

# Overcoming Barriers to the Early Detection and Treatment of Chronic Kidney Disease and Improving Outcomes for End-Stage Renal Disease

Brian J.G. Pereira, MD

## **Abstract**

Chronic kidney disease (CKD) is a growing public health problem. Morbidity and mortality rates from CKD and end-stage renal disease remain high despite the advent of new knowledge, therapies, and clinical practice guidelines. Consequently, the reasons for the underdiagnosis and undertreatment of CKD must be addressed and appropriate preventive and therapeutic interventions implemented. Managed care organizations (MCOs) can facilitate this process by implementing intervention programs that target clinicians and patients with kidney disease. These programs should promote 1) early detection of CKD and comorbid conditions; 2) use of appropriate outcome measures to stratify patient care; 3) implementation of strategies to delay disease progression and prevent or treat complications; and 4) adequate preparation for and timely initiation of renal replacement therapy. Early detection and proactive care of predialysis patients not only improve outcomes and quality of life, but also reduce costs for society and MCOs.

Chronic kidney disease (CKD) is being increasingly recognized as a major public health problem, whose early detection and treatment can improve outcomes and reduce costs.<sup>1-4</sup> Yet, the prevention and treatment of CKD remain suboptimal.<sup>5-12</sup> Morbidity and mortality rates from CKD and end-stage renal disease (ESRD) remain high despite the advent of new knowledge, therapies, and clinical practice guidelines (CPGs). The challenge before us is to educate health-care providers to suspect, detect, and treat

CKD early and aggressively to slow progression toward ESRD. Early detection and proactive care of CKD patients not only improve outcomes and quality of life, but also reduce costs for society and managed care organizations (MCOs).

## **Prevalence, Causes, and Consequences of Chronic Kidney Disease**

Because early disease is often asymptomatic, the prevalence of CKD and the stage at which the disease typically manifests clinically are unclear.<sup>4</sup> The recently released National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) guidelines estimated that 20 million Americans have CKD.<sup>3</sup> Individuals with diabetes and/or hypertension, certain minority groups (eg, African-Americans), and the elderly are at high risk for CKD and also bear the lion's share of the associated complications, morbidity, and mortality.<sup>13-16</sup> Other causes of CKD include glomerulonephritis, interstitial nephritis, vasculopathy, obstructive uropathy, and cystic/hereditary/congenital kidney diseases.<sup>15</sup>

Data from the US Renal Data System (USRDS) show that the prevalence of ESRD more than doubled in the United States over the past decade.<sup>16</sup> By the end of 1997, more than 300,000 patients were being treated for ESRD, including 79,102 new patients entering treatment, 221,596 patients receiving dialysis, and 36,036 patients awaiting kidney transplantation.<sup>16</sup> In addition, more than 63,000 ESRD

patients died in 1997, a death rate that exceeds by more than 20% the death rate from advanced cancer of the colon or breast.<sup>16</sup> An estimated 651,330 Americans will require treatment for ESRD by 2010.<sup>16</sup> While heart disease rates are declining and cancer rates are stabilizing, the prevalence of ESRD is increasing.

One factor contributing to the increasing number of patients with ESRD is the “aging of America.”<sup>2,15</sup> More than 50% of patients who begin renal replacement therapy (RRT) are older than 65 years, indicative of the growing population of older Americans.<sup>2</sup> However, no age group is immune to CKD; one fourth of the individuals undergoing RRT in 1997 were younger than 45 years. Furthermore, patients initiating dialysis have an average of 4 comorbid conditions, including diabetes, hypertension, and other types of cardiovascular disease (CVD) (eg, left ventricular hypertrophy [LVH], heart failure).<sup>2</sup> Hypertension accelerates the progression of kidney disease and is a major risk factor for other types of CVD.<sup>17</sup> The rising prevalence of diabetes in the United States also may be fueling growth of the ESRD population.<sup>13,15</sup> Since the early 1990s, hypertension has accounted for about 25% of new cases of ESRD and diabetes has accounted for 40% of patients requiring RRT.<sup>15,16</sup> Improved survival of patients with diabetes and severe CVD may be further increasing the prevalence of ESRD.<sup>15</sup>

#### **Obstacles to Better End-Stage Renal Disease Outcomes: Factors Engendering Suboptimal CKD Care**

Suboptimal timing and quality of CKD care (ie, pre-ESRD) is a significant source of ESRD-related morbidity and mortality.<sup>6,7,18</sup> Although early detection and management of CKD can prevent disease progression, reduce complications, and reduce costs, several studies suggest that CKD is underdiagnosed and undertreated.<sup>5–12,19</sup> Raising clinicians’ awareness of the fact that the current care of CKD patients is suboptimal is the first step in initiating strategies to improve care. The current state of CKD care is discussed below.

