Anemia, Diabetes, and Chronic Kidney Disease

Uzma Mehdi, MD
Robert D. Toto, MD

Diabetes is the leading cause of chronic kidney disease (CKD) and is associated with excessive cardiovascular morbidity and mortality (1,2). Anemia is common among those with diabetes and CKD and greatly contributes to patient outcomes (3,4). Observational studies indicate that low Hb levels in such patients may increase risk for progression of kidney disease and cardiovascular morbidity and mortality (5). Controlled clinical trials of anemia treatment with erythropoietin stimulating agents (ESAs) demonstrated improved quality of life (QOL) but have not demonstrated improved outcomes (6–10). In some trials, ESA treatment for high Hb levels is associated with worse outcomes such as increased thrombosis risk (6,11). Consequently, the U.S. Food and Drug Administration (FDA) and the National Kidney Foundation (NKF) have modified their recommendations regarding anemia treatment for CKD patients (12). The objectives of this review are to 1) update clinicians on the prevalence, causes, and clinical consequences of anemia; 2) discuss the benefits and risks of treatment; and 3) provide insight into anemia management based on clinical trial evidence in patients with diabetes and kidney disease who are not on dialysis.

DEFINITION AND PREVALENCE OF ANEMIA IN CKD

The NKF defines anemia in CKD as an Hb level <13.5 g/dl in men and 12.0 g/dl in women (13). This definition is based on the fact that these levels are outside the 95% CIs of the mean for normal men and women. Anemia is common in diabetic patients with CKD (5). It is estimated that one in five patients with diabetes and stage 3 CKD have anemia, and its severity worsens with more advanced stages of CKD and in those with proteinuria (7,14,15) For example, in a 5-year prospective observational study conducted in a diabetes clinic in Australia, anemia was found in early kidney disease, and declining Hb levels were more common among those with higher levels of albuminuria (16) The distribution of Hb in patients with diabetes and CKD is similar to that in those without diabetes, but on average, Hb levels are lower. For these reasons, it is recommended that clinicians measure serum creatinine and urine albumin and creatinine to estimate glomerular filtration rate (GFR) and identify and quantitate albumin excretion rate in patients with diabetes and anemia patients.

CAUSES OF ANEMIA

Anemia in diabetic patients with CKD may result from one or more mechanisms. Vitamin deficiencies such as folate and B12 are relatively uncommon, and clinical practice guidelines do not recommend routine measurement of these serum levels. (See below.) The major causes of anemia in CKD patients are iron and erythropoietin deficiencies and hyporesponsiveness to the actions of erythropoietin.

Iron deficiency

Iron deficiency in the general population is a common cause of anemia and is prevalent in patients with diabetes and CKD. In these same patients, dietary deficiency, low intestinal absorption, and gastrointestinal bleeding may result in absolute iron-deficiency anemia. Recent analyses of the National Health and Nutrition Examination Survey IV suggest that up to 50% of patients with CKD stages 2–5 have absolute or relative (functional) iron deficiency (17). In CKD, both absolute and relative iron deficiency are common. Absolute iron deficiency is defined as a depletion of tissue iron stores evidenced by a serum ferritin level <100 ng/ml or a transferrin saturation of <20%. Functional iron deficiency anemia is adequate tissue iron defined as a serum ferritin level ≥100 ng/ml and a reduction in iron saturation. The latter is more common and is strongly associated with upregulation of inflammatory cytokines and impaired tissue responsiveness to erythropoietin, which can inhibit iron transport from tissue stores to erythroblasts (18). Increased levels of inflammatory cytokines such as interleukin-6 enhance production and secretion of hepcidin, a hepatic protein that inhibits intestinal iron absorption and impairs iron transport from the reticuloendothelial system to bone marrow. In addition, erythropoietin, which normally enhances iron transport from macrophages to the blood stream, is impaired, thereby exacerbating relative iron deficiency (19).

Erythropoietin deficiency and hyporesponsiveness

Both deficiency and hyporesponsiveness to erythropoietin contribute to anemia in diabetic patients with CKD (15,20). The cause of erythropoietin deficiency in these patients is thought to be reduced renal mass with consequent depletion of the hormone. Hyporesponsivness is defined clinically as a requirement for high doses of erythropoietin in order to raise blood Hb level in the absence of iron deficiency. It is believed to represent impaired antiapoptotic action of erythropoietin on proerythroblasts. Possible causes of this erythropoietin hyporesponsiveness include systemic inflammation and microvascular damage in the bone marrow (15,20). However, some studies suggest that other factors (i.e., autonomic failure) may play a role in impaired erythropoietin production or secretion by failing kidneys (21).

Nephrotic syndrome

Nephrotic syndrome characterized by edema, hypoalbuminemia, dyslipidemia, and urine protein-to-creatinine ratio ≥3 is not uncommon in patients with diabetic nephropathy and can occur even in early stages of CKD (e.g., stages 1–2) (21,22). The mechanism of anemia in ne-

phrotic syndrome is complex and involves both inflammatory-mediated mechanisms as discussed above as well as absolute iron deficiency. Iron excretion increases in early stages of kidney disease in patients with diabetes and albuminuria and is exacerbated by development of nephrotic-range proteinuria. In nephrotic syndrome, many nonalbumin proteins are excreted in the urine, including transferrin and erythropoietin. Significant losses of transferrin and erythropoietin can occur in nephrotic syndrome, leading to both iron- and erythropoietin-deficiency–caused anemia in patients with diabetes (23). Evidence for increased transferrin catabolism in nephrotic syndrome may contribute to iron deficiency–caused anemia (24). Decreased erythropoietin production, secretion, and hyporesponsiveness can contribute to anemia in nephrotic patients. (See above.)

