous erythropoietic proteins have been successfully used to correct anemia in patients with CKD. Hemoglobin is typically measured on a weekly basis during the initiation phase of therapy and until the target level has been attained. Thereafter, biweekly or monthly determinations are usually sufficient. Potential causes for suboptimal response to exogenous erythropoietic therapy, such as iron deficiency, gastrointestinal

blood loss, and primary hematologic disorders, should be fully investigated as clinically indicated.

Optimal target hemoglobin levels have not been determined, but current recommendations are to maintain the hemoglobin level between 11 and 12 g/dL (hematocrit levels between 33% and 36%).<sup>17</sup> In certain circumstances, as in CKD patients with ischemic heart disease, left ventricular hypertrophy, or chronic obstructive lung disease, it may be medically justifiable to maintain the hemoglobin level above 12 g/dL. Normalization of hemoglobin (ie, correction to levels considered in the normal range) is currently under study in prospective trials.<sup>45</sup> As such, full correction of anemia can not be recommended at this time, given the absence of scientific evidence supporting both beneficial effects and safety employing this approach.

**Exogenous erythropoietic proteins.** Two agents are currently available in the United States for correcting anemia in CKD. Recombinant human erythropoietin alfa (rHuEpo), the first exogenous erythropoietic protein to be developed, has been in clinical use for well over a decade. Subcutaneous injection is the preferred route of rHuEpo administration in CKD patients. Self-administration is easy to learn and well tolerated by most patients; however, some patients experience minor pain at the site of injection. rHuEpo usually is administered on a weekly or twice-weekly basis. More frequent dosing may be required at initiation, depending on the degree of anemia. After attaining target hemoglobin levels, many patients can be successfully maintained on weekly, and in some cases less frequent, injections.<sup>52</sup> The recommended starting dose of rHuEpo is 50 to 100 U/kg.

Darbepoetin is a newer erythropoietic protein with a longer serum half-life than rHuEpo. It differs structurally from rHuEpo by its higher sialic acid-containing carbohydrate content, an important determinant of the serum half-life of these molecules.<sup>53</sup> The safety profile of this long-acting erythropoietic agent is similar to that of rHuEpo. Darbepoetin usually is given no more often than once a week,<sup>54</sup> but emerging evidence demonstrates that administration once every other week has also been successful in correcting anemia.<sup>55</sup> Such reduced frequency of administration is likely to lower the burden of therapy in CKD patients. The starting dose for darbepoetin is 0.45 µg/kg. Most patients will require a dose of 25 or 40 µg. Switching to darbepoetin from rHuEpo can be navigated using available conversion tables. However, the frequency of administration should be reduced to no more than once weekly dosing.

**Iron supplementation.** As erythropoiesis is stimulated and the marrow produces red blood cells, iron stores

are rapidly utilized. As a result, many patients will require iron supplementation to maintain erythropoietic responsiveness and target hemoglobin levels. Oral supplementation usually is effective, but intravenous iron preparations might be required, especially in patients with poor intestinal absorption, intolerance to oral iron, or persistently low iron indices. Iron indices, such as transferrin saturation and serum ferritin, should be followed on a regular basis to guide iron administration.

#### **Areas of Potential Concern**

**Effect on renal function.** An early study reported a rapid progression of renal disease with exogenous erythropoietin in an animal model of renal insufficiency, initially raising concerns that anemia correction might worsen renal function.<sup>56</sup> Later work demonstrated that renal dysfunction in this animal model was most likely caused by uncontrolled hypertension rather than correction of anemia. In addition, this concern has not been substantiated in several human studies, all of which have uniformly shown a neutral effect of exogenous erythropoietic therapy on renal function in CKD patients. This collective experience is summarized in **Table 2**.

Conversely, preliminary data from several studies suggest that correction of anemia may actually slow the progression of CKD. The mechanisms for such a desirable effect may relate to the impact of anemia and hypoxia on interstitial fibrosis and the anti-apoptotic effect of erythropoietin.<sup>63,65–67</sup> However, this area needs further study.

