Mechanism of Increased Mortality Risk with Erythropoietin Treatment to Higher Hemoglobin Targets

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Recent randomized, controlled trials indicate that there is a strong trend for increased risk for death or adverse composite outcomes with erythropoiesis-stimulating agent treatment in kidney disease to hemoglobin targets higher than those currently recommended. The failure of these trials to find a benefit of higher hemoglobin is in stark contrast to findings from large, observational, population-based studies that continue to demonstrate the association of low hemoglobin with adverse outcomes. The mechanisms for the adverse effect of higher hemoglobin targets that are seen in the randomized, controlled trials are poorly understood. This review explores hypotheses involving (*1*) the effect of achieved hemoglobin itself, (*2*) the role of erythropoiesis-stimulating agent treatment, (*3*) the use of iron supplementation, (*4*) increased blood pressure, and (*5*) erythropoiesis-stimulating agent hyporesponsiveness. Because the causal pathway has yet to be determined, further research is strongly encouraged. Clinical practice, however, should avoid erythropoiesis-stimulating agent treatment to higher hemoglobin targets, particularly in those with significant cardiovascular morbidity and those who require disproportionately high dosages of erythropoietin-stimulating agents to achieve recommended hemoglobin levels.

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Treatment with erythropoietin (EPO) analogues (the preferred terminology is now erythropoiesis-stimulating agents [ESA]) has been one of the most valuable advances in the treatment of patients with kidney disease. Before ESA availability, severe anemia was common, resulting in repeated transfusions in some and significantly detracting from patients' quality of life in most. Partial correction of anemia with ESA produces demonstrably improved quality of life and reduced need for blood transfusion (1) and has virtually eliminated secondary iron overload. As a result, >90% of patients with ESRD and many patients (approximately 20%) with nondialysis chronic kidney disease (CKD) are now treated with these agents.

When epoetin α was first approved for use in 1989, the recommended treatment was for partial correction of anemia to a hemoglobin (Hb) of 9 to 10 g/dl with the primary objective of avoiding transfusion (2), even though the initial clinical trials targeted a higher Hb range with mean Hb values maintained at >11 g/dl (1,3–7). By 1997, when the first National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) anemia guidelines were released (3), the mean Hb had slowly increased to approximately 11 with an increase in epoetin α dosage to approximately 5500 U. Since then in the United States, the dosage of epoetin per administration has increased to approximately 7500 U because the Hb target was essentially widened by the second NKF-KDOQI anemia guidelines to 11 to 13 g/dl (4) and the clinical performance measure quality indicator of achieving 80% of patients to an Hb of ≥11 g/dl.

As experience with ESA treatment grew in the 1990s, the question arose whether treatment to higher Hb targets, including complete normalization, could produce additional benefits. The goal was to achieve further and broader improvement in quality of life as well as the potential for improved cardiovascular outcomes; however, interest was dampened after the first large randomized, controlled trial (RCT) of Hb normalization in hemodialysis patients (Normal Hematocrit Cardiac Trial [NHCT]) found a trend toward increased mortality risk with treatment to a hematocrit (Hct) target of 42% (5). In addition, this trial found a significantly increased risk for vascular access thrombosis. Subsequently, four published RCT (6–9) in hemodialysis (HD) patients with ESRD and eight in nondialysis patients with CKD have compared treatment to different Hb targets (9–16). Most of the studies have found improved quality of life at the higher Hb targets; however, none demonstrated significant improvement in mortality or cardiovascular end points.

A major inflection point in thinking about higher Hb targets was the November 2006 publication of two large studies in nondialysis CKD: Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin β (CREATE) (14) and Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) (15). Both studies found trends toward increased mortality risk and for other adverse outcomes as well. In the CHOIR study, a composite end point assessing multiple events was significantly higher in the group that was randomly assigned to the higher Hb target of 13.5 g/dl compared with the group that was randomly assigned to an Hb of 11.3 g/dl. The authors

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found a nearly statistically significant 45% increase in mortality risk in the higher Hb target group. Similarly, the CREATE study found a trend toward increased mortality risk of 48% with a higher Hb target of 13 to 15 g/dl.