ACE inhibitors and angiotensin receptor antagonists
Both of these drug classes may cause a reversible decrease in Hb concentration in patients with diabetes and CKD (25). The mechanisms by which ACE inhibitors and angiotensin receptor blockers lower Hb include a direct blockade of the proerythropoietic effects of angiotensin II on red cell precursors, degradation of physiological inhibitors of hematopoiesis, and suppression of IGF-I. Long-term administration of losartan in 50- to 100-mg doses once daily in patients with diabetes and albuminuria is expected to lower Hb by ~1 g/dl. Importantly, this effect does not diminish the renoprotective effect of losartan. It should be recognized that these classes of agents may induce or worsen symptomatic anemia in nephropathy patients (26).

CONSEQUENCES OF ANEMIA

Quality of life
Anemia is an important cause of physical and mental impairments in diabetic CKD patients including malaise, fatigue, weakness, dyspnea, impaired cognition, and other symptoms. Clinical trials indicate that improving anemia improves cognitive function, sexual function, general well-being, and exercise capacity and reduces the need for blood transfusions (6,8–10,27) There is renewed evidence of anemia in diabetes contributing to retinopathy, neuropathy, diabetic foot ul-

cer, hypertension, progression of kidney disease, and cardiovascular events (15).

Progression of kidney disease
In general, kidney disease in diabetes is progressive, and it has been hypothesized that anemia may contribute to progression of kidney disease (7,16,28,29). Possible mechanisms include renal ischemia caused by reduced oxygen delivery due to low Hb and underlying heart failure. For example, anemia may worsen renal medullary hypoxia, leading to renal interstitial injury and fibrosis (30,31). Whole animal and in vitro studies indicate that renal hypoxia upregulates hypoxia-inducible factor-1α, a transcriptional regulator of the erythropoietin gene as well as heme oxygenase, nitric oxide synthases, extracellular matrix, and apoptosis genes. It is upregulated by renal hypoxia and induces collagen gene expression in renal fibroblasts, thereby increasing interstitial fibrosis. Anemia may also increase renal sympathetic nerve activity, resulting in increased glomerular pressure and proteinuria (which in turn may accelerate progression of kidney disease), and contribute to worsening kidney function by exacerbating underlying heart failure—a common complication in patients with diabetes and kidney disease, (29).

Early animal model studies in renal ablation, hypertension, and diabetes demonstrated that treatment of anemia worsened systemic and glomerular hypertension and renal structural and functional damage, suggesting that anemia may actually be renoprotective (32,33). Recently, Nakamura et al. (34) demonstrated that administration of an erythropoietin-stimulating agent to patients with anemia and CKD decreased urine fatty acid–binding protein—a molecule known to be associated with increased risk for kidney disease progression—suggesting that ESA may have a renoprotective effect independent of Hb level. However, in clinical trials, erythropoietin has not yet been proven to slow kidney disease progression in patients with diabetes and nephropathy. (See below.)

Cardiovascular disease
Observational studies indicate that death is five times more likely than progression to end-stage kidney disease in patients with CKD (35). Moreover, cardiovascular disease is the most common cause of death in patients with diabetes and CKD; and anemia appears to be a risk multiplier for all-cause mortality among those same

patients. Anemia prevalence is up to 10-fold higher among diabetic patients with CKD and heart failure and is a modifiable risk factor among diabetic patients (36, 37). Low Hb concentration is an independent risk factor for left-ventricular hypertrophy, heart failure, and cardiovascular mortality (37–44). Heart failure is common in diabetic patients with nephropathy and may result in reduced renal blood flow, thereby contributing to further reduction in GFR and erythropoietin production. Also, anemia may aggravate tissue hypoxia, and subsequently heart failure, resulting in further renal sodium retention, volume expansion, increased venous return, and increased venomotor. For these reasons, treatment of anemia in patients with diabetes and CKD is a proposed strategy to reduce excessive cardiovascular morbidity and mortality. (See below.)

CLINICAL TRIALS OF ERYTHROPOIETIN-STIMULATING AGENTS — It is important to note that none of the published trials examining the safety and efficacy of ESA for anemia treatment included a placebo control group. With one exception (45), all study subjects (with varying Hb levels) were treated with an ESA.

