Clinical trials have shown a strong detrimental relationship among anemia, chronic kidney disease (CKD), and cardiovascular disease. The baseline presence of anemia, as well as markers for poor renal function, has been shown to predict kidney disease progression and mortality—with the risk of cardiovascular events increasing in patients who are anemic. Observational studies suggest that erythropoietin deficiency and the resulting anemia cause additional harm in patients with CKD. However, the many confounding factors that accompany CKD have thus far complicated efforts to identify the specific mechanism by which anemia increases mortality risk in patients with CKD. Interventional studies in patients with anemia have shown that hemoglobin levels can be raised predictably, safely, and easily with erythropoietin treatment. Although treatment improves patient quality of life, studies have yet to identify the optimal treatment regimen for improving cardiovascular and renal outcomes. Retrospective analyses of the interventional trials suggest that anemia treatment may be best used as a preventative rather than a curative therapy. Because trials of anemia correction have enrolled patients with relatively advanced kidney disease, the benefits of raising hemoglobin levels may have been masked by other confounding conditions. Prospective trials are currently under way that will provide insight into the therapeutic benefits of correcting anemia in patients with CKD. (Adv Stud Med. 2005;5(7A):S715-S719)
because these are observational studies, it is unclear whether anemia plays a causal role or is simply a marker of more severe disease.

In the Reduction of Endpoints in NIDDM [non–insulin dependent diabetes mellitus] with the Angiotensin II Antagonist Losartan (RENAAL) trial, patients with type 2 diabetes mellitus and albuminuria were enrolled, and the primary end points were doubling of serum creatinine, development of end-stage renal disease (ESRD), death, or a combination of the renal outcomes. Anemia was common in this patient population, and reduced Hb levels were correlated with increased risk for the composite end point. Those patients with an Hb below 11.2 g/dL had an increased risk of approximately 320% for the composite end point (Figure 3). In subsequent analyses of the RENAAL data, baseline presence of markers for poor renal function, such as proteinuria, elevated serum creatinine, reduced serum albumin, and reduced Hb were found to be predictors of the composite end point (Table). The risk for congestive heart failure (CHF) in this trial was correlated with Hb levels. The correlation between Hb and risk for CHF was observed at relatively high levels of Hb, suggesting that Hb corrective therapy, such as erythropoietin therapy, may be beneficial, even at relatively high levels of Hb. The Studies of Left Ventricular Dysfunction (SOLVD) trial extends this correlation between Hb levels and poor cardiovascular outcomes. SOLVD showed that for every 1-g/dL decrease in Hb, a patient’s risk for left ventricular hypertrophy (LVH) increased by 6%.

The Atherosclerosis Risk in Communities Study (ARIC) showed a strong correlation between the presence of anemia and the risk for stroke. ARIC researchers investigated the etiology of atherosclerosis and found that patients with renal insufficiency (creatinine clearance <60 mL/min) were not at higher risk for stroke. However, those patients with renal insufficiency who were also anemic were at a risk for stroke 5 times that of patients with renal insufficiency alone (Figure 4).

The observational studies and postanalyses of interventional studies show a clear link among cardiovascular events, CKD, and anemia. Anemia functions as a mortality multiplier in this triad of conditions. There is certainly reason to believe that anemia, or erythropoietin deficiency, could be harmful to patients with kidney disease. However, the many confounding factors that accompany kidney disease, such as chronic inflammation, have thus far prevented researchers from discerning the specific role anemia plays in the poor cardiovascular outcomes of CKD patients.

Figure 1. Anemia Increases Mortality Risk

DM = diabetes mellitus; CKD = chronic kidney disease; CHF = congestive heart failure.


Figure 2. Cardiovascular Risk Increases with Anemia Severity

INTERVENTIONAL STUDIES

Several interventional studies have been designed to address the impact of anemia correction on patient outcomes. In the case of erythropoietin treatment, trials have shown that Hb levels can be raised predictably and easily. However, these trials did not reveal if the highly pharmacologic nature of this current treatment is optimal for improving cardiovascular and renal outcomes. For example, a trial of 146 dialysis patients with LVH who were randomized to therapy to achieve Hb levels of either 10 g/dL or 13.5 g/dL, showed no evidence of improved LVH after 48 weeks of erythropoietin treatment. However, erythropoietin treatment did markedly improve patients’ quality of life. In the absence of readily identifiable signs of physical improvement, improved quality of life is a desirable outcome from erythropoietin treatment.