A recent meta-analysis by Phrommintikul *et al.* (17) in February 2007 found that treatment to higher Hb targets resulted in a 17% increased risk for mortality ($P = 0.03$). This analysis, however, was not based on patient-level data but on aggregation of reported group data. Indeed, the three largest RCT published, CHOIR ($n = 1433$), NHCT ($n = 1232$), and CREATE ($n = 600$) (9,14,15), all found trends toward increased mortality risk. The results of these three largest studies are remarkably consistent: An increase in all-cause mortality of 21 to 48% with the higher Hb targets (but in none of them individually statistically significant [$P = 0.07$, approximately 0.08, and 0.14, respectively]). Although all three studies have design or execution flaws (18), like all RCT, the consistent thread of evidence in the direction of increased risk for death must be taken very seriously (19) (an ongoing trial, the Trial to Reduce Cardiovascular Events with Aranesp Therapy [TREAT] Study, will be substantially larger than these studies and may have an important impact on the body of evidence). Other adverse events—vascular access thrombosis and increased BP—are also increased with higher Hb targets (20). These observations led to a substantial increase in vigilance and concern regarding Hb targets in current use. With this in mind and with similar adverse findings reported from studies of ESA treatment in cancer (21), the US Food and Drug Administration took the dramatic step of drastically increasing the warnings contained in labels for ESA drugs on March 9, 2007 (22).

The purpose of this report is to explore hypotheses for the explanation of increased risk with treatment to higher Hb targets. We consider the direct effect of Hb level, the potential role of ESA treatment and supplemental iron treatment needed to achieve higher Hb levels, hypertension, and factors related to ESA responsiveness. These are summarized in Figure 1. It should be clear that there is no certainty as to any one mechanism of increased risk, and we believe that it may be the summed effect of some or all. Many of the postulated mechanisms in Figure 1 are interactive. Erythropoietin (EPO)-induced elevations in Hb increase viscosity and increase platelet number and aggregation; both are aggravated by periodic HD-induced hemoconcentration. Similarly, blood volume and BP are intimately intertwined during a change in Hb level from one state to another. More iron is always needed for higher Hb levels. An area that needs to be examined is whether nonphysiologic ESA treatment produces direct toxicity. Our purpose is to present the rationale for several hypotheses to stimulate further research directed at better understanding the observed increase in risk.

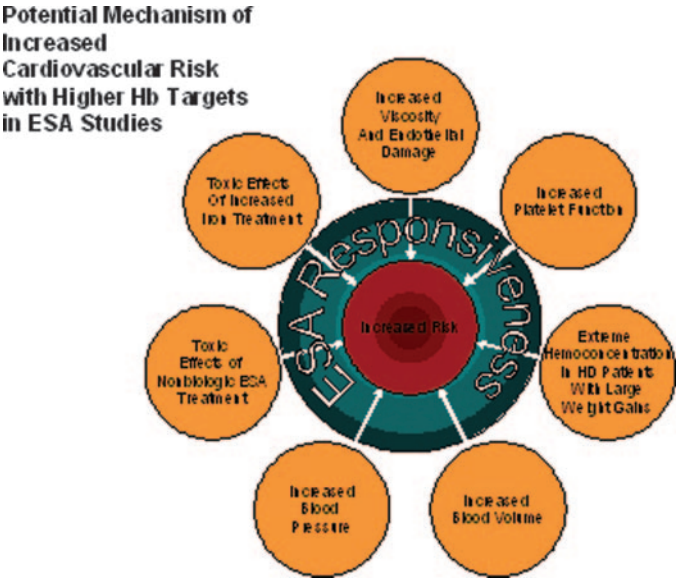

Figure 1. Diagrammatic representation of possible mechanisms that lead to adverse outcomes on normalizing hemoglobin (Hb) with erythropoiesis-stimulating agents (ESA). The large green circle indicates that the risk in a population of patients may be a function of the responsiveness to ESA in general that is mediated by many factors, including comorbidity, inflammation, *etc.* Risk may accrue from the processes, depicted by orange circles, acting on these patients (arrows). Many of the postulated mechanisms in the figure are interactive. Thus viscosity, increased platelet adhesion, and hemoconcentration all may be acting simultaneously and synergistically. BP and blood volume are also interactive on preload and afterload to the heart.

Role of Achieved Hb Level

The primary role of the erythrocyte is transport of oxygen to the body's tissues and organs. The normal Hb of approximately 13 to 17 g/dl (Hct of 40 to 50%) is not random but rather one that optimizes delivery of oxygen (23). Oxygen transport primarily depends on the Hb content of blood. There is a relatively linear increase in oxygen-carrying capacity with progressively higher levels of Hb in normal individuals. In well-dialyzed patients, at the same Hb level, delivery of oxygen to peripheral tissues in HD patients is slightly augmented (20) when compared with those without renal disease.