***Inadequate Focus on Preventive Care.*** Because medicine has traditionally been oriented around acute events, practitioners are still learning the importance of preventive medicine. Modifiable risk factors for progressive kidney damage that are amenable to treatment include hypertension and hyperglycemia.<sup>3,20</sup> Yet a urinalysis was obtained in only 62.7% of patients with diabetes in a recent study of hospitalized hypertensive and diabetic patients.<sup>21</sup> In a study of CKD management in northeastern nephrology clinics, glycosylated hemoglobin (HbA<sub>1c</sub>) levels were available in only 28% of the patients with diabetes.<sup>22</sup>

***Asymptomatic Nature of Early Chronic Kidney Disease.*** The absence of symptoms in patients with early kidney disease complicates efforts to detect and treat CKD early. Clinicians need to maintain an adequate index of suspicion in all patients, especially in those with medical or sociodemographic risk factors for CKD.

***Insufficient Attention to the Patient’s Medical History.*** Various factors (eg, time demands, reimbursement structures) may contribute to the constraints on clinicians, leading to neglect of important components of the patient history.<sup>23</sup> Obtaining a detailed, open-ended patient history, including a family history and medication usage, facilitates early detection of CKD or its risk factors. Careful physical examination for evidence of comorbid diseases or complications of CKD complements this process.

***Use of Inappropriate Measures of Kidney Function or Omission of Laboratory Screening Tests.*** Many clinicians still use the serum creatinine (Cr) level or Cr clearance as a definitive marker of CKD<sup>24,25</sup> instead of measuring or calculating the best measure of overall kidney function, the glomerular filtration rate (GFR).<sup>3</sup> Furthermore, many do not perform routine laboratory screening tests for CKD<sup>4,21</sup> or its complications.<sup>21,22</sup> Experts currently recommend use of validated prediction equations that consider the

patient's serum Cr level, age, sex, race, and/or body size to estimate the GFR.<sup>3</sup> New methods of calculating the GFR are under investigation.<sup>26</sup>

***Lack of Professional Agreement/Paucity of Reliable Clinical Evidence.***

Until the recent release of the NKF-K/DOQI CPGs, a uniform classification of the CKD stages did not exist and the terms used were ambiguous and overlapping.<sup>3</sup> Along with limitations of the available data (eg, often obtained retrospectively, with infrequent proof of causality),<sup>27</sup> such ambiguity has limited the use of preventive and therapeutic interventions.

***Failure to Employ Strategies That Delay Disease Progression.***

Lack of knowledge also may contribute to the undertreatment of early CKD. In the past decade several large clinical trials have been published that demonstrated the benefit of angiotensin-converting enzyme (ACE) inhibitor therapy, and tight blood pressure and glycemic control in slowing the progression of CKD.<sup>28-33</sup> In addition, the Heart Outcomes Prevention Evaluation (HOPE) study and the Microalbuminuria, Cardiovascular, and Renal Outcomes (MICRO-HOPE) substudy recently showed that the ACE inhibitor ramipril reduced cardiovascular risk in patients with early CKD<sup>34,35</sup> and the risk of overt nephropathy in patients with diabetes.<sup>35,36</sup> Ramipril also appears to slow the progression of kidney disease in hypertensive patients with CKD and proteinuria, and may offer benefit to patients without proteinuria.<sup>37</sup> However, only one third or fewer patients with diabetes and/or hypertension and abnormal kidney function were prescribed ACE inhibitors in 1 study.<sup>21</sup> In a study of CKD management in the northeastern United States, only 65% of patients with diabetes and 49% of patients overall were prescribed ACE inhibitors.<sup>22</sup> Despite evidence that tight blood pressure and glycemic control improves outcomes,<sup>3</sup> hypertension remains inadequately treated in more than half of CKD patients<sup>38</sup> and blood glucose monitoring in patients with diabetes is suboptimal.<sup>22</sup>

***Suboptimal Detection and Management of Malnutrition.*** Complications of CKD (eg, malnutrition, anemia, osteodystrophy, metabolic acidosis, dyslipidemia) account for most of dialysis-related morbidity and mortality.<sup>2,39</sup> A variety of factors (eg, lack of knowledge, delayed referral to a nephrologist) may hinder appropriate prevention and management of these complications. For example, many patients have evidence of malnutrition at the start of RRT,<sup>7,40</sup> which is associated with an increased risk of death.<sup>41</sup> However, a pre-ESRD evaluation by a dietitian is uncommon,<sup>42</sup> despite the availability of strategies to optimize CKD patients' nutritional status, such as dietary counseling, vitamin and nutritional supplements, correction of uremic acidosis with oral alkali agents, and judicious use of a low-protein diet.<sup>43</sup>

***Inadequate Detection and Correction of Anemia Associated With Chronic Kidney Disease.***

Neglect of another common and treatable uremic complication, anemia, has also been well documented.<sup>5,7,10,22,40,44-46</sup> Anemia is primarily a result of the inability of the kidneys to secrete adequate amounts of erythropoietin, which is involved in the production of red blood cells.<sup>47,48</sup> Studies suggest that anemia of CKD begins early and that many CKD patients are anemic at first presentation to a nephrologist.<sup>22,46</sup> Anemia can precipitate LVH, exacerbate angina pectoris, restrict aerobic capacity, limit cognitive ability, and diminish sexual function.<sup>49,50</sup> In addition to being an important predictor of CVD in CKD patients,<sup>40,51-53</sup> anemia is also associated with an increased risk of death.<sup>25,54,55</sup>