**Effect on blood pressure control.** A large body of evidence documents the many years of experience using rHuEpo to treat anemia in CKD patients. During initial use of rHuEpo, there were concerns about severe hypertensive crisis, and seizures were prominent.<sup>68</sup> However, these concerns have been nearly eliminated. The increase in blood pressure that develops with rHuEpo is most likely due to an increase in systemic vascular resistance that occurs with rapid anemia correction. In addition, direct or indirect pressor effects of exogenous erythropoietin have been suggested.<sup>69</sup> The hypertensive effects of rHuEpo are mitigated when the rate of hemoglobin correction is slowed to an average of 1 g/dL per month. As shown in **Table 3**, hypertension may still develop with slower rates of anemia correction, so blood pressure monitoring should be a standard component of rHuEpo therapy. However, in some of the studies hypertension was seen only with 24-hour ambulatory measurements, suggesting the continued need to observe blood pressure on a serial basis. Blood pressure control is easily achieved with adjustments in antihypertensive regimens, including the use of calcium channel blockers.<sup>70</sup>

**Table 2.** Studies of the Effect of Anemia Correction with Erythropoietin on Progression of Renal Disease

Year	Author	Patients, N	Duration	Serum Cr, mg/dL (mean ± SD)	Effect on Renal Disease Progression
1989	Kleinman <sup>57</sup>	14	12 weeks	3–11	Neutral (I)
1990	Lim <sup>58</sup>	26	52 weeks	6.0 ± 2.05	Neutral (I)
1990	Watson <sup>59</sup>	11	12 weeks	6.6 ± 1.3	Acceleration (G)
1990	Abraham <sup>60</sup>	8	18 weeks	> 3	Neutral (G, I)
1991	US study <sup>61</sup>	117	26 weeks	5.9 ± 2.5	Neutral (I)
1992	Austrian study <sup>62</sup>	123	12 weeks	6.2 ± 0.2	Neutral (I)
1994	Roth <sup>63</sup>	83	48 weeks	5.5 + 1.6	Neutral (I)
1995	Savica <sup>64</sup>	16	52 weeks	3.45 ± 1.9	Neutral (G, I)
1997	Portoles <sup>42</sup>	11	26 weeks	6.3 ± 1.3	Neutral (I)
1997	Kuriyama <sup>65</sup>	42	28 months	2.9 ± 0.7	Slowing (Cr)
2000	Hayashi <sup>44</sup>	9	52 weeks	6.2 ± 2.0	Neutral (I)
2000	Silverberg <sup>43</sup>	26	30 weeks	2.59 ± 0.77	Neutral (I)
2001	Jungers <sup>66</sup>	20	92 weeks	5.96 ± 0.84	Slowing (CrCl)

Cr = serum creatinine; CrCl = creatinine clearance; G = glomerular filtration rate; I = slope of I/Cr over time.

**Table 3.** Studies of the Hypertensive Effect of Anemia Correction with Erythropoietin

Year	Author	Patients, N	Duration	% Change in Hct/month	Hypertensive Effect, % of patients
1989	Eschbach <sup>68</sup>	17	20 weeks	5–9	59
1989	Lim <sup>48</sup>	14	8 weeks	3–4	0–21
1990	Lim <sup>58</sup>	26	52 weeks	n/a	0
1991	US study <sup>61</sup>	117	26 weeks	5–6	22
1992	Austrian study <sup>62</sup>	123	12 weeks	2–3	0
1994	Roth <sup>63</sup>	83	48 weeks	3	0
1997	Portoles <sup>42</sup>	11	26 weeks	3	55 (Amb)
2000	Hayashi <sup>44</sup>	9	12 weeks	4.25	44 (Amb)
2001	Jungers <sup>66</sup>	20	92 weeks	0.9 g/dL (Hg)	0

Amb = ambulatory blood pressure measurement; Hct = hematocrit; Hg = hemoglobin; n/a = not available.

