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

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Anemia 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.¹⁻⁴

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.⁵ 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.⁶ Specifically, an independent relationship between cardiovascular disease and anemia has been shown in many studies of end-stage renal disease (ESRD) patients.^{7,8} 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.^{9,10} 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.¹¹⁻¹⁵ 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 m² had transferrin saturation values below 20%.¹⁵ 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

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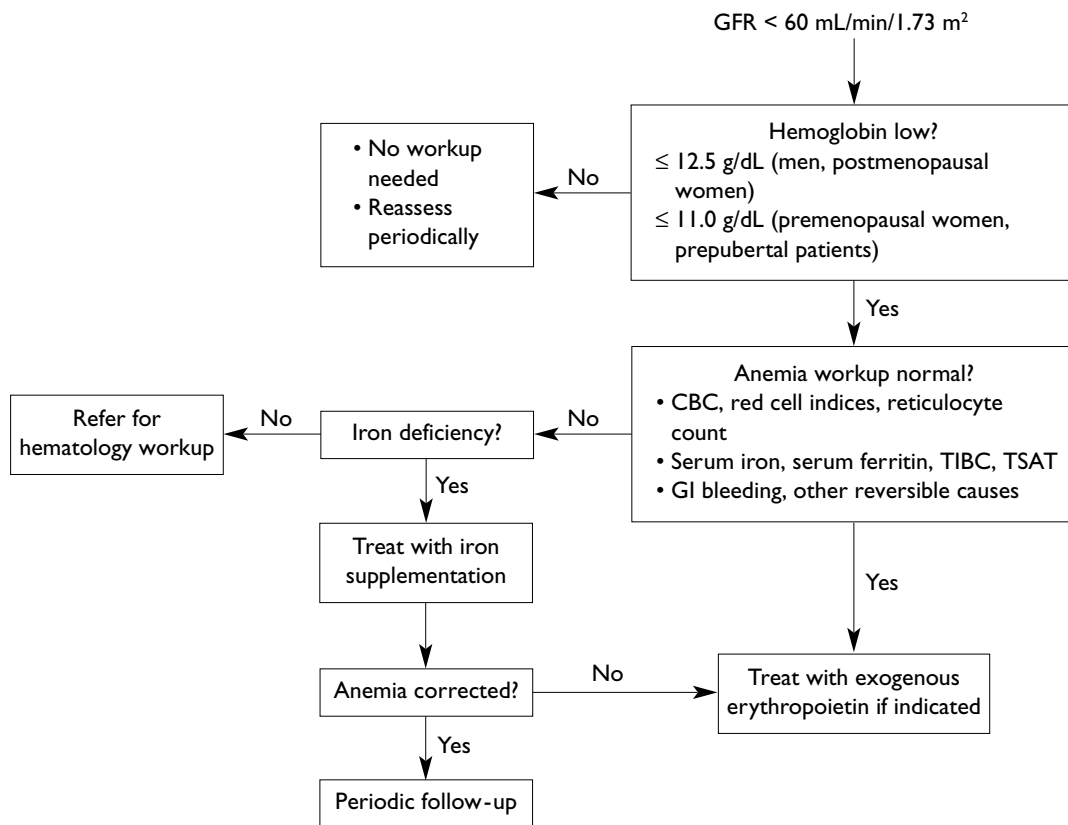


Figure 1. Recommended approach to the evaluation of anemia in patients with chronic kidney disease. GFR = glomerular filtration rate; CBC = complete blood count; GI = gastrointestinal; TIBC = total iron-binding capacity; TSAT = transferrin saturation. (Adapted with permission from National Kidney Foundation [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 B₁₂ 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.¹⁶

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.¹⁷ 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**.^{16,17}

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 m²) 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**.¹⁶ 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.^{16,17}