Reduction in oxygen-carrying capacity with the development of anemia, however, does induce compensatory mechanisms, including systemic vasodilation (24) and increased cardiac output. The increase in cardiac output during anemia correlates well with the degree of anemia and is reversed when the Hct is raised to >30% (18). Both left ventricular mass and end-diastolic volume increase in response to anemia (25). The detrimental effects of anemia, even in individuals without kidney disease, are probably due to both tissue hypoxia and the longer term compensatory effects of increased cardiac work, such as left ventricular hypertrophy (26–30). Conversely, treatment with ESA to correct anemia reverses the physiologic abnormalities, which might explain the improved quality of life that is usually observed.

The benefit of improved oxygen carriage as anemia is corrected, especially in patients with advanced kidney disease, may be significantly offset by increased blood volume and viscosity. Hypervolemia after correction of anemia can produce negative effects on left ventricular ejection fraction and function (31). For improvement of cardiac performance, blood volume expansion must be diligently prevented by appropriate

changes in estimated dry weight (edema-free weight without hypotension) and by BP control. Maintenance of normal blood volume requires equivalent decreases in plasma volume as red cell mass is increased to avoid changes in preload to the heart (32). Relative hypervolemia may be one mechanism that leads to the worsening of BP control during ESA therapy (*vida infra*) in up to 30% of ESA-treated patients (24).

As anemia is corrected with ESA treatment, the target Hb level reflects at the physiologic level a tradeoff between the beneficial effects of increased oxygen carriage and the unfavorable effect of increased blood viscosity. The relationship between viscosity and Hb level is not linear; viscosity increases slowly until Hb increases to >40 to 50%, at which point it inflects sharply higher. Nature seems to strike a balance at a normal Hb level in health of 13 to 16 g/dl. The detrimental effect of increased viscosity is to increase sheer stress on the vascular endothelium. At very high Hb levels, as seen in states of primary or secondary erythrocytosis, this shear stress produces endothelial injury that may result in increased risk for vascular thrombosis (33).

At a superficial level, it would seem "wise" to treat the anemia of kidney disease with a goal of increasing Hb back to the normal range because the body always restores the Hb back to normal when provided with adequate substrates and time; however, individuals with kidney disease differ from those in the healthy state in a number of ways, not the least of which is the great prevalence of atherosclerotic vascular disease. It is highly unlikely that the tradeoff of blood oxygen carriage and viscosity is optimized at normal Hb levels in this population when compared with those without kidney disease. In fact, it is plausible that in patients with CKD, even the relatively small increases in blood viscosity as Hb rises to >13 g/dl may have an accentuated harmful effect when vascular disease is present. Patients with kidney disease and atherosclerosis may have multiple areas of unstable atherosclerotic plaque and/or ulcerations that are vulnerable to increased viscosity-associated sheer stress.

The risk related to elevated Hb may be accentuated by HD-induced hemoconcentration. Hb levels are measured before the dialysis session in HD patients when the patient is most hemodilute. This results in a spuriously low measured Hb concentration but is the value that is actually used to adjust ESA dosage. Because Hb targets tend to be the same in HD and nondialysis CKD, actual time-averaged Hb levels are actually raised to a greater extent in HD patients. This may be particularly relevant among patients who are large interdialytic weight gainers. Even in moderate weight gainers (up to 2 to 3 L per interdialytic period), the time-averaged Hg averages approximately 1 g higher than that obtained before dialysis (34). Changes immediately after dialysis are of course larger. Those who gain 5 to 9% of their dry weight interdialytically would undergo much larger transients, and with the substantial ultrafiltration that they must undergo, these patients may experience extreme hemoconcentration of 5 to 10 Hct points. Although the Hct in clinical trials or in general practice has usually fallen short of those seen in secondary erythrocytosis, significant hemoconcentration can occur. In the NHCT, postdialysis Hct in excess of 53% were occasionally reached in those whose Hct reached the upper target of 45% (A.B., personal observations, 1994–1995). It may be especially risky to target higher Hb levels in such patients because changes in Hct and in viscosity, producing large changes in shear rate and shear stress, may occur over hours. This may partially explain evidence from previous studies of increased mortality risk among HD patients with larger interdialytic weight gains (35).