RENAL OUTCOMES — Several small trials in patients with CKD, including those with diabetes, demonstrated a beneficial effect on kidney disease progression. Kuriyama et al. (45) studied 106 patients with stage 3–4 CKD with or without anemia. Those with anemia were randomized to ESA treatment or no treatment. The time to a doubling of serum creatinine from baseline was the study's primary end point. They found that time to doubling of serum creatinine was significantly longer in the treated group than in the nontreated group and similar to that in the nonanemic control subjects (45). Gouva et al. (46) randomized 88 anemic stage 3–5 CKD patients to early versus late treatment with erythropoietin-α to test the hypothesis that this intervention would slow the rate of progression to end-stage renal disease (ESRD). They found that early correction of anemia was associated with improved renal and patient survival compared with delayed treatment of anemia. Rossert et al. performed a randomized controlled trial involving 390 patients with stage 3–4 CKD and anemia to test the hypothesis

that treatment of anemia with an ESA to reach a higher Hb level would slow decline in kidney function. Subjects were targeted to one of two Hb levels (13–15 or 11–12 g/dl) and followed for 12 months. Although the decline in GFR was numerically less in the high-Hb group, this difference was not statistically significant. Still, those randomized to the high group showed improvement in QOL and vitality (47). However, the two largest trials to date to examine the effect of ESA on progression of kidney disease (as a secondary outcome) did not show any renal benefit of raising Hb to a higher level. (See below.)

CARDIOVASCULAR OUTCOMES
— Roger et al. (9) conducted a prospective, randomized, open-label trial in 155 anemic CKD patients (stage 3–4), testing the hypothesis that ESA treatment could prevent development or progression of left-ventricular hypertrophy. Study subjects were randomized to receive subcutaneous dosing with erythropoietin-α to achieve and maintain Hb in the range of 9–10 or 11–13 g/dl and followed for 2 years with repeated measures of left-ventricular structure and function. They found no difference in the primary outcome of left-ventricular wall thickness; however, those assigned to the higher Hb arm of the study experienced improvement in QOL. Levin et al. (8) conducted a randomized clinical trial to test the hypothesis that prevention or correction of anemia, by immediate versus delayed treatment with erythropoietin-α in patients with CKD, would delay or prevent left-ventricular hypertrophy. The primary outcome was the change in left-ventricular mass index. They randomized 176 CKD patients who had experienced a decrease of 1 g/dl Hb in the prior year and a baseline Hb level of 11–13.5 g/dl to treatment with epoetin-α to maintain Hb in the range of 12–14 g/dl or to maintain a target Hb range of 9–10.5 g/dl; the subjects were followed for 24 months with repeated measures of left-ventricular structure and function. Despite significant difference in Hb level between groups, they found no significant difference in left-ventricular mass index. Those assigned to higher Hb experienced improvement in QOL (Table 1).

Ritz et al. randomized 172 anemic patients with type 1 or type 2 diabetes and stage 1–3 CKD to treatment with epoetin-α and a target Hb level of either 13–15 or 10.5–11.5 g/dl and followed them for 19 months. The primary outcome was the change in left-ventricular mass index, and secondary outcomes included kidney function and QOL. There were no significant differences in left-ventricular mass index in those randomized to the higher target; however, QOL measures were significantly better in the higher Hb arm. There were no differences in kidney function decline and no significant differences in adverse events (48).

CARDIOVASCULAR EVENTS
— Singh et al. (11) tested the hypothesis that a higher Hb level would reduce risk for the composite cardiovascular outcome of stroke, myocardial infarction, heart failure, and all-cause cardiovascular mortality among patients with various causes of CKD including diabetes (~46%). In this trial, the Correction of Hb and Outcomes in Renal Insufficiency (CHOIR) trial, 1,432 patients with anemia and stage 3–4 CKD were randomized to an Hb target of 11.5 or 13–13.5 g/dl and followed for an average of 16 months (11). During the trial, Hb levels were significantly higher in those randomized to the higher Hb arm. The composite event rate was higher in those assigned to the higher Hb arm; however, there was no difference in the rate of development of ESRD. Also, in contrast to the results of other studies, there was no improvement in QOL in those randomized to the higher target. The authors concluded that use of a target Hb level of 13.5 g/dl (compared with 11.3 g/dl) was associated with increased risk and no incremental improvement in QOL. Post hoc analysis demonstrated that a higher fraction of patients in the higher Hb arm had prior coronary events, hypertension, and dropout prior to an event or completion of the study. In the Cardiovascular risk Reduction by Early Anemia Treatment with Epoetin beta (CREATE), Drueke et al. (6) randomized 603 patients with stage 3–4 CKD, from various causes including diabetes (~25%), to early versus late treatment with epoetin-α to test the hypothesis that a higher Hb level would reduce risk for cardiovascular morbidity and mortality. Subjects were randomized to an Hb target range of 11–11.5 or 13–15 g/dl and followed for an average of 36 months. They found no significant differences in the primary composite outcome, but there was a trend toward a higher event rate in the higher Hb arm. In addition, multiple QOL measures were significantly improved in those

Table 1—*Randomized controlled cardiovascular outcome trials of anemia treatment with erythropoietin-stimulating agents in patients with chronic kidney disease*

	N	Diabetes (%)	Study design	Stage of study population	HCT/Hb target	Follow-up (months)	Primary outcome	Results	QOL
Roger et al.	155	24–33	Open label	3–5	9–10/12–13	24	ΔLVMI	No benefit	Improved
Levin et al.	172	35–41	Open label	2–5	9–10.5/12–14	22.6	LVMI	No benefit	Improved
Singh et al.	1,432	48	Open label	4–5	11–11.5/13–13.5	16	Death or cardiovascular event	Worse in high Hb arm	No difference
Druecke et al.	603	25	Open label	4–5	11–11.5/13–15	36	Death or cardiovascular event	No benefit	Improved
Ritz et al.	176	100	Open label	Stage 1–3	13–15/10.5–11.5	18	LVH	No benefit	Improved
Mix et al.	4,000	100	Double-blind and placebo controlled	3–4	13.0/<11.0	24–48	Death or cariovascular events	Trial ongoing	Trial ongoing