Measurement of serum erythropoietin level is of no additional diagnostic value in patients with GFR values less than 60 mL/min/1.73 m². 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.⁵ 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.¹⁶ 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.¹⁶ A transferrin saturation less than 20% usually indicates functional iron deficiency.¹⁶ Newer tests, such as the proportion of hypochromic red blood cells (> 10% with corpuscular hemoglobin < 28 g/dL)¹⁸ and reticulocyte hemoglobin content,^{19,20} 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.^{21–23} Left ventricular hypertrophy and ischemic heart disease are among the most common cardiovascular manifestations in the CKD population.^{3,21,22,24,25} 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.²¹ Left ventricular hypertrophy, as documented by echocardiographic criteria, was present in 74% of CKD patients initiating dialysis in Canada.²⁶

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.^{3,24} 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.³ 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.^{3,24}

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.²⁶ In addition, the risk of death during the first year following a myocardial infarction (MI) was almost twice that of the general population.²⁷ 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.²⁸ Several additional studies have documented worse outcomes after MI in CKD patients.^{29–31} 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.^{29–31} CKD also is associated with an increased risk for death after coronary revascularization surgery and valvular surgery.^{29,32–34}

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.²⁴ A decline in hemoglobin of 1 g/dL was independently associated with a 6-fold increased risk for left ventricular hypertrophy.²⁴ 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.³ 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.³

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.^{35,36}

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.^{37–41} 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.^{42–44} 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.⁴⁵ 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.⁴⁶ Additional benefits of anemia correction in CKD that have been reported in the literature include (1) improved sense of well-being, quality of life,⁴⁷ neurocognitive function,⁴⁸ and work capacity⁴⁹; (2) reduced need for packed red blood cell transfusions; (3) reduced allo-sensitization prior to renal transplantation⁵⁰; and (4) reduced hospitalization.⁵¹

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%).¹⁷ 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.⁴⁵ 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.⁵² 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.⁵³ 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,⁵⁴ but emerging evidence demonstrates that administration once every other week has also been successful in correcting anemia.⁵⁵ 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.⁵⁶ 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.^{63,65–67} 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.⁶⁸ 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.⁶⁹ 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.⁷⁰

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 ⁵⁷	14	12 weeks	3–11	Neutral (I)
1990	Lim ⁵⁸	26	52 weeks	6.0 ± 2.05	Neutral (I)
1990	Watson ⁵⁹	11	12 weeks	6.6 ± 1.3	Acceleration (G)
1990	Abraham ⁶⁰	8	18 weeks	> 3	Neutral (G, I)
1991	US study ⁶¹	117	26 weeks	5.9 ± 2.5	Neutral (I)
1992	Austrian study ⁶²	123	12 weeks	6.2 ± 0.2	Neutral (I)
1994	Roth ⁶³	83	48 weeks	5.5 + 1.6	Neutral (I)
1995	Savica ⁶⁴	16	52 weeks	3.45 ± 1.9	Neutral (G, I)
1997	Portoles ⁴²	11	26 weeks	6.3 ± 1.3	Neutral (I)
1997	Kuriyama ⁶⁵	42	28 months	2.9 ± 0.7	Slowing (Cr)
2000	Hayashi ⁴⁴	9	52 weeks	6.2 ± 2.0	Neutral (I)
2000	Silverberg ⁴³	26	30 weeks	2.59 ± 0.77	Neutral (I)
2001	Jungers ⁶⁶	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 ⁶⁸	17	20 weeks	5–9	59
1989	Lim ⁴⁸	14	8 weeks	3–4	0–21
1990	Lim ⁵⁸	26	52 weeks	n/a	0
1991	US study ⁶¹	117	26 weeks	5–6	22
1992	Austrian study ⁶²	123	12 weeks	2–3	0
1994	Roth ⁶³	83	48 weeks	3	0
1997	Portoles ⁴²	11	26 weeks	3	55 (Amb)
2000	Hayashi ⁴⁴	9	12 weeks	4.25	44 (Amb)
2001	Jungers ⁶⁶	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.⁷¹ The effect of ACE inhibitors on anemia correction in CKD patients has not been specifically studied,^{72,73} 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,^{72,73} 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

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