The *NKF-K/DOQI Clinical Practice Guidelines for Anemia of Chronic Kidney Disease: Update 2000* indicate that patients should have hemoglobin (Hgb) and hematocrit (Hct) levels of 11 to 12 g/dL and 33% to 36%, respectively.<sup>56</sup> However, natural variations in Hgb/Hct concentrations hinder efforts to maintain these levels,<sup>57</sup> and many clinicians may not even aim for these targets.<sup>7,10,46,58</sup>

Although rates of correction of anemia in dialysis patients have improved since the introduction of recombinant human erythropoietin (r-HuEPO) therapy,<sup>59</sup> many patients beginning dialysis are still anemic.<sup>7,10,60</sup> Most have never received erythropoietin to raise their Hct levels<sup>7,10,46</sup> despite the benefits of this therapy, such as decreased morbidity and mortality, improved exercise capacity, improved health-related quality of life, and reduced LVH.<sup>40,53,59,61</sup>

An analysis of 155,076 Americans who began chronic dialysis therapy between 1995 and 1997 showed that 51% of patients had a Hct level < 28% and only 23% had received erythropoietin pre-ESRD.<sup>7</sup> In addition, trend analyses have shown that patients often do not receive sufficient doses of erythropoietin, with many receiving < 25% of the recommended amount.<sup>58</sup> Other factors that contribute to inadequate correction of renal anemia include logistics barriers around the frequency of dosing of r-HuEPO, economic disincentives, lack of access to treatment (eg, no transportation), and lack of clinical knowledge.<sup>58,60</sup>

#### ***Inadequate Preparation for and Timing of Renal Replacement Therapy.***

Ideal preparation for RRT includes appropriate patient education, informed choice of RRT modality, and the timely placement of permanent vascular access.<sup>6,18,19,62,63</sup> However, evidence suggests that these steps do not always take place.<sup>6,64</sup> For example, patients are infrequently instructed to protect the arm selected for permanent vascular access.<sup>42</sup> In fact, most patients experience a delay in obtaining permanent access for initiating treatment or begin RRT without such access.<sup>22,64,65</sup> The timing of initiation dialysis is another indicator of the quality of care for patients with kidney disease.<sup>6,18,66</sup> However, kidney function at the start of dialysis appears to vary widely among patients in the United States with ESRD, with a substantial percentage of patients beginning dialysis at very low levels of predicted GFR.<sup>8</sup>

***Late Referral to a Nephrologist.*** Late referral to a nephrologist is common in

the United States and is associated with poor CKD care.<sup>67</sup> These patients are more likely to have hypoalbuminemia, a Hct level < 28%, and a predicted GFR < 5 mL · min<sup>-1</sup> · 1.73 m<sup>-2</sup> at the start of dialysis, and less likely to have received erythropoietin therapy or have functioning permanent vascular access.<sup>5,67</sup>

***Casual Use of Nephrotoxic Medications.*** In 1 study, nonsteroidal anti-inflammatory drugs were prescribed to 6% of diabetic and 8.8% of hypertensive patients with abnormal kidney function at hospital discharge.<sup>21</sup> The number of individuals with CKD who purchase over-the-counter nephrotoxic drugs is unclear. Careful review of all of a patient's medications is a crucial part of appropriate medical care.

#### ***Imperfectly Organized Care Model/ Lack of Continuity of Care.***

Most patients with CKD require care from a team of healthcare providers rather than continuous care from 1 source; this team typically includes multiple physicians (eg, primary care physicians [PCPs], nephrologist, cardiologist) and a variety of ancillary team members (eg, nurses, dietitians, social workers).<sup>27</sup> Although team care offers advantages, inadequate communication among health professionals may lead to redundant or conflicting therapeutic approaches or treatment discontinuities.<sup>27</sup> The fragmented delivery of CKD and ESRD care has been associated with poor outcomes and increased costs.<sup>68</sup>

#### ***Variability in the Quality of Care.***

Patients with the same stage of CKD do not all receive the same treatment. Not only do patient age, sex, and race influence diagnosis and treatment, but also where the patient lives.<sup>16</sup> For example, prescribing patterns of r-HuEPO for CKD patients differ throughout the country,<sup>7,10,16</sup> as does the quality of dialysis care.<sup>16</sup> Also, the use of catheters varies among facilities, a finding that is not explained by geography, race, or for-profit versus not-for-profit models.<sup>27</sup> These findings emphasize the need for clinician

adherence to professionally agreed-upon standards of care.

