

Resolved: Targeting a Higher Hemoglobin Is Associated with Greater Risk in Patients with CKD Anemia

ABSTRACT

Some time has passed since the torrent of discussion surrounding the cardiovascular risk of pushing up hemoglobin concentrations in dialysis patients with erythropoietin. The debate here reflects a look back on the tension produced by confusing data and outcomes. Is it the target hemoglobin *per se* or the high doses of erythropoietin in subsets of resistant patients that is the problem? You decide.

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Pro

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Mark Twain popularized a phrase attributed to Benjamin Disraeli: "There are three kinds of lies: lies, damned lies, and statistics."¹ This holds true in considering the question of whether erythropoietin toxicity as opposed to the target hemoglobin explains adverse risk in treating the anemia of chronic kidney disease (CKD). Studies implicating erythropoietin exposure with toxicity, including our own, are essentially observational in nature, represent secondary analyses, or both. Thus, these studies cannot exclude the possibility of confounding. Nor can these studies exclude other forms of bias. As Gregg Easterbrook said: "Torture numbers, and they'll confess to anything." As has been noted elsewhere, so far and to a large extent, observational studies have only begun to examine the complex relationship between erythropoietin dose, hemoglobin concentration, and a patient's underlying comorbidities.^{2,3} To conclude there is a causal relationship between erythropoietin exposure and risk for cardiovascular complications, death, or both is premature. Until randomized trials are performed to test whether erythropoietin exposure is associated with toxicity, "statistical sleight of hand" could be invoked to explain the observations supporting erythropoietin dose toxicity.

The very purpose of randomized controlled trials (RCTs) is to evaluate the effect of a predetermined intervention in two or more balanced groups. RCTs are considered by most to be at the top of the hierarchy of evidence-based research. RCTs limit spurious causality and bias.⁴ Indeed, RCTs have already tested whether targeting a higher hemoglobin level in CKD patients is

associated with increased risk.^{5–7} In these studies, to achieve a higher hemoglobin concentration requires on average higher doses of erythropoietin. However, the targeted intervention was not erythropoietin dose *per se*. If a higher hemoglobin concentration is achieved by using lower doses of erythropoietin, then investigators are required to stick to the lower dose of erythropoietin. This point was made recently by Bradbury *et al.*⁸ Furthermore, as Coyne also notes,⁹ the association between a higher dose of erythropoietin and adverse outcome could be explained by patient's comorbidities (*i.e.*, patients exposed to a higher erythropoietin dose are erythropoietin-resistant because they are sicker and thus have worse outcomes). The intervention in anemia randomized trials was the targeting of a higher hemoglobin concentration. The two groups were balanced because randomization worked. However, to date, no randomized study has been conducted to test the hypothesis that exposure to erythropoietin, where exposure to erythropoietin represents the intervention, is associated with increased risk. The best evidence suggests that targeting a higher hemoglobin concentration (≈ 13 g/dl) is associated with increased risk. Until further evidence emerges, perhaps from other randomized trials such as the Trial to Reduce Cardiovas-

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cular Events with Aranesp Therapy (TREAT), discussed in detail elsewhere,³ this is a resolved issue.

Three randomized trials, with reasonable sample size (>500 subjects) and with a design examining hard endpoints, have been published: the Normal Hematocrit Study,⁵ the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study,⁶ and Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin beta (CREATE) study.⁷ The Normal Hematocrit study⁵ was a randomized controlled study of 1233 hemodialysis patients with established heart disease. The effect of targeting with erythropoietin a hematocrit of 42% was compared with targeting a hematocrit of 30%. After 29 mo of follow-up, there were 183 deaths and 19 first nonfatal myocardial infarctions (MIs) in the “normal” hematocrit group and 150 deaths and 14 first nonfatal MIs in the “low” hematocrit group. The study was stopped by the Data Safety Monitoring Board because of concerns of increased mortality and cardiovascular disease risk in patients randomized to the higher hematocrit group (relative risk 1.9, 95% confidence interval [CI] of 0.9 to 1.9). Subjects randomized to the higher hematocrit group also had very nearly statistically significant higher rates of nonfatal MI or death. Several ideas were entertained to explain these findings. These include hemoconcentration in the normalized hemoglobin group, hypertension, lower dialysis adequacy, and iron exposure. The CHOIR and CREATE studies examined nondialysis CKD patients.^{6,7} The CHOIR study was an open-label, randomized trial that studied 1432 patients with CKD: 715 patients randomized to receive erythropoietin targeted to achieve a hemoglobin concentration of 13.5 g/dl, and 717 patients randomized to receive erythropoietin targeted to achieve a hemoglobin concentration of 11.3 g/dl.⁶ The median study duration was 16 mo. The primary endpoint was a composite of death, MI, hospitalization for congestive heart failure (CHF), excluding hospitalization during which renal replacement therapy occurred, and stroke. Two-hundred twenty-two composite events occurred: 125 events among the high hemoglobin group and 97 among the low hemoglobin group ($P = 0.03$, hazard ratio of 1.34, with 95% CI of 1.03 to 1.74). The higher rate of composite events was explained largely by a higher rate of death (48% higher risk, $P = 0.07$) or CHF hospitalization (41% higher risk, $P = 0.07$). Although neither death nor CHF hospitalization were significantly higher in the higher *versus* lower hemoglobin concentration group, the study was not powered for this purpose.