HCT, hematocrit; HD, hemodialysis; LVH, left ventricular hypertrophy; LVMI, left-ventricular mass index.

randomized to the higher Hb arm. In contrast to the CHOIR study, the time to ESRD, a secondary outcome, was shorter in the higher Hb arm. Post hoc analysis demonstrated that the study was underpowered to detect a difference in the primary outcome variable as a result of the lower-than-expected overall event rate in both arms of the study.

The increased risk for adverse outcomes during ESA treatment of anemia in clinical trials of patients with CKD is not completely understood. One possibility is that higher Hb increases risk for thrombosis. Another possibility is that those who experience adverse cardiovascular events have higher comorbidity, are relatively resistant to erythropoietin, and require higher doses of ESA to achieve higher Hb and that the higher doses of ESA are vasculotoxic (49). Further studies are needed to determine whether higher doses versus resistance to action of ESA cause harm in anemic patients with CKD. The Trial of Reduction of End points with Aranesp Therapy (TREAT) is an ongoing large-scale, randomized, double-blind, and placebo-controlled study including 4,000 anemic patients with type 2 diabetes and CKD (50). The primary outcome is a composite of all-cause mortality and cardiovascular morbidity. This ongoing trial is unique in many respects, including the double-blind, placebo-controlled design; the population of exclusively anemic patients with type 2 diabetes and CKD; and a large sample size. This study will add important new information concerning benefits and risks of ESA treatment of anemia in patients with diabetes and CKD. Results are expected in 2010.

In summary, two clear messages emerge from the anemia treatment trials. *1*) Treating patients to achieve a higher compared with a lower Hb target typically improves QOL. *2*) Treatment to reach a higher Hb level does not reduce risk for cardiovascular events and may cause harm.

CLINICAL PRACTICE GUIDELINES FOR EVALUATION OF ANEMIA — The NKF clinical practice guidelines for diagnosis and management of anemia in patients with CKD recommend a routine history and physical examination, a complete blood count, a reticulocyte count, evaluation of serum iron and total iron binding capacity and serum ferritin level, and a fecal test for occult blood for eval-

uation of anemia (13,51). Additional tests to evaluate anemia should be guided by this initial evaluation (e.g., serum folic acid, vitamin B12 level, Coombs test, etc.). Despite the high prevalence of anemia in the CKD population, treatment with erythropoietin or iron often is not used in the predialysis period. For example, nearly 70% of patients initiated on dialysis are anemic by the NKF definition but are not treated with erythropoietin, and >50% of these patients have severe anemia (hematocrit <30%).

RECOMMENDATIONS FOR TREATMENT OF ANEMIA

NKF clinical practice guidelines
The NKF currently recommends that when treating anemia in CKD with an ESA, the Hb target range should be 11–12 g/dl and should not exceed 13 g/dl (51). In addition, the NKF recommends that treatment should be individualized, taking into account patient characteristics including symptoms, Hb level, and evaluation for other causes of anemia. (See above.) If the initial evaluation indicates absolute iron deficiency as the cause, treatment with supplemental iron and a search for the cause of iron loss should be undertaken. If absolute iron deficiency is not present and causes other than kidney disease are excluded, then treatment with an ESA should be administered at a dose sufficient to increase Hb within the target range of 11–12 g/dl. Importantly, ESA-treated patients should, in general, receive iron to ensure that adequate stores are available for erythropoietic response (51). The NKF notes that with few exceptions, anemia treatment trials in CKD patients demonstrated that treatment with an ESA to achieve Hb values in the range of 11–13 g/dl is associated with improved QOL.

Food and Drug Administration
In early 2007, the Food and Drug Administration (FDA) promulgated new recommendations for use of ESA in patients with CKD, advising them that ESA can increase risk for heart attack, stroke, blood clots, heart failure, and death when given to maintain higher Hb (52). Drugs affected by their recommendation included epoetin-α and darbepoetin. The FDA advised practitioners to use the lowest dose of an ESA needed to avoid blood transfusion, targeting blood Hb in the range of 10–12 g/dl, and to withhold the dose of ESA when Hb level exceeds 12

g/dl. Manufacturers of ESA accordingly added black box warnings noting these recommendations (53).

In summary, the NKF and FDA recommendations are in conflict. Whereas there is agreement that ESAs are valuable for treating anemia, they differ with regard to the level of Hb at which to initiate ESA and the upper limit of the Hb target. The NKF supports the safety of ESA use and recognizes the importance of individualizing anemia treatment. Further studies on the safety of ESA use in the diabetes population, as well as efforts to better understand the explanation for the association of higher Hb with worse cardiovascular outcomes reported in clinical trials, are needed.

