

*“Anemia often develops early in the course of chronic kidney disease (CKD), well before the onset of end-stage renal disease, and then worsens as CKD progresses.”*

# II Anemia & Chronic Kidney Disease

## **Key Points**

- Anemia is a common complication of chronic kidney disease (CKD), develops early, and worsens as CKD progresses.
- CKD-related anemia has multiple adverse consequences, affecting quality of life, cognitive function, exercise capacity, immune response, and heart function.
- Early identification and treatment of CKD-related anemia to prevent serious consequences is an idea promoted as the Renal Anemia Management Period (RAMP) by concerned nephrologists.
- Benefits of anemia correction in patients with CKD include decreased morbidity, hospitalization, and mortality; and improvement in quality of life, exercise capacity, cognitive function, and sexual function.



### CKD: An Insidious Disease

Chronic kidney disease (CKD) is an insidious disease that gradually impairs kidney function. In its earliest stages, patients may be unaware they have the disease, but over a period ranging from several years to several decades, CKD will often progress to end-stage renal disease (ESRD), requiring renal replacement therapy (dialysis or kidney transplantation) to sustain life.

CKD arises as a consequence of diabetes mellitus, hypertensive nephrosclerosis, chronic glomerulonephritis, polycystic kidney disease, and a host of other disorders.<sup>1</sup> Diabetes and hypertension are the two leading causes of ESRD, accounting for approximately 43% and 27% of all new ESRD cases, respectively.<sup>2</sup>

### Staging and Prevalence of CKD

While the terminology of the formal literature has been inconsistent and confusing, this monograph has adopted the CKD staging terminology recently proposed by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) and uses the term *chronic kidney disease* to encompass the entire spectrum of kidney disease, from its earliest stages through ESRD.<sup>3,4</sup>

As serum creatinine (SCr) levels are an imperfect indicator of the severity of kidney disease, the NKF-K/DOQI staging and prevalence estimates are based on glomerular filtration rates (GFRs) derived using a formula developed by Levey and colleagues<sup>5</sup> from data in the Modification of Diet in Renal Disease Study.

Table 2-1

#### NKF-K/DOQI Classification and Prevalence Estimates for Chronic Kidney Disease

Stages	Description	GFR (mL/min/1.73m <sup>2</sup> )	Prevalence in US Population* (in millions)	Action
	At increased risk	≥90 (with CKD risk factors)	N/A	Screening, CKD risk reduction
1	Kidney damage with normal or ↑ GFR	≥90	5.9 (3.3%)	Diagnosis and treatment; Treatment of comorbid conditions; Slowing progression of CVD
2	Kidney damage with mild ↓ GFR	60-89	5.3 (3.0%)	Estimating progression
3	Moderate ↓ GFR	30-59	7.6 (4.3%)	Evaluating and treating complications
4	Severe ↓ GFR	15-29	0.4 (0.2%)	Preparation for kidney replacement therapy
5	Kidney failure	<15 (or dialysis)	0.3 (0.1%)	Replacement (if uremia present)

\*Adapted and reprinted with permission from NKF-K/DOQI, 2002.<sup>6</sup> Data for stages 1-4 from the Third National Health and Nutrition Examination Study (NHANES III, 1988-1984).<sup>7</sup> Population of 177 million adults (age ≥18 years). CKD = chronic kidney disease, CVD = cardiovascular disease. Stages 1-5 represent individuals with CKD; first row represents individuals at risk for CKD.

The resulting estimated total of 19.5 million people in the United States who have CKD marks the disease as a major public health concern, affecting more than the number of Americans with diabetes (estimated at 17 million)<sup>8</sup> and nearly half the number of those with hypertension (estimated at 50 million).<sup>9</sup> Because CKD typically progresses to its most severe form, ESRD, the public health concern is underscored by the most recent data from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDKD). The combined 1995 to 1999 prevalence of ESRD patients was 392,847 on dialysis and 8,287 with transplants.<sup>2</sup> Expecting this alarming trend to continue, the NIDDKD has estimated that the prevalence of ESRD will reach over half a million by 2010.<sup>10</sup>

The NKF-K/DOQI prevalence estimates, together with the high costs associated with CKD, prompted the National Institutes of Health to establish the National Kidney Disease Education Program (NKDEP), an aggressive public education campaign currently underway. The NKDEP initiative likely will recommend interventions based on this K/DOQI staging. For patients first diagnosed with CKD, a primary goal will be to slow progression through the use of angiotensin-converting enzyme inhibitors, blood pressure control, and, in patients with diabetes, blood sugar control. Emphasis will be given to preventive and therapeutic approaches related to uremic complications, malnutrition, anemia, bone disease, acidosis, and medical comorbidities, such as cardiovascular disease.