Another effect of increasing Hb and correcting anemia is to improve platelet function. To an extent, correction of the coagulation disorder is a desirable change, reducing the tendency to excessive bleeding risk with severe anemia; however, the improvement in platelet function does not come without some consequences. Up to 11% of patients experience clotting of dialyzers or lines after epoetin therapy, and, depending on the type of membranes used, the heparin requirements at final target Hct of 10 to 12.5 g/dl have to be increased by 50% (36); however, at even higher levels of Hb, the benefit-to-risk ratio may be reduced, and, in fact, it is plausible that at such levels, it might be harmful. At higher Hb targets in CKD, the increased platelet function could potentially be detrimental, increasing platelet exposure and activation at areas of vascular plaque and injury, thereby increasing risk for thrombosis.

It is not possible from the current literature to determine the relative quantitative importance of increased Hb itself as a cause of the increased risk with targeting of higher Hb levels. In fact, a *post hoc* analysis of the NHCT, the largest randomized trial on Hb target conducted to date among HD patients, found that achieved Hct level to normal was not associated with increased risk for death. In both the high Hct target group and the lower target groups, there was a trend toward increased risk for death with lower achieved Hct. This association of increasing mortality with increasing anemia at Hb <11 g/dl has been documented repeatedly by US Renal Data System analyses (4). The *post hoc* analysis of the NHCT at first glance seems to contradict the primary outcome of the study, increased risk for death at the higher Hct target; however, the *post hoc* analysis is of unclear significance and may be flawed. The integral intertwining of health status and achieved Hct creates unavoidable and vitiating survivor bias. Sicker patients in both groups may have lower and falling Hct levels and increased risk for death as a result of their declining health status. The relationship between lower Hct level and increased risk for death probably reflects poor health status rather an effect of Hct level. The intention-to-treat primary finding of a trend for increased risk for death with targeting of the higher Hct level stands as the more credible and reliable result.

It is unclear whether it is possible to design studies that could adequately examine the relative pathogenic role of higher Hb itself in explaining the increased mortality risk with targeting of higher Hb levels. Any treatment to increase Hb limits the ability to isolate the Hb effect, because the treatment itself may have an adverse impact. One approach would be a study of different interventions, such as differing ESA, intravenous iron, or androgens to increase Hb level to a lower and higher Hb target. If risk with the higher Hb were increased to a similar extent by each intervention, then this would partially support the causative role of increased Hb.

Role of Treatments Used to Achieve Higher Hb Levels

ESA

A second hypothesis is that some aspect of anemia therapy itself, the amount of ESA used and/or iron treatment, may play a causative role in increased mortality risk. Most of the Hb target studies in HD used epoetin α (a first-generation epoetin) as the ESA treatment. This drug, like epoetin β, is very similar in structure and function to native EPO; therefore, there would not seem to be a reason to suspect any toxic effect. However, treatment with ESA of patients with CKD is distinctly different from the normal biology of EPO. Using US Renal Data System administrative claims data, a retrospective cohort study (37) of 94,569 prevalent HD patients in 2000 and 2001 showed that epoetin α dosage requirement was an independent predictor of total mortality in HD patients after adjustment for Hct and other baseline variables. This effect of ESA dosage was found for every Hct cohort studied; patients who were administered higher dosages of epoetin had significantly lower Hct values and greater mortality rates. The steepest increase in relative risk for death was found after the 72.5th dosage percentile, that is, in poor responders. We discuss this issue further later in our discourse.

Treatment with ESA is distinctly different from the normal biology of EPO. In the healthy steady state, small amounts of EPO are continually produced to maintain low levels of serum EPO in the range of approximately 12 to 15 U/L (38,39). The effect is similar to a pharmacologic continuous infusion because renal EPO is not stored but continuously produced and secreted. These low EPO concentrations stimulate enough erythrocyte production to replace sufficiently those cells lost continuously to senescence (40,41). When anemia occurs, serum EPO levels may increase to substantially higher levels (42–44). The relationship between anemia and Hb and EPO response was studied in experiments of Al-Huniti *et al.* (45). Acute phlebotomy in sheep that lowered Hb from 10 g/dl to <4 g/d produced a rapid increase in serum EPO concentration, from 15 to 836 U/L by days 1.5 to 3.7; however, this response was temporary because serum EPO levels decreased within the next 3 to 4 d. As Hb concentration rose, EPO levels reached near basal concentrations (46). The response in humans depends on conditions. After a 1-U phlebotomy of 400 ml, one study (47) reported only a doubling of EPO levels in men and women, peaking at 7 to 14 d and then gradual decline to baseline by 8 wk. In another study of phlebotomy (48), linear regression analysis of the Hb/log EPO relationship for 18 patients revealed no differences in the endogenous EPO response to phlebotomy, as determined by the slopes and intercepts, for men *versus* women or as a function of age. With chronic anemia, serum EPO concentration remains chronically elevated (46,49–51).