**Workforce Shortages.** Whereas an estimated 15,000 nephrologists will be needed by 2010, only 4200 exist today.<sup>27</sup> As the shortage of specialists becomes more acute, experts believe that PCPs will need to become more involved in the diagnosis and continuing care of CKD patients.<sup>1</sup> Physician “extenders” (eg, nurses, nephrology nurse practitioners, physician assistants) can assist with such care, but these practitioners are also in short supply.<sup>27,69</sup>

#### **Improving the Care of Chronic Kidney Disease Patients: the National Kidney Foundation Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines**

In 1995, the NKF launched the Dialysis Outcomes Quality Initiative (DOQI) in response to concern about the quality of care for patients with kidney disease.<sup>3</sup> This effort led to the development of CPGs related to key areas of dialysis care, including the management of anemia of

CKD and provision of adequate hemodialysis, peritoneal dialysis, and vascular access. These CPGs were published in 1998 and updated in 2001.<sup>3</sup>

In developing the DOQI CPGs, experts recognized the need to improve the health status of patients with ESRD to optimize dialysis outcomes. This prompted the NKF to broaden the focus of their guideline initiative to encompass all phases of kidney disease and their monitoring and management.<sup>3</sup> The new initiative, called the Kidney Disease Outcomes Quality Initiative (K/DOQI), was launched in 2000.<sup>2,3</sup>

Early K/DOQI efforts included the 2000 updates of the original NKF DOQI guidelines and publication of the final NKF-DOQI CPG on nutrition. However, the centerpiece of K/DOQI is the recent release of the *NKF-K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification*.<sup>3</sup> These CPGs designate stages of CKD (from mild impairment to ESRD) and stress prevention/control of comorbid conditions and disease progression. More specifically, they provide

**Table.** Stages and Prevalence of Chronic Kidney Disease (Age  $\geq 20$  Years)

Stage	Description	GFR (mL · min <sup>-1</sup> · 1.73 m <sup>-2</sup> )	Prevalence*	
			n (1000s)	%
1	Kidney damage with normal or $\uparrow$ GFR	$\geq 90$	5900	3.3
2	Kidney damage with mild $\downarrow$ GFR	60 to 89	5300	3.0
3	Moderate $\downarrow$ GFR	30 to 59	7600	4.3
4	Severe $\downarrow$ GFR	15 to 29	400	0.2
5	Kidney failure	<15 (or dialysis)	300	0.1

\*Data for stages 1 through 4 from NHANES III (1988–1994).<sup>70</sup> Population of 177 million adults aged  $\geq 20$  years. Data for stage 5 from USRDS (1998)<sup>71</sup> include approximately 230,000 patients undergoing dialysis, and assume 70,000 additional patients not on dialysis. GFR estimated from serum creatinine levels using MDRD Study equation based on age, sex, race, and calibration for serum creatinine. For stages 1 and 2, kidney damage estimated by spot albumin-to-creatinine ratio  $> 17$  mg/g in men or  $> 25$  mg/g in women on 2 measurements.

GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; NHANES = National Health and Nutrition Examination Survey; USRDS = US Renal Data System.

Source: National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, stratification, executive summary. K/DOQI, Kidney Disease Outcomes Quality Initiative. *Am J Kidney Dis* 2002;39(suppl 1). Reprinted with permission.

1) standardized terminology for classifying and evaluating kidney disease (Table), 2) an approach to disease stratification based on GFR, and 3) appropriate methods for monitoring kidney function, comorbidity, and complications, from initial injury until ESRD.<sup>3</sup> They also will serve as a springboard for the development of interventional CPGs that will guide the treatment of all stages of kidney disease.<sup>3</sup> Interventional K/DOQI CPGs currently in development include those related to hypertension, dyslipidemia, and bone disease.<sup>3</sup>

### Optimizing Quality of Care

Optimizing quality of CKD care (eg, early detection, use of interventions to delay disease progression, modification of comorbid conditions, prevention of uremic complications, adequate preparation for RRT) can slow the decline in kidney function, reduce complications, and lower healthcare costs.<sup>72</sup> Collectively, the available and forthcoming NKF CPGs will outline the following methods to optimize some of these outcome measures:

**Early Identification of Patients With Chronic Kidney Disease.** Early detection improves outcomes by permitting the advantages of early intervention (eg, slowing of disease progression; reduced complications). Obtaining a detailed patient history, combined with routine laboratory studies and blood pressure assessment, facilitates this process. The new NKF-K/DOQI CPGs<sup>3</sup> recommend that clinicians assess the risk for development of CKD in all patients at routine health visits, based on clinical and sociodemographic characteristics. At-risk individuals should undergo tests to establish the presence of markers of kidney damage (eg, proteinuria, abnormal urine sediment, abnormal imaging studies), blood pressure level, and level of kidney function (ie, GFR).<sup>3</sup> Patients with evidence of CKD (eg, markers of kidney damage, abnormal GFR) should be further evaluated to determine the underlying diagnosis, presence of any comorbid conditions or complications, disease severity, risk of loss of kidney

function, and risk for cardiovascular disease.<sup>3</sup> Asymptomatic but at-risk individuals should be instructed in risk factor reduction and undergo repeat periodic screening, if appropriate.<sup>3</sup>