### **Anemia Common in CKD**

Anemia is a common complication of CKD, mainly due to the inability of the kidneys to secrete enough erythropoietin to stimulate adequate hematopoiesis. Additional factors that may cause or contribute to CKD-related anemia include iron deficiency,<sup>11</sup> severe hyperparathyroidism,<sup>12</sup> acute and chronic inflammatory conditions,<sup>13</sup> aluminum toxicity,<sup>14</sup> folate deficiency,<sup>15</sup> shortened red blood cell survival,<sup>16</sup> hypothyroidism,<sup>17</sup> and hemoglobinopathies such as  $\alpha$ -thalassemia.<sup>18</sup>

Anemia often develops early in the course of CKD, well before the onset of ESRD (stage 5, on dialysis),<sup>10,12,14,18-21</sup> and then worsens as CKD progresses. Anemia is thus an important clinical factor for millions of Americans with CKD stages 3 through 5.

Hb/Hct levels in dialysis patients (stage 5, on dialysis) are meticulously followed by the Medicare system, and detailed analyses of these levels and treatment results are readily available. Less is known, however, regarding Hb/Hct levels in the millions of Americans with CKD not requiring dialysis.

One frequently cited paper that sheds light on the prevalence of anemia in CKD patients prior to ESRD—and the quality of their care—is a retrospective analysis by Obrador and colleagues<sup>21</sup> of more than 130,000 US patients initiating dialysis between April 1995 and June 1997. Sixty-eight percent of these patients had a Hct value <30%, considered to indicate severe anemia, and 51% had a Hct value <28% immediately before starting dialysis. Of those with Hct <28%, epoetin had not been prescribed for 80%.

Obrador and colleagues based their analysis on information collected on Medicare's Medical Evidence Form (MEF). A recent comparison of MEF data to actual Medicare claims<sup>22</sup> (n = 89,193) suggests that the MEF overestimates epoetin use in CKD patients prior to ESRD. The percentage of untreated patients suggested by Obrador and colleagues, therefore, may be even higher. In any event, the evidence is clear that anemia related to CKD stages 1 through 4 is underrecognized and undertreated in the United States.

### Consequences of CKD-Related Anemia

The clinical consequences of anemia have been studied more in CKD than in any other disease state. The condition affects almost every organ system. In addition to contributing to the development of left ventricular hypertrophy (LVH), as described below, anemia impairs cognitive function,<sup>23</sup> decreases exercise capacity,<sup>24</sup> erodes quality of life,<sup>25</sup> and may weaken immune responses.<sup>26</sup> In patients with ESRD, severe anemia is associated with increases in hospitalization,<sup>27</sup> health care costs,<sup>28,29</sup> and mortality.<sup>30-32</sup>

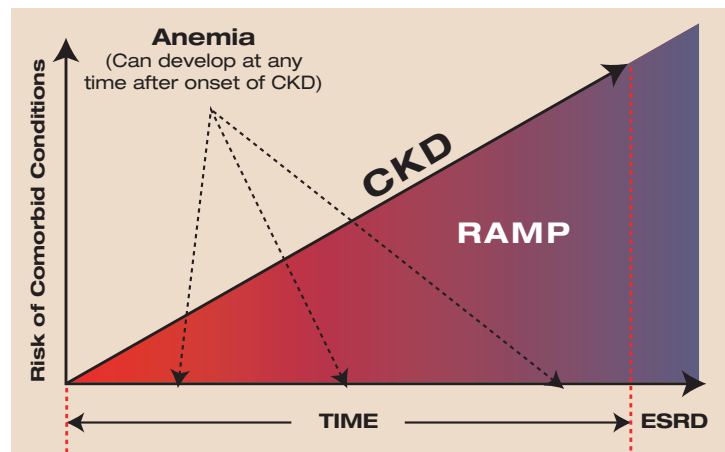
Cardiovascular disease (CVD) is the cause of death in nearly half of dialysis patients.<sup>33</sup> Many of the risk factors for CVD are also risk factors for CKD, including hypertension, diabetes, and male gender. Complications of CKD create additional cardiovascular risk factors, such as volume overload, anemia, increased oxidant stress, hypoalbuminemia, divalent ion abnormalities, hypokalemia and hyperkalemia, and metabolic acidosis.<sup>34</sup>