In a study that examined the response to rapid two-unit phlebotomy performed by J. Caro (unpublished data, 1988), the data obtained in Figure 2 were obtained and show an orderly feedback process. Note that after a second-unit phlebotomy 24 h after the first, circulating mean EPO levels increased 10-fold from 10 to 15 U/L to approximately 200 U/L as Hb fell from the baseline values of 15 to 12 g/dl. During the subsequent 2 wk, there was a progressive increase in the Hb as the deficit was corrected partially with the production of approximately 1 U of packed cells and was associated with a progressive decrease in EPO level from 10-fold elevations to only a two-fold elevation. Once full correction of anemia occurred, EPO concentrations returned to normal. Surprising, the response of endogenous EPO to blood loss is preserved in HD patients, although blunted (51).

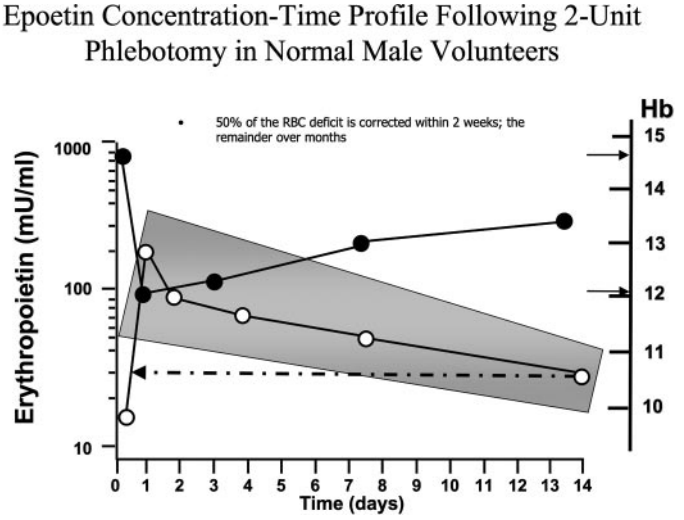

Figure 2. Endogenous response to a two-unit phlebotomy within a 24-h period in normal individuals. All data were collected after completion of the second phlebotomy (time zero). Hb decreases from a normal value of 15 to 12 g/dl by the end of day 1. Endogenous erythropoietin (EPO) increases from normal levels of approximately 15 to 200 mU/ml. This increase in EPO levels leads to a progressive increase in the Hb such that during the first 2 wk, approximately half of the original deficit (one unit) is reconstituted. The rest of the deficit would be corrected during the next 6 wk (data not shown), assuming adequate iron availability. As the deficit corrects, EPO levels decrease toward their original values. The trapezoid defines the 95% confidence limits for the data. EPO levels do not show discontinuity, and the relationship of Hb and EPO show the operation of the normal feedback process.

Treatment with ESA results in serum EPO kinetics that is distinctly different from normal biology. After injection, there is a rapid increase in serum levels, although somewhat slower for subcutaneous than for intravenous administration, as shown in Figure 3. Even after a modest dosage of only 3000 U given intravenously, the concentration of EPO peaks at 7 ng/ml (approximately 1000 U/L). After subcutaneous administration of the same dosage, peak levels are much lower at approximately 1 to 1.5 ng/ml (peak 130 to 200 mU/ml). Peak concentrations of EPO are proportional to dosage, and the mean dosage of approximately 8000 U/dose in HD patients in 2005 would produce peak levels of EPO that exceeded 3000 U/L, levels reached only at Hb levels of 5 g/dl with clinical anemia (43). With subcutaneous injection of epoetin α, 40,000 U, a dosage often used with monthly administration, serum concentrations may reach levels that usually are seen only at extremes