The potential negative effect of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers on rHuEpo responsiveness has been studied extensively in ESRD patients. The data are conflicting, but a prospective, crossover study showed no effect of ACE inhibitors on hemoglobin levels or rHuEpo dosing.<sup>71</sup> The effect of ACE inhibitors on anemia correction in CKD patients has not been specifically studied,<sup>72,73</sup> but there is concern that ACE inhibitors may inhibit the breakdown of an already accumulating

negative tetrapeptide regulator of erythropoiesis (ie, AcSDKP). This inhibitory effect is likely to be overcome by the use of standard doses of exogenous erythropoietic agents,<sup>72,73</sup> thereby permitting the use of ACE inhibitors despite the presence of anemia.

### CONCLUSION

Anemia is a common and often early complication of CKD. Deficient renal production of erythropoietin is the major cause of anemia in CKD patients, although

iron deficiency also contributes significantly. Anemia is associated with significant cardiovascular disease and worse outcomes in CKD patients, even at moderate levels of GFR reduction. Correction with exogenous erythropoietic therapy is fairly easy to achieve, and long-term experience with these agents has documented both efficacy and safety. Beneficial effects of anemia correction are increasingly being reported. Many large studies are currently in progress to further elucidate the role of anemia correction in improving outcomes in the CKD population. The sixth and final article in this series will examine issues in preparing CKD patients for the initiation of renal replacement therapy.

**HP**

## REFERENCES

1. Kazmi WH, Kausz AT, Khan S, et al. Anemia: an early complication of chronic renal insufficiency. *Am J Kidney Dis* 2001;38:803–12.
2. Hsu CY, Bates DW, Kuperman GJ, Curhan GC. Relationship between hematocrit and renal function in men and women. *Kidney Int* 2001;59:725–31.
3. Levin A, Thompson CR, Ethier J, et al. Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. *Am J Kidney Dis* 1999;34:125–34.
4. Astor BC, Muntner P, Levin A, et al. Association of kidney function with anemia: the Third National Health and Nutrition Examination Survey (1988–1994). *Arch Intern Med* 2002;162:1401–8.
5. Collins AJ, Li S, St Peter W, et al. Death, hospitalization, and economic associations among incident hemodialysis patients with hematocrit values of 36 to 39%. *J Am Soc Nephrol* 2001;12:2465–73.
6. Foley RN, Parfrey PS, Harnett JD, et al. The impact of anemia on cardiomyopathy, morbidity and mortality in end-stage renal disease. *Am J Kidney Dis* 1996;28:53–61.
7. Ma JZ, Ebben J, Xia H, Collins A. Hematocrit level and associated mortality in hemodialysis patients. *J Am Soc Nephrol* 1999;10:610–9.
8. Silberberg JS, Barre PE, Prichard SS, Sniderman AD. Impact of left ventricular hypertrophy on survival in end-stage renal disease. *Kidney Int* 1989;32:286–90.
9. McGonigle RJ, Boineau FG, Beckman B, et al. Erythropoietin and inhibitors of in vitro erythropoiesis in the development of anemia in children with renal disease. *J Lab Clin Med* 1985;105:449–58.
10. Eschbach JW, Adamson JW. Anemia of end-stage renal disease (ESRD). *Kidney Int* 1985;28:1–5.