**Use of Appropriate Measures to Determine Disease Severity and Stage of Chronic Kidney Disease.** Accurate determination of the severity and stage of CKD facilitates the selection of appropriate clinical interventions. The new NKF-K/DOQI CPGs<sup>3</sup> state that disease severity should be established based on the presence of markers of kidney damage, presence of high blood pressure, and level of kidney function (ie, GFR), and that disease stage should be assigned based on the GFR (Table).<sup>3</sup> Prediction equations that factor in the serum Cr concentration as well as the patient's age, sex, race, and/or body size should be used to estimate the GFR.<sup>3</sup> In patients with an estimated GFR < 15 mL · min<sup>-1</sup> · 1.73 m<sup>-2</sup>, a 24-hour urine specimen should also be obtained to determine information that will facilitate decisions regarding the need for RRT (ie, Cr clearance, Kt/V urea, estimated dietary protein intake).<sup>3</sup> Screening for proteinuria typically involves checks of untimed ("spot") urine specimens.<sup>3,73</sup>

**Use of Interventions to Slow Rate of Glomerular Filtration Rate Decline.** CKD patients experience a progressive decline in kidney function (ie, GFR) that can be slowed by specific interventions. The new NKF-K/DOQI CPGs<sup>3</sup> recommend that clinicians determine the rate of GFR decline to ascertain both the interval until the onset of kidney failure and the effectiveness of interventions. The rate of GFR decline should be assessed by computing the GFR from past and ongoing serum Cr levels and by identifying risk factors for fast declines (eg, type of kidney disease). Measurement of serum Cr for GFR estimates should be obtained at least yearly and more frequently in certain patients.<sup>3</sup> ACE inhibitors provide vasculoprotection and renoprotection (ie, slow rate of GFR decline; decrease progression of microalbuminuria to frank proteinuria)<sup>20,34-36,74</sup> to

diabetic and nondiabetic patients with CKD and are cost effective in patients with diabetes.<sup>75</sup> Their beneficial effect is mediated by factors in addition to a decrease in blood pressure and urinary protein excretion.<sup>74</sup>

The new NKF-K/DOQI CPGs<sup>3</sup> also stress the need for tight blood pressure control in hypertensive CKD patients, by identification of target blood pressure levels and use of appropriate pharmacologic and nonpharmacologic interventions.<sup>3</sup> Experts recommend that blood pressure be reduced to 130/85 mm Hg<sup>17</sup> or even lower<sup>13,76-78</sup> in patients with proteinuria in excess of 1 g per 24 hours, hypertension, and/or diabetes. A recent meta-analysis suggests that antihypertensive regimens that include ACE inhibitors are more effective than regimens without ACE inhibitors in slowing the progression of nondiabetic kidney disease.<sup>74</sup> Maintaining strict glycemic control (HbA<sub>1c</sub> ≤ 6.05%) in CKD patients with diabetes also slows the rate of GFR decline.<sup>3,20</sup>

**Identification and Modification of Comorbid Conditions.** Comorbid conditions that accompany CKD (eg, diabetes, hypertension, other CVD, neuropathy) contribute to high morbidity and mortality among ESRD patients, and thus, warrant effective prevention, timely diagnosis, and prompt treatment. For example, CVD (eg, LVH, heart failure, coronary artery disease, peripheral vascular disease, cerebrovascular disease) is highly prevalent among CKD patients<sup>79</sup> and is a leading cause of morbidity and mortality.<sup>16,34,40,51</sup> Therefore, the new NKF-K/DOQI CPGs recommend that clinicians assess the presence of both “traditional” and “nontraditional” (CKD-related) CVD risk factors (eg, hypertension, diabetes, smoking, abnormal lipid profiles, cardiac fibrosis and hypertrophy, malnutrition, enhanced sympathetic activity)<sup>40,79</sup> in CKD patients and implement risk factor reduction programs, as necessary.<sup>3</sup> Additional NKF-K/DOQI CPGs related to the management of hypertension and dyslipidemia in patients with CKD are in development.<sup>3</sup>

**Prevention and Treatment of Complications of Decreased Kidney Function.** Complications of CKD contribute to the morbidity and mortality of CKD and may appear in patients with only moderate decreases in their GFR.<sup>3</sup> The new NKF-K/DOQI CPGs recommend that any patient with a GFR < 60 mL · min<sup>-1</sup> · 1.73 m<sup>-2</sup> be assessed for anemia, malnutrition, bone disease, or disorders of calcium and phosphorus metabolism, as well as impaired functioning and well-being.<sup>3</sup> Abnormalities in other laboratory parameters (eg, decreased Hgb or cholesterol level, hypoalbuminemia, metabolic acidosis) also should prompt evaluation of potential complications.<sup>56,80</sup>

The *NKF-K/DOQI Clinical Practice Guidelines for Anemia of Chronic Kidney Disease: Update 2000* outline the appropriate evaluation and treatment of anemia of CKD,<sup>3,56</sup> including the use of appropriate use of iron replacement and erythropoietin therapy to achieve target Hgb levels (11 to 12 g/dL) and Hct levels (33% to 36%). Iron deficiency will occur in most hemodialysis patients receiving r-HuEPO because of the increased demand for iron (driven by the accelerated erythropoiesis) and ongoing blood losses.<sup>81</sup> Poor iron intake and increased demand for iron are also seen in patients receiving peritoneal dialysis and r-HuEPO.<sup>81</sup>