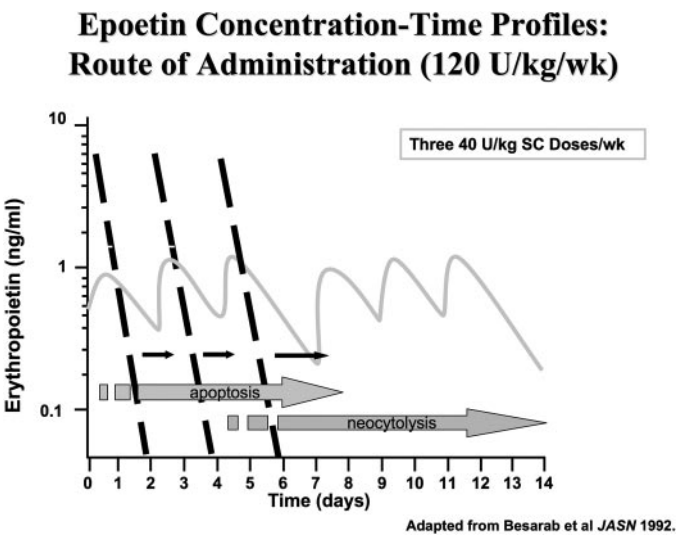

Figure 3. EPO profiles after intravenous and subcutaneous administration of epoetin β at varying intervals. Two processes decrease efficient erythrocyte production/maturation/survival: Apoptosis (bone marrow) and neocytolysis (premature destruction of young cells). Both are triggered by low EPO levels or a rapid decrease in EPO levels. Results shown are based on pharmacokinetic modeling using a low to modest EPO dosage of 40 U/kg thrice weekly (120 U/kg per wk). Intravenous administration raises peak levels to 1000 mU/ml. Subcutaneous peak levels are much lower. Intravenous route does not sustain EPO levels, contributing to both apoptosis and neocytolysis. These processes are reduced with subcutaneous administration, which maintains over dosing intervals. Dosing at longer intervals intravenously does not augment erythropoiesis despite the higher EPO levels attained.

of severe anemia. As shown in Figure 2, the serum EPO concentration after exogenous epoetin α or β declines rapidly after administration. By 48 h after intravenous administration, the serum concentration of EPO is reduced by 98.5%. With subcutaneous administration of epoetin α/β at extended dose intervals, the depletion of EPO is amplified. During monthly administration of epoetin α, serum levels of EPO may remain at low levels for periods up to several weeks.

Taken together, the aspects of ESA treatment that differ from normal biology are the very rapid rise in serum levels after injection, the high peak serum concentration, the rapid decline in levels, and the decline in some patients to very low serum concentrations. The potential of these divergences from normal biology to cause harm (or, conversely, beneficial effects) resides in the possible effects of EPO on nonerythroid receptors, particularly in the central nervous system, spinal cord, retina, vasculature, and heart, where EPO acts in a paracrine manner (52). Binding of EPO to its receptor affects cellular growth signals, generally promoting cellular survival. The minimal effective exogenous dosage that is required to mimic or augment the paracrine functions of EPO in some organs (*e.g.*, brain, heart) is higher than those needed for treatment of anemia (53). In these tissues, EPO acts through a heterodimeric receptor that differs from the homodimeric receptor used for erythropoiesis (54).

At high concentrations, native EPO may have cytoprotective effects that can be offset by undesired procoagulant and vasoactive actions. In contrast, carbamylated recombinant human EPO, a heterodimeric receptor-specific ligand, reduces procoagulant activity and increases renal blood flow. This form of EPO and asialated EPO may be more effective agents for cytoprotection in cerebral ischemia, spinal cord compression, and crush injuries than the parent hormone (55). Another aspect that must be kept in mind is that the cytoprotective effects of EPO are achieved by a short burst of EPO over hours or days, periods too short to induce much erythropoiesis or affect coagulation or blood rheology. Treatment of anemia, by contrast, requires prolonged exposure to repeated bursts of EPO.

There is an abundance of EPO receptors in the heart, although the biologic significance is not yet fully understood. The presence of anemia induces certain cardiac compensations, and EPO would be a logical molecule to stimulate some of these changes. Alternatively, EPO may play a role in response to injury from temporary hypoxia. Indeed, studies have indicated potential benefit for EPO administration after experimental cardiac ischemia. In contrast, the chronic and repeated nonbiologic stimulation of cardiac EPO receptors during ESA treatment for anemia could have untoward effects, particularly on remodeling of the myocardium through prevention of apoptosis. Repetitive stimulation and resetting of cardiac growth signals could disorder cardiac modeling, increase vulnerability to stress, or impair the ability of higher Hb to diminish left ventricular hypertrophy. To be clear, these are hypotheses, and none has yet been tested in experimental or other systems.