The CREATE study enrolled approximately 600 patients.⁷ Subjects were randomized to an early anemia correction or a late anemia correction group. The early anemia correction group received erythropoietin beta therapy immediately for a target hemoglobin concentration of 13 to 15 g/dl. The late anemia correction group did not receive treatment until their hemoglobin concentration was <10.5 g/dl; their target hemoglobin concentration was 10.5 to 11.5 g/dl. The study showed that “complete correction” was not associated with a statistically significantly higher rate of the first cardiovascular event (58 events in the high hemoglobin concentration group *versus* 47

events in the low hemoglobin concentration group, hazard ratio of 0.78, 95% CI of 0.53 to 1.14, $P = 0.20$). However, left ventricular mass index remained stable in both groups, but dialysis was required in more patients in the higher *versus* lower hemoglobin concentration group (127 *versus* 111, $P = 0.03$).

Collectively, in the three RCTs, Normal Hematocrit, CHOIR, and CREATE, the intervention was aiming for a target hemoglobin concentration of approximately 13 g/dl. In all three studies, either increased risk or no benefit was demonstrated with regard to cardiovascular outcomes by aiming to completely correct the hemoglobin concentration in CKD patients. The CHOIR study was larger and showed a statistically significant difference for the primary endpoint, whereas the Normal Hematocrit study was stopped early, and the CREATE study was underpowered for the primary event. Both Normal Hematocrit and CREATE showed a trend for increased risk but did not reveal statistically significant differences for the primary endpoint.

The Normal Hematocrit study, CREATE, and CHOIR have received criticisms.^{10,11} Several of the limitations have been rebutted.¹² The criticisms leveled at CREATE focused on the unanticipated lower event rate (6% *versus* 15%). This resulted in the study being underpowered for the primary endpoint comprised of 8 cardiovascular events, including sudden death. Although there was no statistically significant difference between the two groups, an absolute increase in the number of composite events in the higher hemoglobin concentration group was observed (22% higher risk with a hazard ratio [HR] of 0.78 favoring the lower hemoglobin concentration group with 95% CI of 0.53 to 1.14). The critique of the CHOIR trial centers on the high withdrawal rate, the slight imbalance in two baseline covariates, and the use of high erythropoietin doses.¹¹ This has been addressed elsewhere in some detail.¹² Another issue related to a slight imbalance between the higher and the lower hemoglobin concentration group in the baseline covariates of history of coronary artery bypass graft and a history of hypertension. However, it is widely accepted that minor differences in baseline covariates may occur by chance alone if one compares a large number of baseline covariates. The difference in the baseline covariates reflects only 2 of 100 baseline variables that were measured. It is unlikely that these baseline differences in cardiovascular comorbidity explain the striking differences between groups. Related covariates such as a history of MI, peripheral vascular disease, and percutaneous angioplasty are all similar between groups. With respect to the history of hypertension, the baseline and subsequent BP are similar between groups, as were the use of concomitant BP medications.

How do these results from randomized studies reconcile with extensive evidence from observational analyses suggesting greater adverse risk with lower hemoglobin concentrations and lower risks with higher hemoglobin levels? Several studies have been published supporting the notion that there is greater risk associated with a lower hemoglobin concentration and conversely a lower risk with a higher hemoglobin level in both dialysis and nondialysis CKD patients.^{13–17} However, a recent analysis is worthy of review.¹⁸ Messana *et al.* examine the association of quarterly average achieved hematocrit with mortality in dialysis patients

using a time-dependent, comorbidity-adjusted model. They studied Medicare dialysis patients from 2002 to 2004 ($n = 393,967$); 100,086 deaths were identified. They demonstrated an association between mortality and low hematocrit in dialysis patients, which arguably reflected, at least in part, the presence of comorbidities. However, they also demonstrated an association of greater mortality with higher hemoglobin concentrations that is not reported by other observational studies.