11. Fudin R, Jaichenko J, Shostak A, et al. Correction of uremic iron deficiency anemia in hemodialyzed patients: a prospective study. *Nephron* 1998;79:299–305.
12. Schustack A, Meshiaj D, Waiss Z, Gotloib L. Intramuscular iron replenishment and replacement combined with testosterone enanthate in maintenance hemodialysis anemia: a follow-up of up to 8 years on 16 patients. *Clin Nephrol* 1985;23:303–6.
13. Akmal M, Sawelson S, Karubian F, Gadallah M. The prevalence and significance of occult blood loss in patients with predialysis advanced chronic renal failure (CRF), or receiving dialytic therapy. *Clin Nephrol* 1994;42:198–202.
14. Panesar A, Agarwal R. Safety and efficacy of sodium ferric gluconate complex in patients with chronic kidney disease. *Am J Kidney Dis* 2002;40:924–31.
15. Hsu CY, McCulloch CE, Curhan GC. Epidemiology of anemia associated with chronic renal insufficiency among adults in the United States: results from the Third National Health and Nutrition Examination Survey. *J Am Soc Nephrol* 2001;13:504–10.
16. IV. NKF-K/DOQI Clinical Practice Guidelines for Anemia of Chronic Kidney Disease: update 2000 [published erratum appears in *Am J Kidney Dis* 2000;38:442]. *Am J Kidney Dis* 2000;37(1 Suppl 1):S182–238.
17. National Kidney Foundation (NKF) Kidney Disease Outcome Quality Initiative (K/DOQI) Advisory Board. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Kidney Disease Outcome Quality Initiative. Am J Kidney Dis* 2002;39(2 Suppl 2):S1–246.
18. MacDougall IC, Cavill I, Hulme B, et al. Detection of functional iron deficiency during erythropoietin treatment: a new approach. *BMJ* 1992;304:225–6.
19. Fishbane S, Galgano C, Langley RC Jr, et al. Reticulocyte hemoglobin content in the evaluation of iron status of hemodialysis patients. *Kidney Int* 1997;52:217–22.
20. Mittman N, Sreedhara R, Mushnick R, et al. Reticulocyte hemoglobin content predicts functional iron deficiency in hemodialysis patients receiving rHuEPO. *Am J Kidney Dis* 1997;30:912–22.
21. Cullerton BF, Larson MG, Wilson PW, et al. Cardiovascular disease and mortality in a community-based cohort with mild renal insufficiency. *Kidney Int* 1999;56:2214–9.
22. Levin A, Djurdjev O, Barrett B, et al. Cardiovascular disease in patients with chronic kidney disease: getting to the heart of the matter. *Am J Kidney Dis* 2001;38:1398–407.
23. Shlipak MG, Fried LF, Crump C, et al. Cardiovascular disease risk status in elderly persons with renal insufficiency. *Kidney Int* 2002;62:997–1004.
24. Levin A, Singer J, Thompson CR, et al. Prevalent left ventricular hypertrophy in the predialysis population: identifying opportunities for intervention. *Am J Kidney Dis* 1996;27:347–54.
25. Tonelli M, Bohm C, Pandeya S, et al. Cardiac risk factors and the use of cardioprotective medications in patients with chronic renal insufficiency. *Am J Kidney Dis* 2001;37:484–9.
26. Foley RN, Parfrey PS, Harnett JD, et al. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. *Kidney Int* 1995;47:186–92.
27. Herzog CA, MA JZ, Collins AJ. Poor long-term prognosis after acute myocardial infarction among patients on long-term dialysis. *N Engl J Med* 1998;339:799–805.
28. Henry RM, Kostense PJ, Bos G, et al. Mild renal