ANEMIA MANAGEMENT — The first step in the management of anemia is evaluating the underlying cause. (See above on diagnosis and evaluation.) If absolute iron deficiency is present, the patient should be put on oral or intravenous iron therapy. Several oral iron preparations are available for treatment including ferrous gluconate, fumarate, and sulfate. Doses of 300–325 mg of one of these agents three times daily can increase the Hb level significantly in such patients. Notably, significant gastrointestinal side effects may lead to poor adherence and compliance with oral iron. An alternative is to administer intravenous iron on a periodic basis. Several studies indicate that these preparations are effective and safe in predialysis populations (11,54,55). Dahdah et al. (54) administered intravenous iron dextran to anemic, iron-deficient (serum ferritin <100 ng/ml or transferrin saturation <20%) patients with an estimated GFR <50 ml/min and not on dialysis in doses of either 200 mg/week for 5 weeks or 500 mg/week for 2 weeks. Significant increases in Hb occurred within 2 weeks; all patients tolerated infusions without serious adverse reactions. Intravenous iron preparations including ferric sodium gluconate, iron sucrose, and iron dextran are available and can be administered safely. Among these agents, iron dextran has been associated with the highest incidence of adverse reactions, although the incidence of such reactions is low with all three preparations. Although some studies indicate that intravenous iron is in general more efficacious than oral iron for achieving increases in Hb in patients with CKD, oral iron is also effective (55). Moreover, no definite advantages have been shown with intravenous

versus oral iron in patients with CKD not on dialysis (56).

An initial dose of 10,000 units epoetin-α once weekly or 0.75 μg/kg darbepoetin-α every other week subcutaneously are effective for increasing Hb concentration by 1–2 g/dl over 4–8 week periods (27). Darbepoetin can be administered subcutaneously every other week at outset and then administered once monthly to maintain Hb target. Ling et al. (57) demonstrated efficacy of maintaining Hb in the range of 10–12 g/dl (total dose of 88 μg) after extending the dosing interval from every other week to once every 4 weeks. Provenzano et al. (58) found that an increased dosing interval from weekly to once monthly using epoetin-α in doses up to 40,000 units maintained Hb in a similar range.

Extended dosing of short- and long-acting ESA, including the hematopoietic and adverse effects, has recently been reviewed (59). Currently, the only ESA approved by the FDA for extended interval dosing is darbepoetin. In clinical practice, darbepoetin is often administered every other week initially, until the Hb target is achieved, before extending dosing to every 4 weeks. Extended dosing may require an increase in dose (27,57).

Monitoring response to treatment

Patients should be evaluated for improvement in symptoms including fatigue, vitality, physical functioning, and cognitive function. Initially, Hb level should be measured every other week to monitor the hematopoietic response and monthly thereafter. In general, if an Hb level deviates from the target range (see above), the dose of the ESA should be adjusted either upward or downward by 25%. In most patients, increases or decreases in ESA dose should not be made more frequently than monthly. Also, for safety reasons, if Hb is rising at a rate of >1 g/dl within a 4-week period, the dose should be held, as more rapid increases may be associated with increased risk for adverse events such as hypertension.

Functional iron deficiency should be suspected in any patient not responding to ESA treatment, and patient compliance with iron therapy should be investigated. Routine measurement of iron stores including serum iron, iron binding capacity, and ferritin should be monitored monthly for 3 months then quarterly once Hb target is achieved (56,60).

Adverse side effects of therapy

In clinical trials, up to 25% of patients experience an increase in blood pressure or develop overt hypertension (blood pressure >140/90 mmHg) (8,27,47,61–63). Thus, ESA should not be used to treat anemia in patients with uncontrolled blood pressure. Moreover, increases in blood pressure should be looked for in any anemic CKD patient treated with an ESA, and dose adjustments in ESA, iron, or antihypertension medications should be undertaken as needed. Common side effects include local pain or tissue reaction to subcutaneous injection and development of flu-like symptoms within hours or days of administration of an ESA.

A rare but serious form of pure red cell aplasia can occur during ESA treatment, including in those treated with epoetin and darbepoetin (64,65). The anemia is sudden in onset and can occur as early as 2 months after initiation of treatment. As noted above, ESA may increase risk for death and cardiovascular events and thrombotic events. The risk is reported in those with Hb levels >12 g/dl in some clinical trials. Therefore, it is prudent to modify the dose of ESA to reduce the likelihood of excursions of Hb exceeding 13 g/dl as recommended by the NKF (51). Adverse effects of iron use are described above and include gastrointestinal side effects with oral preparations and anaphylactic reactions with intravenous preparations.

AREAS OF UNCERTAINTY

— Analysis of available evidence from clinical trials clearly indicates that there is enough uncertainty regarding the risk-to-benefit ratio of treatment of anemic CKD patients with ESA to warrant additional major randomized clinical trials (66). TREAT is an ongoing study that will provide additional new information on whether treatment per se can improve cardiovascular outcomes in patients with type 2 diabetes, anemia, and CKD (50). Because nearly 50% of new cases of ESRO in the U.S. are attributed to diabetes, further studies are needed to help guide management of anemia. Areas of uncertainty that remain include establishment of the optimal individual Hb level—the level at which patient QOL is maximized and morbidity and mortality risks are minimized. The optimal dose of a given ESA, the frequency of dosing, and the indication and target Hb range remain controversial. For example, should ESA dosing begin at an Hb level of 10, 11, or

12 g/dl? Another area of uncertainty concerns the diagnosis and management of erythropoietin hyporesponsiveness, for which there is no widely accepted, standardized definition. This confounds the analysis of clinical trials in which higher doses of ESA and higher Hb occur in those randomized to higher Hb targets. Additional studies are needed to understand the nature and extent of hyporesponsiveness to erythropoietin in patients with CKD—an area of high priority for future research. However, it is not established whether the benefits of improved QOL measures outweigh the risks of cardiovascular morbidity and the economic costs related to treatment to achieve a higher Hb level. Another area of uncertainty related to hyporesponsiveness is the role of iron use in treating anemia. New research that provides a better understanding of the role of inflammation in iron metabolism, utilization, and the response to ESA treatment is another important research priority.