LVH is a common finding in patients with CKD,<sup>35-37</sup> resulting from alterations in left ventricular wall stress caused, at least in part, by hypertension and anemia.<sup>35,36</sup> It has been shown to progress with the degree of CKD.<sup>38</sup> LVH is a significant risk factor for cardiovascular events independent of blood pressure in hypertensive men,<sup>38</sup> and for cardiac and all-cause mortality in patients who require dialysis or kidney transplant.<sup>39</sup>

### Early Identification of Anemia Recommended

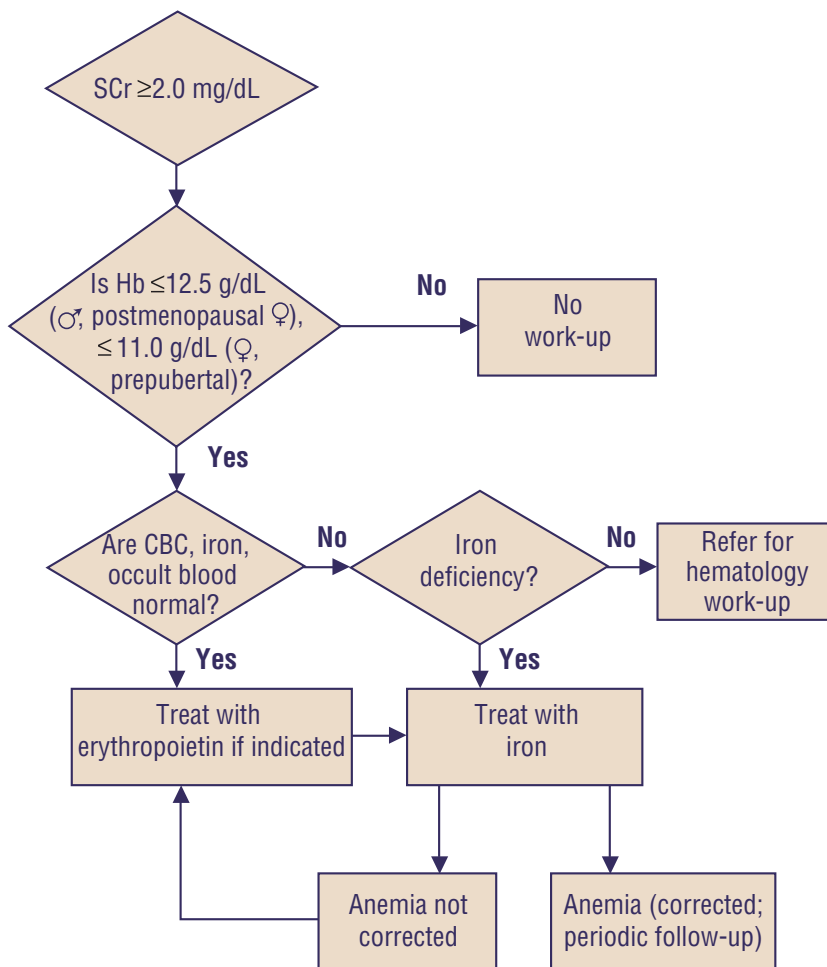
Concerned by the facts that anemia develops early in CKD and worsens as the disease progresses, a panel of

**Figure 2-1.** The RAMP (Renal Anemic Management Period) calls for timely and appropriate treatment of CKD to prevent anemia and other comorbidities.<sup>40</sup>



nephrologists developed a concept called the Renal Anemia Management Period (RAMP). The RAMP model emphasizes the progressive nature of CKD and the need for timely and appropriate treatment—well before the development of ESRD—to prevent anemia and other comorbidities that can potentially lead to irreversible, physiological damage, such as LVH.<sup>40</sup> Rather than representing data from a specific study, the RAMP model notes trends identified in many studies.

Guidelines from the NKF-K/DOQI recommend that an anemia work-up be initiated when the Hb/Hct value declines to approximately 80% of the mean value defined for healthy, normal subgroups, as anemia is likely to be present.<sup>6</sup> For example, in adult men and postmenopausal women with CKD, an anemia work-up should be initiated at Hb  $\leq 12.5$  g/dL (Hct  $< 37\%$ ); in premenopausal women and prepubertal CKD patients, the corresponding levels are Hb  $\leq 11$  g/dL (Hct  $< 33\%$ ).



**Figure 2-2.** Anemia Work-Up for CKD Patients. Differences in average Hb/Hct values between adult men and women are likely due to differences in estrogen and testosterone production that emerge at puberty and subside after menopause.

The NKF-K/DOQI guidelines recommend that Hb levels in patients with ESRD be maintained between 11 g/dL and 12 g/dL. The same target Hb range (11 g/dL to 12 g/dL) has come to apply also to patients with CKD who do not have ESRD, despite a lack of studies on the long-term effects of maintaining such a Hb range in this population.