- insufficiency is associated with increased cardiovascular mortality: the Hoorn Study. *Kidney Int* 2002;62:1402–7.
29. Shlipak MG, Heidenreich PA, Noguchi H, et al. Association of renal insufficiency with treatment and outcomes after myocardial infarction in elderly patients. *Ann Intern Med* 2002;137:555–62.
  30. Beattie JN, Soman SS, Sandberg KR, et al. Determinants of mortality after myocardial infarction in patients with advanced renal dysfunction [published erratum appears in *Am J Kidney Dis* 2001;38:701]. *Am J Kidney Dis* 2001;37:1191–200.
  31. Wright RS, Reeder GS, Herzog CA, et al. Acute myocardial infarction and renal dysfunction: a high-risk combination. *Ann Intern Med* 2002;13:563–70.
  32. Anderson RJ, O'Brien M, MaWhinney S, et al. Renal failure predisposes patients to adverse outcome after coronary artery bypass surgery. VA Cooperative Study #5. *Kidney Int* 1999;55:1057–62.
  33. Anderson RJ, O'Brien M, MaWhinney S, et al. Mild renal failure is associated with adverse outcome after cardiac valve surgery. *Am J Kidney Dis* 2000;35:1127–34.
  34. Szczech LA, Reddan DN, Owen WF, et al. Differential survival after coronary revascularization procedures among patients with renal insufficiency. *Kidney Int* 2001;60:292–9.
  35. Stevens L, Stigant C, Levin A. Should hemoglobin be normalized in patients with chronic kidney disease? *Semin Dial* 2002;15:8–13.
  36. Metivier F, Marchais SJ, Guerein AP, et al. Pathophysiology of anaemia: focus on the heart and blood vessels. *Nephrol Dial Transplant* 2000;15 Suppl 3:14–8.
  37. Massimetti C, Pontillo D, Feriozzi S, et al. Impact of recombinant human erythropoietin treatment on left ventricular hypertrophy and cardiac function in dialysis patients. *Blood Purif* 1998;16:317–24.
  38. Silberberg J, Racine N, Barre P, Sniderman AD. Regression of left ventricular hypertrophy in dialysis patients following correction of anemia with recombinant human erythropoietin. *Can J Cardiol* 1990;6:1–4.
  39. Zehnder C, Zuber M, Sulzer M, et al. Influence of long-term amelioration of anemia and blood pressure control on left ventricular hypertrophy in hemodialyzed patients. *Nephron* 1992;61:21–5.
  40. Pascual J, Teruel JL, Moya JL, et al. Regression of left ventricular hypertrophy after partial correction of anemia with erythropoietin in patients on hemodialysis: a prospective study. *Clin Nephrol* 1991;35:280–7.
  41. Wizemann V, Kaufmann J, Kramer W. Effect of erythropoietin on ischemia tolerance in anemic hemodialysis patients with confirmed coronary artery disease. *Nephron* 1992;62:161–5.
  42. Portoles J, Torralbo A, Martin P, et al. Cardiovascular effects of recombinant human erythropoietin in predialysis patients. *Am J Kidney Dis* 1997;29:541–8.
  43. Silverberg DS, Wexler D, Blum M, et al. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. *J Am Coll Cardiol* 2000;35:1737–44.
  44. Hayashi T, Suzuki A, Shoji T, et al. Cardiovascular effects of normalizing the hematocrit level during erythropoietin therapy in predialysis patients with chronic renal failure. *Am J Kidney Dis* 2000;35:250–6.
  45. Eckardt KU. The CREATE trial—building the evidence. Cardiovascular risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) Trial. *Nephrol Dial Transplant* 2001;16 Suppl 2:16–8.
  46. Fink J, Blahut S, Reddy M, Light P. Use of erythropoietin before the initiation of dialysis and its impact on mortality. *Am J Kidney Dis* 2001;37:348–55.
  47. Revicki DA, Brown RE, Feeny DH, et al. Health-related quality of life associated with recombinant human erythropoietin therapy for predialysis chronic renal disease patients. *Am J Kidney Dis* 1995;25:548–54.
  48. Lim VS, DeGowin RL, Zavala D, et al. Recombinant human erythropoietin treatment in pre-dialysis patients. A double-blind placebo-controlled trial. *Ann Intern Med* 1989;110:108–14.
  49. Clyne N, Jogestrand T. Effect of erythropoietin treatment on physical exercise capacity and renal function in predialytic uremic patients. *Nephron* 1992;60:390–6.
  50. Vella JP, O'Neill D, Atkins N, et al. Sensitization to human leukocyte antigen before and after the introduction of erythropoietin. *Nephrol Dial Transplant* 1998;13:2027–32.
  51. Holland DC, Lam M. Predictors of hospitalization and death among pre-dialysis patients: a retrospective cohort study. *Nephrol Dial Transplant* 2000;15:650–8.
  52. Piccoli A, Malagoli A, Komminos G, Pastori G. Subcutaneous epoetin-alpha every one, two, and three weeks in renal anemia. *J Nephrol* 2002;15:565–74.
  53. Egrie JC, Browne JK. Development and characterization of novel erythropoiesis stimulating protein (NESP). *Nephrol Dial Transplant* 2001;16 Suppl 3:3–13.
  54. Locatelli F, Olivares J, Walker R, et al. European/Australian NESP 980202 Study Group. Novel erythropoiesis stimulating protein for treatment of anemia in chronic renal insufficiency. *Kidney Int* 2001;60:741–7.
  55. Suranyi MG, Lindberg JS, Navarro J, et al. Treatment of anemia with darbepoetin alfa administered de novo once every other week in chronic kidney disease. *Am J Nephrol* 2003;23:106–11.
  56. Garcia DL, Anderson S, Rennke HG, Brenner BM. Anemia lessens and its prevention with recombinant human erythropoietin worsens glomerular injury and hypertension in rats with reduced renal mass. *Proc Natl Acad Sci U S A* 1988;85:6142–6.
  57. Kleinman KS, Schweitzer SU, Perdue ST, et al. The use of recombinant human erythropoietin in the correction of anemia in predialysis patients and its effect on renal function: a double-blind, placebo-controlled trial. *Am J Kidney Dis* 1989;14:486–95.
  58. Lim VS, Fangman J, Flanigan MJ, et al. Effect of recombinant human erythropoietin on renal function in