The *K/DOQI Clinical Practice Guidelines for Nutrition in Chronic Renal Failure* provide guidance about the management of malnutrition in CKD patients, which may include dietary counseling, education, modification, or specialized nutritional therapy.<sup>80</sup> NKF-K/DOQI CPGs related to the management of bone disease in CKD patients are currently in development.<sup>3</sup>

**Adequate Preparation for Renal Replacement Therapy.** Adequate preparation for and the timely initiation of RRT improve outcomes and reduce costs. A variety of NKF CPGs provide guidance on these issues. The *NKF-K/DOQI Clinical Practice Guidelines for Vascular Access:*

*Update 2000* address issues related to establishing and maintaining permanent vascular access for dialysis (eg, patient evaluation, types of dialysis access, preservation of sites, timing of access placement, monitoring for complications).<sup>82</sup> The *NKF-K/DOQI Clinical Practice Guidelines for Peri-toneal Dialysis Adequacy: Update 2000* and the *NKF-K/DOQI Clinical Practice Guidelines for Hemodialysis Adequacy: Update 2000* outline methods to optimize dialysis outcomes.<sup>83,84</sup>

#### **Early Referral to a Nephrologist.**

Whereas late referral to a nephrologist has been associated with parameters of poor quality predialysis care (ie, hypoalbuminemia, anemia, reduced erythropoietin use, lower predicted GFR at the start of dialysis),<sup>5,67</sup> early referral is associated with lower morbidity and mortality rates, briefer hospital stays, longer RRT-free survival, and lower costs.<sup>85-87</sup> PCPs are more likely to be the first to detect CKD and should refer patients to a nephrologist early.<sup>11</sup>

#### **Correction of Anemia of Chronic Kidney Disease: Roles of Epoetin Alfa and Darbepoetin Alfa**

**Introduction to the Marketplace.** The introduction of r-HuEPO more than a decade ago provided the first effective treatment for the anemia of CKD.<sup>45,88</sup> Epoetin alfa, one type of r-HuEPO, is an amino acid glycoprotein manufactured by recombinant DNA technology that has the same biological effects as endogenous erythropoietin.<sup>89</sup> Correction of anemia of CKD with erythropoietin has been associated with a variety of beneficial effects, including improved quality of life, partial regression of LVH, reduced frequency of cardiac complications, and shorter hospital stays.<sup>45,53,59,61,90,91</sup>

The US Food and Drug Administration's recent approval of darbepoetin alfa (also known as novel erythropoiesis-stimulating protein) should further enhance the care of patients with anemia of CKD. Darbepoetin alfa is an erythropoiesis-stimulating protein that is produced in Chinese hamster

cells by recombinant DNA technology.<sup>92</sup> It represents a new generation of long-acting proteins that bind to the same receptor as r-HuEPO and stimulate erythropoiesis by the same mechanism of action. However, structural differences (darbepoetin alfa has 2 more N-linked oligosaccharide chains) provide darbepoetin alfa with greater in vivo potency, greater metabolic stability, and an approximately 3-fold longer serum half-life.<sup>93-95</sup> Thus, darbepoetin alfa can be dosed less frequently than r-HuEPO,<sup>93-95</sup> enhancing patient convenience and compliance with treatment.<sup>96</sup>

**Epoetin Alfa: Indications, Dosing, Tolerability, and Monitoring.** Epoetin alfa is indicated for the treatment of anemia associated with several conditions, including chronic renal failure (ie, CKD).<sup>89,97</sup> In dialysis or CKD patients, epoetin alfa is indicated to raise or maintain the red blood cell level and to decrease the need for blood transfusions.<sup>89,97</sup>

The recommended starting dose of epoetin alfa is 50 to 100 Units/kg 3 times weekly (TIW) in adults with anemia of CKD and 50 Units/kg TIW in pediatric dialysis patients.<sup>89,97</sup> The dose should be reduced as the Hct level approaches 36% (or increases by more than 4 points during any 2-week interval) and increased if the response is unsatisfactory after 8 weeks of therapy.<sup>89,97</sup> The maintenance dose should be individualized to maintain the Hct in the suggested target range. Epoetin alfa may be given as an intravenous (IV) or subcutaneous (SC) injection.<sup>89,97</sup> When considered appropriate by the physician, a patient may self-administer these injections.<sup>89,97</sup> Epoetin alfa is usually administered as an IV bolus TIW in hemodialysis patients.<sup>89,97</sup>

Epoetin alfa is generally well tolerated. However, clinicians and patients should familiarize themselves with contraindications, warnings, and precautions before initiating treatment. In US studies of treatment in adult dialysis patients the most frequently reported adverse events of epoetin alfa therapy were hypertension, headache, tachycardia, nausea/vomiting, clotted vascular access, shortness of



breath, hyperkalemia, and diarrhea, which are typical symptoms seen in this group of patients.<sup>89,97</sup> There has been no evidence of the development of antibodies to epoetin alfa, and serious allergic reactions are rare.<sup>89,97</sup>

