ANEMIA, CHRONIC KIDNEY DISEASE, AND CARDIOVASCULAR DISEASE: THE CLINICAL TRIALS

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ABSTRACT

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.


Published trials point to a detrimental relationship among anemia, chronic kidney disease (CKD), and cardiovascular disease (CVD), in which mortality risk from either of these diseases is compounded when anemia is also present. Physiologically, it makes sense that anemia could increase the mortality risk in patients with CKD who are at high risk for a cardiovascular event. These patients suffer varying degrees of relative hypoxia, depending on the severity of their anemia. Additionally, the potential lack of and blunted response to erythropoietin leaves their bodies ill prepared to combat anemia or produce the progenitor cells necessary for tissue repair. Completed observational and interventional studies suggest the breadth and depth of this relationship among CKD, anemia, and the increased risk for cardiovascular events.

OBSERVATIONAL STUDIES

In a Medicare population study, mortality risk was calculated for the presence of various diseases and conditions over a 2-year follow-up period.1 Compared with patients who had no known comorbidity, patients with diabetes mellitus had a 50% increased risk of death. Anemia and CKD were independently associated with a 100% increased risk of death. Mortality risk was further increased in patients who had multiple comorbidities, with anemia being a significant multiplier of mortality risk (Figure 1). The level of increased risk for a cardiovascular event has also been shown to strongly correlate with the severity of anemia. In a study of dialysis patients, the risk of mortality from a cardiac event became greater at lower hemoglobin (Hb) levels (Figure 2).2 The large number of patients in this retrospective study (N = 50,579) gives significant weight to the results. However,
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

Figure 2. Cardiovascular Risk Increases with Anemia Severity

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

**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 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.

**Dr Atta:** There is also the notion that the use of high doses of epoetin alfa may be associated with poor outcomes, and it may be that those patients who need higher doses of epoetin alfa definitely are sicker, or they may have a lot of inflammation; so, you need to give them very high doses. The PROMPT study tried to extend the use of erythropoietin, which has a halflife of 8 hours, to a dose every 2 weeks, every 3 weeks, and every 4 weeks. Instead of giving 10,000 units every week, 40,000 units were given every 4 weeks. It is important to determine what kind of impact such a large dose would have not only on anemia but also on other organs.

**Dr Fishbane:** Yes, I think what was shown in the PROMPT study was that using a high dose of epoetin alfa can, in about 80% of patients, successfully enable dosing to be extended to 4-week intervals in a reasonably unselected population. My theory would be that this is exactly the opposite way that we really want to treat these patients. We should not overload the erythropoietin receptors with excessively high levels, and thereby completely turn off any active erythropoietin receptor. This approach definitely corrects hemoglobin, but it would be interesting to study the effect on the brain and the heart, which are loaded with erythropoietin receptors. There are current studies in models to try to better understand the likely effects.

**Dr Agarwal:** I would also like to comment on the PROMPT study. In every group that received 40,000 units every 4 weeks, the response was lesser than in groups that were dosed once every week or every 2 weeks—more like 76% or so. This is not bad, but the follow-up was only about 19 weeks, and there was a slight trend for the hemoglobin curve to go down. I wish that there had been a little longer follow-up in this study. In comparison, in the extended dosing study of darbepoetin alfa, the patients recruited were already on darbepoetin every 2 weeks and were maintaining stable Hb. The dose and the administration interval of darbepoetin were doubled, so that darbepoetin was given every month instead of every 2 weeks. Eighty-six percent of those who completed the trial actually were able to maintain the target Hb level, and the follow-up was 29 weeks. So, coming back to your point, we may need to follow the example of the endocrinologists and use longer-lasting agents less frequently.

**Dr Fishbane:** The PROMPT study really does show exactly what you are saying; that the levels were tending to drop off with epoetin alfa. In tissue culture studies, which are a long way from the clinic, we are looking at different ways of exposing tissues to erythropoietin and the resulting effects. It seems to me that the way that the body has developed a response to erythropoietin receptors in the brain, heart, kidneys, and bone marrow seems to work much more effectively with some type of continuous exposure. It may be that we need to have continuous low levels present as well as spiked levels on top of that. Further research is needed so we can better understand how to do this effectively.

### REFERENCES