There is little evidence from analysis of ESA treatment studies to support or refute the ESA hypothesis. In the NHCT, there was no relationship between EPO dosage and risk for mortality (10). We recently conducted analyses of this trial and confirmed that the epoetin α dosage, at least at baseline, was not associated with an increase in risk (Kilpatrick, R., Critchlow, C. W., Fishbane, S., Besarab, A., Stehman-Breen, C., Krishnan, M., and Bradbury, B. D., unpublished data, 2007). The dosage in responders (using the initial response after randomization) when Hb target was reached was much lower than in those who were nonresponders. The ability to study the independent causal effect of ESA in the clinical setting is difficult because of confounding related to variable interpatient responsiveness. In contrast, *in vitro* studies are more likely to shed light on potential nonerythroid toxicity. In the future, non–EPO-based ESA drugs that are under development may provide an opportunity to explore this hypothesis more extensively.

Iron Supplementation

An ancillary treatment that is often used with ESA therapy is iron supplementation. The possibility that iron contributes to increased risk was suggested by the results of the NHCT. Not unexpected, because iron must be administered in greater amounts to produce more Hb, intravenous iron was administered more frequently to patients in the normal Hct group and risk for mortality was increased for patients who were treated with intravenous iron during the 6 mo before death or censoring (odds ratio 2.4; $P < 0.001$) (9). A potential harmful role for

iron would seem to be a plausible hypothesis. Iron increases oxidative stress *via* the Fenton reaction. In HD patients, treatment with intravenous iron is associated with systemic evidence of increased oxidative stress (56), oxidation of plasma proteins (57), and evidence of vascular injury (58). In addition, increased concentration of serum ferritin has been associated in some but not all studies with increased risk for death as a result of cardiovascular causes (59). Among HD patients, treatment with intravenous iron and mortality risk has been reported in some studies to be associated with increased risk for death (60); however, recent studies by the same group using a temporal lag model, a more sensitive analytic technique, did not find increased risk with iron treatment (61).

Despite the plausible link between exogenous iron administration and cardiovascular injury, it would seem unlikely that iron supplementation could play a significant role in explaining the increased risk for death in the higher Hb target studies. It is true that iron treatment was associated with increased risk for death in the NHCT (9); however, data on iron treatment were collected inconsistently in that trial. In addition, investigators were urged to use intravenous iron treatment in the higher Hct group to help achieve the Hct target because iron deficiency would blunt the response to EPO. It is therefore difficult to dissociate the effect of higher Hb from the iron treatment, because iron therapy was needed to achieve the target Hb levels. More pointed, whereas iron supplementation is commonly used in HD, it is far less frequently used in nondialysis CKD. The CREATE study (14) provided limited information on iron treatment, reporting only on the percentage of patients who were administered at least one dose. The CHOIR study report (15) provided insufficient information to analyze iron treatment, and, in fact, relative iron deficiency may have been responsible in part for the failure of the higher Hb group to reach the prescribed target. Parenteral iron was used only in a few percent of patients. In neither study is it possible to determine the quantity or extent of iron treatment. Nonetheless, it is unlikely that patients would have received nearly as much intravenous iron supplementation in these studies as in the NHCT (conducted in HD patients). Because these studies demonstrated an even higher relative risk for death than the NHCT and because iron was probably used less frequently in these trials, a substantial causative role in risk for iron supplementation seems unlikely.

Role of Hypertension

Hypertension is a common and widely known complication of ESA treatment. It is estimated that 20 to 40% of patients who are treated with ESA have new onset or a worsening of BP that requires intensification of antihypertensive therapy (62,63). In addition, the meta-analysis of Phrommintikul *et al.* (20) found that risk for higher BP was significantly increased in the higher Hb target groups of included studies (relative risk 1.27; 95% confidence interval 1.08 to 1.50; $P = 0.004$); therefore, despite that investigators in trials presumably monitored and treated BP changes, elevated BP remained a complication in the ESA treatment to higher Hb target studies.

Hypertension is one of the most clearly established independent risk factors for cardiovascular events and death. A cornerstone of cardiac risk reduction is effective treatment with antihypertensive drugs. This may be particularly relevant in CKD, in which the prevalence of cardiovascular disease and risk for future cardiac events is exceedingly high. Increased BP induced by ESA treatment to high Hb targets in this population could be especially problematic. In fact, relatively small increases in BP are associated with substantive increases in cardiovascular risk; therefore, it is highly plausible that increased BP could partially explain the increased risk for death in the higher Hb target groups.