SUMMARY

— Anemia is common and contributes to both poor QOL and increased risk for adverse outcomes including death. Treatment of anemia improves QOL; however, thus far, evidence is lacking for a benefit of anemia treatment on progression of kidney disease and cardiovascular outcomes. The NKF recommends that physicians consider treating anemia in patients with diabetes and kidney disease when Hb is <11 g/dl in patients. Further, they recommend a Hb target of 11–12 g/dl, not to exceed 13 g/dl, when using an ESA as part of the therapeutic regimen for managing anemia. Currently available ESA combined with iron supplementation can be used safely and effectively to achieve this goal. However, available clinical trial evidence leaves sufficient uncertainty regarding the optimal Hb target and ESA dose for a given individual. For this reason, the NKF recommends individualizing treatment of anemia with ESA. Additional randomized clinical trials are needed to more precisely define these parameters for an individual patient. Future studies are also needed to elaborate the mechanisms of anemia in patients with diabetes and CKD including the role of iron metabolism, inflammation, and resistance.

References

1. USRDS. United States Renal Data Systems Annual Data Report. Am J Kid Dis 2007; 49(Suppl. 1):S10–S294
2. Herzog CA, Mangrum JM, Passman R. Sudden cardiac death and dialysis patients. Semin Dial 2008;21:300–307
3. Vlagopoulos PT, Tighiouart H, Weiner DE, Griffith J, Pettitt D, Salem DN, Levey AS, Sarnak MJ. Anemia as a risk factor for cardiovascular disease and all-cause mortality in diabetes: the impact of chronic kidney disease. J Am Soc Nephrol 2005; 16:3403–3410
4. Toto RD. Heart disease in diabetic patients. Semin Nephrol 2005;25:372–378
5. New JP, Aung T, Baker PG, Yongsheng G, Pylypczuk R, Houghton J, Rudenski A, New RP, Hegarty J, Gibson JM, O'Donoghue DJ, Buchan IE. The high prevalence of unrecognized anaemia in patients with diabetes and chronic kidney disease: a population-based study. Diabet Med 2008;25:564–569
6. Drueke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, Burger HU, Scherhag A, the CREATE Investigators. Normalization of Hb level in patients with chronic kidney disease and anemia. N Engl J Med 2006;355:2071–2084
7. Mohanram A, Zhang Z, Shahinfar S, Keane WF, Brenner BM, Toto RD. Anemia and end-stage renal disease in patients with type 2 diabetes and nephropathy. Kidney Int 2004;66:1131–1138
8. Levin A, Djurdjev O, Thompson C, Barrett B, Ethier J, Carlisle E, Barre P, Magner P, Muirhead N, Tobe S, Tam P, Wadgymar JA, Kappel J, Holland D, Pichette V, Shoker A, Soltys G, Verrelli M, Singer J. Canadian randomized trial of Hb maintenance to prevent or delay left ventricular mass growth in patients with CKD. Am J Kidney Dis 2005;46:799–811
9. Roger SD, McMahon LP, Clarkson A, Disney A, Harris D, Hawley C, Healy H, Kerr P, Lynn K, Parnham A, Pascoe R, Voss D, Walker R, Levin A. Effects of early and late intervention with epoetin alpha on left ventricular mass among patients with chronic kidney disease (stage 3 or 4): results of a randomized clinical trial. J Am Soc Nephrol 2004;15:148–156
10. Horl WH, Vanrenterghem Y, Canaud B, Mann J, Teatini U, Wanner C, Wikström B. Optimal treatment of renal anaemia (OPTA): improving the efficacy and efficiency of renal anaemia therapy in haemodialysis patients receiving intravenous epoetin. Nephrol Dial Transplant 2005; 20(Suppl. 3):iii25–iii32
11. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, Reddan D, the CHOIR Investigators. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med 2006;355:2085–2098
12. Fishbane S, Nissenson AR. The new FDA label for erythropoietin treatment: how does it affect Hb target? Kidney Int 2007; 72:806–813
13. Macdougall IC, Eckardt KU, Locatelli F. Latest US KDOQI Anaemia Guidelines update–what are the implications for Europe? Nephrol Dial Transplant 2007;22: 2738–2742
14. Astor BC, Muntner P, Levin A, Eustace JA, Coresh J. Association of kidney function with anemia: the Third National Health and Nutrition Examination Survey (1988-1994). Arch Intern Med 2002;162:1401-1408
15. Thomas MC. Anemia in diabetes: marker or mediator of microvascular disease? Nat Clin Pract Nephrol 2007;3:20–30