Patients with uncontrolled hypertension should not be treated with epoetin alfa.<sup>89,97</sup> Therefore, blood pressure must be adequately controlled prior to initiating epoetin alfa therapy and closely monitored and controlled during therapy.<sup>89,97</sup> Because of the increased risk of seizures during early therapy, patients also should be monitored for neurologic symptoms.<sup>89,97</sup>

Patient monitoring also includes laboratory studies. Transferrin saturation should be at least 20% and the ferritin level at least 100 ng/mL before therapy is begun.<sup>89,97</sup> Virtually all patients will eventually require supplemental iron to increase or maintain transferrin saturation to levels that will adequately support epoetin alfa-stimulated erythropoiesis.<sup>89,97</sup> Other laboratory studies that should be conducted at regular intervals include complete blood counts and serum chemistry tests (eg, blood urea nitrogen, uric acid, creatinine, phosphorus, potassium).<sup>89,97</sup>

***Darbepoetin Alfa: Indications, Dosing, Tolerability, and Monitoring.*** Darbepoetin alfa is also indicated for the treatment of anemia associated with chronic renal failure (ie, CKD), including patients undergoing dialysis and predialysis patients.<sup>92</sup> It is labeled for administration as a single weekly IV or SC injection, and the recommended starting dose is 0.45 µg/kg of body weight.<sup>92</sup> Doses should be slowly adjusted to attain, but not exceed, a target Hgb level of 12 g/dL.<sup>92</sup> The Hgb level should be monitored weekly during initiation or adjustment of therapy and at least monthly thereafter.<sup>92</sup>

Darbepoetin alfa is generally well tolerated and has a safety profile similar to that of r-HuEPO.<sup>98,99</sup> To date, in more than 1500 patients treated with darbepoetin alfa, no cases of antibody formation have been documented.<sup>98,99</sup> Blood pressure and Hgb levels should be monitored carefully in patients receiving darbepoetin alfa ther-

apy, and darbepoetin should not be used in patients with uncontrolled hypertension or sensitivity to the active substance or any excipients.<sup>92</sup>

Predialysis patients may require lower maintenance doses of darbepoetin alfa than dialysis patients<sup>92</sup>; nevertheless, their Hgb level, blood pressure, renal function, and fluid/electrolyte balance should be monitored carefully.<sup>92</sup> Darbepoetin alfa, because it decreases plasma volume, may reduce the efficiency of dialysis, and hence, dialysis regimens may need to be adjusted accordingly.<sup>92</sup>

***Effectiveness of Epoetin Alfa and Darbepoetin Alfa Therapies.*** Studies evaluating the effectiveness of epoetin alfa therapy have produced consistent results. In clinical trials, 95% of adult patients experienced a clinically significant increase in Hct at starting doses of 50 to 150 Units/kg TIW.<sup>89,97</sup> These patients were virtually transfusion-independent after about 2 months of therapy.<sup>89,97</sup> Clinical trials have also suggested that predialysis and dialysis patients respond to epoetin alfa therapy in a similar manner. That is, both populations demonstrated a sustained dose-dependent rise in Hct, which was similar with IV or SC administration.<sup>89,97</sup>

A phase 3 clinical trial also evaluated the quality of life of patients receiving epoetin alfa therapy.<sup>89,97,100,101</sup> Patients whose Hct levels reached target range (32% to 38%) showed significant improvement in multiple quality-of-life parameters (eg, energy and activity level; functional ability; health status; sleep, eating, and sex life; life satisfaction; well-being; happiness). They also demonstrated significant improvement in energy and strength.<sup>101,102</sup>

Other studies have evaluated and compared the efficacy of darbepoetin alfa and r-HuEPO. In 2 open-label studies, darbepoetin alfa or epoetin alfa was administered for correction of anemia to patients with CKD who had not received prior erythropoietin therapy.<sup>92</sup> The first study assessed the response in dialysis patients, whereas the second evaluated the response in predialysis patients. Drug

dosages were adjusted in both studies, as necessary, to maintain Hgb levels in the study target range (11 to 13 g/dL.) In the first study, 72% of the 90 patients treated with darbepoetin alfa and 84% of the 31 patients treated with epoetin alfa achieved the target Hgb range by 20 weeks.<sup>92</sup> In the second study, 93% of the 129 patients treated with darbepoetin alfa and 92% of the 37 patients treated with epoetin alfa achieved the target Hgb range by 24 weeks.<sup>92</sup>

**Conversion From Recombinant Human Erythropoietin to Darbepoetin Alfa Therapy.** Studies also have specifically assessed the ability of darbepoetin alfa to maintain target Hgb levels in patients when administered at a reduced dosing frequency compared with r-HuEPO. The results of these studies suggested that patients receiving r-HuEPO 2 or 3 times per week could switch to darbepoetin alfa once weekly, and those receiving r-HuEPO once per week could switch to darbepoetin alfa once every other week, and maintain their Hgb levels.<sup>98,103-106</sup> Data also suggest that the efficacy of SC and IV darbepoetin alfa therapy is similar.<sup>98,105,107</sup> Darbepoetin alfa should be administered every other week to anemia patients with chronic renal failure currently receiving epoetin alfa every week. Moreover, the recommended darbepoetin alfa vial strength is 25 µg every week and 60 µg every other week.<sup>92</sup>