Reporting on BP from the ESA intervention trials has generally been relatively sparse and inconsistent. The CHOIR study report did not contain sufficient information on BP to allow for any meaningful analysis. Results from the CREATE study indicated an approximate 52% increase in risk for increased BP in the 13- to 15-g/L target group. The initial report of the NHCT did not indicate an increase in BP in the normal Hct target group. Particularly helpful were reports from a substudy of this trial (64,65), in which ambulatory BP monitoring was used. In these two studies totaling approximately 60 patients each in the low and higher Hct target groups, no increase in hypertensive burden was observed with targeting of normal Hct. Correction of Hct to normal did not cause increased BP as assessed by interdialytic ambulatory BP monitoring or by the measurement of routine predialysis and postdialysis BP; neither was there a change in the abnormal diurnal BP pattern that is seen in most patients who are on HD (66). However no detailed data on changes in antihypertensive regimens for the two groups were provided. In the second study reported (67), during the first 28 wk of the ramp up, changes in antihypertensive regimen were needed in only 15% of patients, and the frequency was identical in both groups; however, all investigators were encouraged to make downward adjustments in dry weight, if possible, as Hb increased (A.B. personal observation, 1994–1995). Not often recognized are the changes in tissue body fluid compartments that occur with anemia (68). During *de novo* correction of anemia in patients with epoetin β, estimated dry weight decreased, and the magnitude of the decrease was inversely proportional to the increase in Hg needed to reach an Hb target of 10.5 to 12.5 g/dl (A.B. unpublished observations, 1990–1995) starting with an Hb of 7 to 8.5 g/dl, again reiterating the importance of trying to minimize edema and maintain blood volume constant (69) and minimizing effects on nitric oxide (31).

Taken together, evidence from this literature is inconsistent, but generally demonstrates increased BP with higher Hb targets. The potential role of hypertension in explaining some of the increased risk of death in these trials has not yet been adequately studied.

Role of EPO Responsiveness

There is great variability in response to ESA treatment (67,70,71). Some patients require small dosages to achieve Hb targets; others require much higher dosages. In a re-analysis of the NHCT (72), we found great variability in responsiveness, with an enormous range in baseline epoetin α dosage from 900 to 42,600 U/wk. This variability is surprising in that in a clinical

trial, with restricted entry criteria, less variability would be expected than in routine clinical practice. We consider the hypothesis that some aspect of treatment hyporesponse could partially explain increased risk for death in the higher Hb groups of the ESA studies.

In our recent analysis, we found that responsiveness to ESA was a highly significant predictor of 1-yr mortality in the high Hct group of the NHCT. This does not explain the differential risk for mortality between the low- and high-Hct groups, but it suggests a possible causal pathway. Increased risk related to ESA hyporesponsiveness may reflect characteristics of the treated patient, such as comorbidity and inflammation; however, in our analysis, increased risk was not eliminated after correction for multiple confounders. It is possible that unmeasured confounders could explain the increased risk; however, an alternative explanation is that some aspect of ESA or related treatments, when administered to highly hyporesponsive patients, could be harmful. This is an early and underdeveloped hypothesis; it is presented more to stimulate thought rather than to suggest any definitive role in causality.

The conclusion from this reanalysis is important to keep in mind. In contrast to conventional wisdom, this study suggests that epoetin dosing requirements could provide important prognostic information beyond that predicted by Hct alone. Epoetin-poor responders who continue to have low Hct values despite the administration of higher epoetin dosages may not necessarily benefit from more epoetin. The observations are consistent with other observations (51) of possible harm from escalating dosages of intravenous epoetin. Such hyporesponsive patients must be carefully evaluated for processes that blunt responsiveness and considered for other adjunctive therapies.

Conclusions

We have presented a series of hypotheses to explain the mechanism of increased risk for death with targeting of higher Hb levels with ESA treatment in kidney disease. It is clear that current published studies do not permit delineation of the relative contributions of each of these factors. We strongly encourage further research aimed at elucidating the causal pathways. Given current knowledge, however, clinical treatment with ESA should avoid the higher Hb targets used in these studies. This is consistent with recent changes in labeling by the Food and Drug Administration and practice guidelines of the NKF-KDOQI anemia guidelines. The only uncertainty is whether the upper boundary for maintenance is 12 or 13 g/dl, because there are no RCT to guide us in this intermediate Hb range.

Disclosures

None.

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