16. Thomas MC, Tsalamandris C, MacIsaac RJ, Jerums G. The epidemiology of Hb levels in patients with type 2 diabetes. Am J Kidney Dis 2006;48:537–545
17. Fishbane S, Pollack S, Feldman HI, Joffe MM. Iron indices in chronic kidney disease in the National Health and Nutritional Examination Survey 1988–2004. Clin J Am Soc Nephrol 2009;4:57–61
18. Mezzano S, Droguett A, Burgos ME, Ardiles LG, Flores CA, Aros CA, Caorsi I, Vío CP, Ruiz-Ortega M, Egido J. Renin-angiotensin system activation and interstitial inflammation in human diabetic nephropathy. Kidney Int 2003;(Suppl): S64–S70
19. Thomas MC, MacIsaac RJ, Tsalamandris C, Jerums G. Elevated iron indices in patients with diabetes. Diabet Med 2004;21: 798–802
20. Erslev AJ, Besarab A. Erythropoietin in the pathogenesis and treatment of the anemia of chronic renal failure. Kidney Int 1997;51:622–630
21. Winkler AS, Marsden J, Chaudhuri KR, Hambley H, Watkins PJ. Erythropoietin depletion and anaemia in diabetes mellitus. Diabet Med 1999;16:813–819
22. Bosman DR, Winkler AS, Marsden JT, Macdougall IC, Watkins PJ. Anemia with erythropoietin deficiency occurs early in diabetic nephropathy. Diabetes Care 2001;24:495–499
23. Howard RL, Buddington B, Alfrey AC. Urinary albumin, transferrin and iron excretion in diabetic patients. Kidney Int 1991;40:923–926
24. Vaziri ND. Erythropoietin and transferrin metabolism in nephrotic syndrome. Am J Kidney Dis 2001;38:1–8
25. Marathias KP, Agroyannis B, Mavromoustakos T, Matsoukas J, Vlahakos DV. Hematocrit-lowering effect following inactivation of renin-angiotensin system with angiotensin converting enzyme inhibitors and angiotensin receptor blockers. Curr Top Med Chem 2004;4: 483–486
26. Mohanram A, Zhang Z, Shahinfar S, Lyle PA, Toto RD. The effect of losartan on Hb concentration and renal outcome in diabetic nephropathy of type 2 diabetes. Kidney Int 2008;73:630–636
27. Toto RD, Pichette V, Navarro J, Brenner R, Carroll W, Liu W, Roger S. Darbepoetin alfa effectively treats anemia in patients with chronic kidney disease with de novo every-other-week administration. Am J Nephrol 2004;24:453–460
28. Rossert J, Froissart M. Role of anemia in progression of chronic kidney disease. Semin Nephrol 2006;26:283–289
29. Mohanram A, Toto RD. Outcome studies in diabetic nephropathy. Semin Nephrol 2003;23:255–271
30. Norman JT, Fine LG. Intrarenal oxygenation in chronic renal failure. Clin Exp Pharmacol Physiol 2006;33:989–996
31. Iwano M, Neilson EG. Mechanisms of tubulointerstitial fibrosis. Curr Opin Nephrol Hypertens 2004;13:279–284
32. 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: 6142–6146
33. Lafferty HM, Anderson S, Brenner BM. Anemia: a potent modulator of renal hemodynamics in models of progressive renal disease. Am J Kidney Dis 1991; 17(Suppl. 1):2–7
34. Nakamura T, Sugaya T, Kawagoe Y, Suzuki T, Ueda Y, Koide H. Effect of erythropoietin on urinary liver-type fatty-acid-binding protein in patients with chronic renal failure and anemia. Am J Nephrol 2006;26:276–280
35. Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Arch Intern Med 2004;164:659–663
36. Herzog CA, Puumala M, Collins AJ. NHANES III: the distribution of Hb levels related to chronic kidney disease (CKD), diabetes (DM), and congestive heart failure (CHF) (Abstract). J Am Soc Nephrol 2002;13:428A
37. Collins AJ, Li S, Gilbertson DT, Liu J, Chen SC, Herzog CA. Chronic kidney disease and cardiovascular disease in the Medicare population. Kidney Int 2003 (Suppl):S24–S31
38. Burrows L, Muller R. Chronic kidney disease and cardiovascular disease: patho-

physiologic links. Nephrol Nurs J 2007; 34:55–63

39. Foley RN, Parfrey PS, Sarnak MJ. Epidemiology of cardiovascular disease in chronic renal disease. J Am Soc Nephrol 1998;9(Suppl.):S16–S23

40. Levin A. Identification of patients and risk factors in chronic kidney disease–evaluating risk factors and therapeutic strategies. Nephrol Dial Transplant 2001; 16(Suppl.):57–60

41. McClellan WM, Jurkovitz C, Abramson J. The epidemiology and control of anaemia among pre-ESRD patients with chronic kidney disease. Eur J Clin Invest 2005; 35(Suppl. 3):58–65

42. Silverberg DS, Wexler D, Iaina A, Schwartz D. The interaction between heart failure and other heart diseases, renal failure, and anemia. Semin Nephrol 2006;26:296–306