A trial in which patients were randomized to achieve hematocrit levels of either 30% ± 3% or 42% ± 3% through hemodialysis and epoetin was terminated early for safety concerns. There was a nearly statistically significant trend for increased mortality with the higher hematocrit target. This study suggests that normalizing hematocrit in patients undergoing dialysis who have CVD may not be beneficial owing to reduced efficiency of dialysis, the additional cardiac stress from greater blood viscosity, or other unidentified mechanisms. Nevertheless, data from this study are useful, and post hoc analysis has shown that observational data from this study mirrors data from other observational studies. That is, in the low hematocrit group, lower levels of hematocrit were associated with increased mortality. A study of 416 patients, most of whom had ESRD, randomized patients to achieve either normal Hb levels (135–160 g/L) or low Hb levels (90–120 g/L) through treatment with epoetin alfa. Mortality risk was not different between the 2 groups by intent-to-treat analysis. However, observational data from post hoc analysis showed that higher Hb levels (136 vs <122 g/L) were associated with lower mortality risk.

A study of left ventricular mass index, which randomized patients with CKD to achieve normal (120–130 g/L) or low levels (90–100 g/L) of Hb (with erythropoietin treatment as necessary), showed no difference between treatment groups. Although this study did not achieve good Hb level separation between treatment groups to adequately test the hypothesis, the results nonetheless suggest that anemia correction may not reverse established cardiovascular damage. Therefore, anemia treatment may have to be viewed as a preventative rather than a curative therapy. This trial also suggests that the benefits of anemia correction may be difficult to recognize in patients with stage 3 or 4 kidney disease, who typically have a multitude of confounding comorbid conditions that must be taken into account.
ONGOING STUDIES

Currently, 3 large trials are under way. The Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial has been designed to investigate the optimal target hemoglobin level in erythropoietin therapy while investigating the therapeutic benefits of erythropoietin treatment on cardiovascular outcomes and all-cause mortality in patients with CKD. The Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) trial has been designed to investigate the effect of early anemia correction on cardiovascular outcomes, including left ventricular mass index, in patients with CKD. The Trial to Reduce Cardiovascular Events with Aranesp® Therapy (TREAT) is a randomized, placebo-controlled trial designed to investigate the impact of anemia correction on cardiovascular events in patients with CKD and diabetes mellitus. TREAT is a trial of darbepoetin, an agent that may allow reduced dosing regimens because of its extended serum half-life compared with epoetin alfa.

Anemia is clearly associated with increased mortality and increased risk of cardiovascular events in patients with CKD. The specific mechanism by which anemia multiplies mortality has yet to be identified. Patients with CKD and CVD have many comorbid conditions, including anemia, that contribute to their increased risk of mortality. Currently, erythropoietin treatment is effective in raising Hb levels. In the published interventional trials, we have yet to see treatment benefit for the cardiovascular events associated with CKD. However, these trials have enrolled patients with relatively advanced kidney disease. Future and ongoing trials that prospectively study the benefits of anemia correction will provide the information necessary to help physicians choose among treatment options and to better recognize therapeutic benefits.

DISCUSSION

Dr Lepor: How do you reconcile the fact that in the intervention trials, there was such a difference between the intent-to-treat versus the goal levels? Is it because there are some erythropoietin resistance issues suggesting the responders are the ones who benefit? This is similar to patients with aspirin and clopidogrel resistance; they still thrombose their stents, but patients who are not resistant do well. Is this an accurate or false analogy?

Dr Fishbane: That is a great question that may be examined in different ways. Generally, one of the difficult things in the observation of this relationship is that it is self-evident to us as nephrologists when one of our patients gets sick. Hb levels plummet and remain low after the patient has been hospitalized for infections. The Hb levels stay low for months, until the entire inflammatory cascade works out. So, in observational studies, whether it is as part of an interventional trial or not, it is very likely that the sicker patients have lower Hb levels, and therefore, a higher risk of death. However, there are some quirky data within the normal hematocrit study and some other studies that suggest that there is more to it than that—that maybe your hypothesis might be correct in terms of achieving the higher levels. It is also possible that higher levels of Hb actually are very healthy, and that the way we approach erythropoietin treatment can be compared with insulin therapy, where over the course of 50 years we began with very short-acting bursts of insulin and advanced to improving glucose levels to improve survival.

But in hemodialysis patients, we still administer doses 3 times per week that have effects throughout
the body. For instance, the heart is filled with erythropoietin receptors. Every time dosing produces super surges of erythropoietin, growth signals in the heart are turned on and off, and the full cascade of signal transduction, turning genes on and off, is induced. It might be that reaching heart Hb levels is a very positive thing, but the unsophisticated way that we currently use erythropoietin may not be very helpful. This is one theory of many. We need to learn more, as the endocrinologists did, as to how to replace this hormone in a way that more closely mirrors homeostasis. We currently are not doing this.

*For more excerpts from the faculty discussion, visit www.JHASIM.com or www.UTASIP.com.

REFERENCES