A consensus on the optimal Hb levels at varying stages of CKD has not been reached, but the current Centers for Medicaid and Medicare Services policy restricts reimbursement for the initiation of anemia treatment to Hb  $\leq 10$  g/dL, even though evidence indicates that adverse anemia-related sequelae occur at Hb  $\leq 11$  g/dL.<sup>35,36</sup>

### Referral Concerns

Many of the suboptimal outcomes related to CKD may result from late referral of patients with CKD to a nephrologist. Although guidelines from the National Institutes of Health 1993 Consensus Statement on Morbidity and Mortality of Dialysis<sup>41</sup> recommend that patients be referred to nephrologists when SCr levels rise to 1.5 mg/dL for women and 2 mg/dL for men, a 1999 US Renal Data System report<sup>10</sup> indicated that only 20% to 25% of patients with CKD are referred to a nephrologist before they need dialysis.

Arora and colleagues<sup>42</sup> reported that, of 135 patients with CKD followed at a major tertiary medical center, 22% were referred less than 4 months before initiation of dialysis. Compared with earlier referrals, these late referrals were more likely to have Hct  $< 28\%$  (55% of patients referred late vs. 33% of patients referred early) and less likely to have

received treatment with epoetin (17% of those referred late vs. 40% of those referred early).

One study of 1,658 patients with elevated serum creatinine levels, conducted by Nissenson and colleagues, found that patients with CKD tended to be transferred to a nephrologist only when levels reached 4.0 mg/dL. In addition, only 7.4% of patients received epoetin, which was unlikely to be prescribed unless the patient had visited a nephrologist.<sup>43</sup>

A multidisciplinary approach may facilitate patient identification and improve the management of CKD.<sup>44</sup> One study of CKD patients prior to ESRD demonstrated that inclusion in a multidisciplinary CKD clinic program produced greater increases in time to renal replacement therapy, Hb levels, and epoetin treatment at initiation of dialysis compared to standard nephrology care or no care.<sup>45</sup>

The proposed NKF-K/DOQI staging of CKD, coupled with the National Kidney Disease Education Program, may promote a greater sensitivity on the part of primary care physicians to be alert for CKD and its complications in patients with a GFR  $< 60$  mL/min/1.73 m<sup>2</sup> (stage 3). The evaluation of patients at stage 3 should include the measurement of dietary energy and protein intake, weight, Hb, serum albumin, serum total cholesterol, parathyroid hormone, calcium, and phosphorus, as well as patient functioning and well-being.<sup>46</sup>

### Beneficial Effects of Anemia Management

Findings of several studies suggest that partial correction of anemia to Hb levels of 11 g/dL to 12 g/dL may decrease morbidity and reduce hospital-

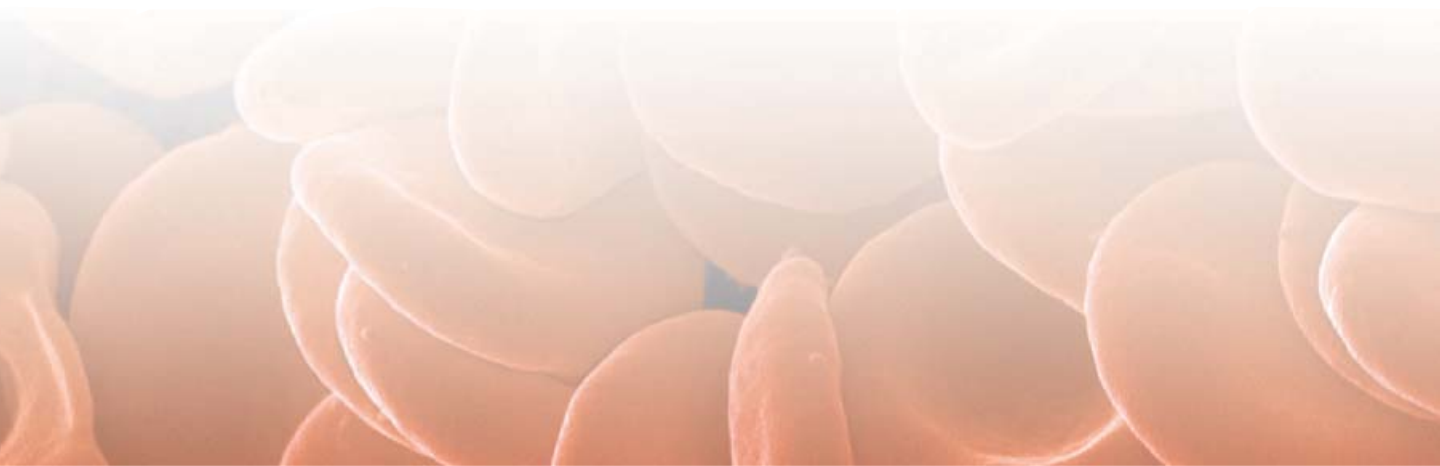
ization and mortality among patients with CKD.<sup>26,27,47-52</sup> Hayashi and colleagues found that 4 months of epoetin treatment increased the mean Hct and decreased the left ventricular mass index (LVMI) in CKD patients prior to ESRD,<sup>53</sup> and similar progressive improvements were seen after 12 months. Another study of renal failure patients showed a trend of decreased left ventricular thickness and a significant decrease in LVMI as Hb levels were increased with epoetin therapy.<sup>54</sup> Other study findings have shown that benefits of correcting anemia in patients with CKD include improvements in quality of life,<sup>51,54</sup> exercise capacity,<sup>24,51</sup> cognitive function,<sup>49</sup> and sexual function.<sup>50</sup>