43. Astor BC, Arnett DK, Brown A, Coresh J. Association of kidney function and Hb with left ventricular morphology among African Americans: the Atherosclerosis Risk in Communities (ARIC) study. Am J Kidney Dis 2004;43:836–845

44. Joss N, Patel R, Paterson K, Simpson K, Perry C, Stirling C. Anaemia is common and predicts mortality in diabetic nephropathy. Q J Med 2007;100:641–647

45. Kuriyama S, Tomonari H, Yoshida H, Hashimoto T, Kawaguchi Y, Sakai O. Reversal of anemia by erythropoietin therapy retards the progression of chronic renal failure, especially in nondiabetic patients. Nephron 1997;77:176–185

46. Gouva C, Nikolopoulos P, Ioannidis JP, Siamopoulos KC. Treating anemia early in renal failure patients slows the decline of renal function: a randomized controlled trial. Kidney Int 2004;66:753-760

47. Rossert J, Levin A, Roger SD, Hörl WH, Fouqueray B, Gassmann-Mayer C, Frei D, McClellan WM. Effect of early correction of anemia on the progression of CKD. Am J Kidney Dis 2006;47:738–750

48. Ritz E, Laville M, Bilous RW, O'Donoghue D, Scherhag A, Burger U, de Alvaro F; Anemia Correction in Diabetes Study Investigators. Target level for Hb correction in patients with diabetes and CKD: primary results of the Anemia Correction in Diabetes (ACORD) Study. Am J Kidney Dis 2007;49:194–207

49. Szczech LA, Barnhart HX, Inrig JK, Reddan DN, Sapp S, Califf RM, Patel UD, Singh AK. Secondary analysis of the CHOIR trial epoetin-alpha dose and achieved Hb outcomes. Kidney Int 2008; 74:791–798

50. Mix TC, Brenner RM, Cooper ME, de Zeeuw D, Ivanovich P, Levey AS, McGill JB, McMurray JJ, Parfrey PS, Parving HH, Pereira BJ, Remuzzi G, Singh AK, Solomon SD, Stehman-Breen C, Toto RD, Pfeffer MA. Rationale—Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT): evolving the management of cardiovascular risk in patients with chronic kidney disease. Am Heart J 2005;149:408–413

51. KDOQI. Clinical practice guideline and clinical practice recommendations for anemia in chronic kidney disease: 2007 update of Hb target. Am J Kidney Dis 2007;50:471–530

52. FDA/Center for Drug Evaluation and Research: Erythropoiesis-stimulating agents (ESAs): epoetin alfa (marketed as Procrit, Epogen), darbepoetin alfa (marketed as Aranesp) [article online], 2007. Available from http://www.fda.gov/cder/drug/advisory/RHE200711.htm. Accessed 1 April 2008

53. Fishbane S, Besarab A. Mechanism of increased mortality risk with erythropoietin treatment to higher Hb targets. Clin J Am Soc Nephrol 2007;2:1274–1282

54. Dahdah K, Patrie JT, Bolton WK. Intravenous iron dextran treatment in predialysis patients with chronic renal failure. Am J Kidney Dis 2000;36:775–782

55. Van Wyck DB, Roppolo M, Martinez CO, Mazey RM, McMurray S. A randomized, controlled trial comparing IV iron sucrose to oral iron in anemic patients with non-dialysis-dependent CKD. Kidney Int 2005;68:2846–2856

56. Fishbane S. Iron management in nondialysis-dependent CKD. Am J Kidney Dis 2007;49:736–743

57. Ling B, Walczyk M, Agarwal A, Carroll W, Liu W, Brenner R. Darbepoetin alfa administered once monthly maintains Hb concentrations in patients with chronic kidney disease. Clin Nephrol 2005;63: 327–334

58. Provenzano R, Bhaduri S, Singh AK. Extended epoetin alfa dosing as maintenance treatment for the anemia of chronic kidney disease: the PROMPT study. Clin Nephrol 2005;64:113–123

59. Carrera F, Disney A, Molina M. Extended dosing intervals with erythropoiesis-stimulating agents in chronic kidney disease: a review of clinical data. Nephrol Dial Transplant 2007;22(Suppl. 4):iv19–iv30

60. Fishbane S. Safety in iron management. Am J Kidney Dis 2003;4(Suppl. 5):18–26

61. Strippoli GF, Craig JC, Manno C, Schena FP. Hb targets for the anemia of chronic kidney disease: a meta-analysis of randomized, controlled trials. J Am Soc Nephrol 2004;15:3154–3165

62. Aranesp (darbepoetin alfa) for injection [article online]. Available from http://www.aranesp.com/pdf/aranesp_pi.pdf. Accessed 1 April 2008

63. Procrit (epoitin alfa): for injection [article online]. Available from http://www.procrit.com/procrit/shared/OBI/PI/ProcritBooklet.pdf#page=1. Accessed 1 April 2008

64. Howman R, Kulkarni H. Antibody-mediated acquired pure red cell aplasia (PRCA) after treatment with darbepoetin. Nephrol Dial Transplant 2007;22:1462–1464

65. Rossert J, Froissart M, Jacquot C. Anemia management and chronic renal failure progression. Kidney Int 2005;(Suppl): S76–S81

66. Parfrey PS. Target Hb level for EPO therapy in CKD. Am J Kidney Dis 2006;47: 171–173