(continued on page 46)

(from page 38)

- humans. *Kidney Int* 1990;37:131–6.
59. Watson AJ, Gimenez LF, Cotton S, et al. Treatment of the anemia of chronic renal failure with subcutaneous recombinant human erythropoietin. *Am J Med* 1990;89:432–5.
  60. Abraham PA, Opsahl JA, Rachael KM, et al. Renal function during erythropoietin therapy for anemia in predialysis chronic renal failure patients. *Am J Nephrol* 1990;10:128–36.
  61. Double-blind, placebo-controlled study of the therapeutic use of recombinant human erythropoietin for anemia associated with chronic renal failure in predialysis patients. The US Recombinant Human Erythropoietin Predialysis Study Group [published erratum appears in *Am J Kidney Dis* 1991;18:420]. *Am J Kidney Dis* 1991;18:50–9.
  62. Effectiveness and safety of recombinant human erythropoietin in predialysis patients. Austrian Multicenter Study Group of r-HuEPO in Predialysis Patients. *Nephron* 1992;61:399–403.
  63. Roth D, Smith RD, Schulman G, et al. Effects of recombinant human erythropoietin on renal function in chronic renal failure predialysis patients. *Am J Kidney Dis* 1994;24:777–84.
  64. Savica V, Costantino G, Monardo P, Bellinghieri G. Subcutaneous low doses of recombinant human erythropoietin in predialysis patients do not interfere with the progression of renal failure. *Am J Nephrol* 1995;15:10–4.
  65. Kuriyama S, Tomonari H, Yoshida H, et al. Reversal of anemia by erythropoietin therapy retards the progression of chronic renal failure, especially in nondiabetic patients. *Nephron* 1997;77:176–85.
  66. Jungers P, Choukroun G, Oualim Z, et al. Beneficial influence of recombinant human erythropoietin therapy on the rate of progression of chronic renal failure in predialysis patients. *Nephrol Dial Transplant* 2001;16:307–12.
  67. Rossert J, McClellan WM, Roger SD, Verbeelen DL. Epoetin treatment: what are the arguments to expect a beneficial effect on renal disease progression [editorial]? *Nephrol Dial Transplant* 2002;17:359–62.
  68. Eschbach JW, Kelly MR, Haley NR, et al. Treatment of the anemia of progressive renal failure with recombinant human erythropoietin. *N Engl J Med* 1989;321:158–63.
  69. Vaziri ND. Cardiovascular effects of erythropoietin and anemia correction. *Curr Opin Nephrol Hypertens* 2001;10:633–7.
  70. Ni Z, Wang XQ, Vaziri ND. Nitric oxide metabolism in erythropoietin-induced hypertension: effect of calcium channel blockade. *Hypertension* 1998;32:724–9.
  71. Abu-Alfa A, Cruz D, Perazella MA, et al. ACE inhibitors do not induce recombinant human erythropoietin resistance in hemodialysis patients. *Am J Kidney Dis* 2000;35:1076–82.
  72. Le Meur Y, Lorgeot V, Comte L, et al. Plasma levels and metabolism of AcSDKP in patients with chronic renal failure: relationship with erythropoietin requirements. *Am J Kidney Dis* 2001;38:510–7.
  73. Abu-Alfa A, Perazella MA. Angiotensin-converting enzyme inhibitors and anemia in chronic kidney disease: a complex interaction [letter]. *Am J Kidney Dis* 2002;39:896–7.

Copyright 2003 by Turner White Communications Inc., Wayne, PA. All rights reserved.