More recently, Jadoul et al<sup>108</sup> reported preliminary studies that suggest that darbepoetin alfa could maintain Hgb levels when administered once every 4 weeks in chronic CKD patients previously treated with epoetin alfa every other week. Although additional studies are necessary to confirm these results, they ventured that “darbepoetin alfa will provide greater flexibility in treating the anemia of CKD by simplifying anemia management for both physicians and patients.”<sup>108</sup>

**Managed Care and Health Economics: Health Care Financing Administration End-Stage Renal Disease Data on the Effect of Correction of Anemia on**

### **Patient Mortality, Hospitalization, and Costs**

The cost of care for ESRD patients continues to rise with the growing number of patients. In 1997, Medicare expenditures for ESRD were estimated at \$11.76 billion.<sup>1</sup> These costs are projected to increase to \$28.3 billion by 2010.<sup>1,109</sup> Substantial geographic variability in Medicare expenditures for ESRD also exists.<sup>110</sup> These data illustrate the need to improve the efficiency and quality of care for ESRD patients, including the use of interventions to reduce the risk and/or impact of complications.

Correction of anemia of CKD represents an example of an intervention that can improve outcomes and reduce costs. A retrospective study of the association between Hct level and mortality in a Medicare hemodialysis cohort showed that patients with Hct levels < 30% were at significantly higher risk for all-cause and cause-specific death than patients with Hct levels ranging from 30% to 33%.<sup>90</sup> Conversely, patients with Hct levels of 33% to 36% were at the lowest risk for all-cause and cardiac mortality. Another study of Medicare r-HuEPO-treated patients<sup>91</sup>

Additional information can be found at the following electronic resources:

1. [www.hcfa.gov/quality/3m.htm](http://www.hcfa.gov/quality/3m.htm)  
HCFA and ESRD Network Organization: 2000 Annual Report, ESRD Clinical Performance Measures (CPMs) Project, formerly known as the ESRD Core Indicators Project.
2. [www.kidney.org](http://www.kidney.org)  
The National Kidney Foundation (NKF) web site, with links to clinical practice guidelines.
3. [www.nephronline.org](http://www.nephronline.org)  
Continually updated web resource for clinicians and renal patients.
4. [www.renalweb.com](http://www.renalweb.com)  
This site includes renal web dialysis outcomes, links to other web resources, news and essential articles in the field, links to PubMed searches on MEDLINE, K/DOQI CPGs, information about reimbursement issues, and Medicare's comparison of the quality of care at various US dialysis facilities.
5. [http://www.niddk.nih.gov/fund/reports/nkdep/images/NKDEP\\_finalsummary.pdf](http://www.niddk.nih.gov/fund/reports/nkdep/images/NKDEP_finalsummary.pdf)  
Government resource on CKD.
6. <http://www.usrds.org/adr.htm>  
Online access to US Renal Data System (USRDS) Annual Data Reports.

revealed a similar association between Hct level and risk of hospitalization. In this study, patients with Hct levels < 30% were at significantly increased risk for hospitalization compared with patients with Hct levels of 30% to 33%.<sup>91</sup> Conversely, patients with Hct levels of 33% to 36% were at lowest risk for future hospitalization.

Another study of Medicare hemodialysis patients evaluated the relationship between Hct level and Medicare-allowable per-member-per-month (PMPM) expenditures.<sup>111</sup> Compared with reference patients with Hct levels of 30% to 33%, the Medicare-allowable PMPM expenditures were significantly greater for patients with Hct levels < 27% and 27% to 30%.<sup>111</sup> Conversely, these expenditures were significantly less for patients with Hct levels of 33% to 36% and 36% and higher.<sup>111</sup>

Other studies provide additional information about the costs of inadequately managed renal anemia and the benefits of appropriate treatment. Levin et al<sup>52,112</sup> showed that each 0.5 g/dL decrease in the Hgb was associated with an increased risk of LVH by 1.32, whereas each 6% increase in Hct resulted in a 50% decrease in hospital days.<sup>25</sup> Other data have suggested that the cost of care is lower in patients who receive epoetin alfa early.<sup>57,58</sup> Collectively, these data suggest that appropriate management of renal anemia, including erythropoietin therapy, can improve outcomes and lower MCO costs.

### Summary

With the growing number of ESRD patients, the time has come to focus the national spotlight on CKD as a public health problem. Clinicians, patients, and healthcare organizations need to be better educated about the benefits of early detection and treatment of CKD. Reasons for the underdiagnosis and undertreatment of CKD must be addressed and appropriate preventive and therapeutic interventions implemented. Improving medical partnerships between clinicians and patients is one step toward optimizing care. Clinicians need to instruct patients in methods of risk factor reduction and identify means to slow progression of CKD.

Clinicians must remain alert to early warning signs, comply with the latest K/DOQI practice guidelines, and be willing to implement preventive and therapeutic interventions. MCOs also need to take an active role in improving ESRD outcomes. Their efforts should include implementation of interventions to educate clinicians and patients as well as the evaluation of clinician performance based on appropriate outcome measures.

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