Since its introduction in the late 1980s, epoetin has become widely accepted as an effective and well-tolerated therapy for anemia. Its clinical benefits to thousands of patients with CKD (before and during dialysis) are well documented. Because of its relatively short half-life, however, it generally has to be adminis-

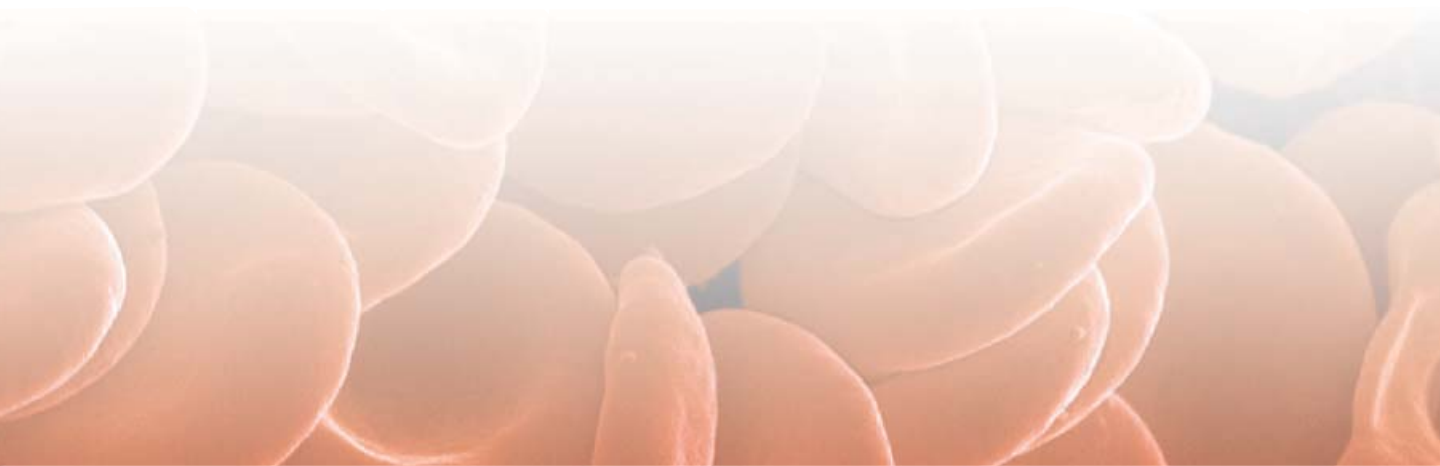
tered two to three times per week.

Recently, darbepoetin alfa (novel erythropoiesis stimulating protein, NESP), a longer-acting erythropoietic agent than epoetin, has been approved by the Food and Drug Administration for the treatment of patients with the anemia of CKD whether on dialysis or not. Due to longer serum half-life (25 hours vs. 8.5 hours), darbepoetin alfa should be administered less frequently than epoetin alfa. For example, patients who had been receiving epoetin once weekly should be administered darbepoetin alfa once every 2 weeks.<sup>55</sup>

Two large multicenter studies in dialysis patients who switched therapies demonstrated that darbepoetin alfa is as effective as epoetin in maintaining Hb levels.<sup>56,57</sup> Similar comparability was demonstrated in a European multicenter study of CKD patients before the need for dialysis.<sup>58</sup> In addition to less frequent dosing requirements, darbepoetin alfa appears to be well tolerated, with a safety profile comparable to that of epoetin.<sup>51,52</sup>



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