Besarab *et al.* argued recently that it is “too simplistic to solely attribute the outcomes achieved in RCTs to ‘target hemoglobin’ or to ‘epoetin toxicity.’”¹⁹ This is because in both RCTs and observational studies there is the possibility of significant confounding from malnutrition or inflammatory processes and other patient comorbidities. Indeed, recent analyses support a more complex relationship that may involve an important role for inflammation manifest clinically as “erythropoietin hyporesponsiveness.”^{20–23} However, although inflammation is likely a powerful confounder in observational studies, the fundamental power of RCTs is that patient comorbidities are balanced out between the intervention and the control groups by virtue of randomization. Thus, the effect of the intervention can be evaluated independent of the confounding effect of patient factors.

Several studies representing observational analyses or *post hoc* or planned secondary analyses of RCTs examine the relationship between erythropoietin exposure and adverse risk in treating anemia in the CKD population.^{24–27} Zhang *et al.* were one of the first groups to report on the relationship between erythropoietin dose and outcome among dialysis patients.²⁴ They retrospectively studied a cohort of 94,569 prevalent hemodialysis patients from 2000 and 2001. A Cox proportional hazard regression analysis with adjustment for baseline variables was performed to examine the dose–response relationship between erythropoietin and all-cause mortality. For every hematocrit strata studied, patients administered higher doses of erythropoietin had significantly lower hematocrit values and greater mortality rates. With the cubic spline function, a significant nonlinear relationship between increased erythropoietin dose and mortality was found regardless of hematocrit value ($P < 0.0001$), with the steepest increase in relative risk for death found after the 75th dose percentile.

Bradbury *et al.*, more recently, explored a Fresenius North America cohort.²⁵ Prevalent hemodialysis patients were randomly selected from July 2000 to June 2002 and required to have a 9-mo baseline period. These selection criteria generated a sample of 22,955 patients. The relationship among erythropoietin dose, hemoglobin concentration, and baseline patient characteristics was evaluated using Cox proportional hazard models and time-dependent models fitted with time-varying log erythropoietin and hemoglobin concentrations. As well, the relationship with lagged log erythropoietin and hemoglobin concentration was explored. In the unadjusted model, the authors observed an increased mortality risk with an increasing erythropoietin dose (HR of 1.31 per log unit increase, 95% CI of 1.26 to 1.36). However, adjustment for baseline patient characteristics resulted in attenuation in the mortality risk es-

timate (HR of 1.21, 95% CI of 1.15 to 1.28). In the lagged time-dependent analyses, the risk estimates further attenuated with estimates that ranged from HR of 0.93 (95% CI of 0.92 to 0.95) to HR of 1.01 (95% CI of 0.99 to 1.03) for the 1- and 2-mo lagged models, respectively. These data suggest that, although there did seem to be some association between erythropoietin exposure and mortality, the mortality risk estimates were highly sensitive to the analytic method used.

Streja *et al.* explored the relationship among erythropoietin exposure, iron deficiency, and thrombocytosis in a large previously characterized DaVita cohort.²⁶ The database comprised 40,787 maintenance hemodialysis patients during the period from July to December 2001 and examined predictors of subsequent 3-yr survival. A higher hemoglobin concentration >13 g/dl was associated with greater mortality (case-mix-adjusted death relative risk of 1.21, 95% CI of 1.02 to 1.44, $P = 0.03$) in the presence of thrombocytosis (platelet count $>300,000/\mu\text{l}$) but not in the absence of thrombocytosis. There was an association with erythropoietin exposure; however, this was at very high erythropoietin doses of $>20,000$ units/wk and mortality over 3 yrs (relative risk of death 1.59, 95% CI 1.54 to 1.65, $P < 0.001$).

Observational studies evaluating the potential for erythropoietin toxicity have uniformly not considered predialysis erythropoietin exposure. There is also a considerable amount of missing data that has required imputation. As well, the heretofore cited observational analyses share one important limitation, namely, the estimation of the causal effect of exposure to erythropoietin on mortality may be biased because of confounding; covariates associated with treatment, such as patient factors, also may be associated with potential response. This is likely to be true even if adjustment is made and time-varying models are constructed because of the problem of time-varying exposure. To adjust for covariates that are time-dependent confounders, some argue that marginal structural models (MSMs) are necessary (for example, Bradbury and co-workers²¹).

Marginal structural models are popular because the coefficients may be directly interpretable causally and provide unbiased marginal estimates even in the presence of time-dependent confounding.^{27–30} However, MSMs do not completely eliminate the problem of confounding because unmeasured confounders remain a significant problem. Furthermore, although such MSMs are designed to assess causality in longitudinal datasets, these models are limited to the study of nondynamic treatment regimes (regimes that are “fixed in advance”), for example, treatment with a fixed dose of a drug throughout pregnancy regardless of intervening events before delivery.²⁶ Dynamic regimes, such as the treatment of CKD anemia, require structural nested models or G-estimation where varying doses of erythropoietin are given in the context of changing hemoglobin levels over time.

Alternative methods to circumvent the problem of confounding also have been tried. In a recently published study by Zhang *et al.*,³¹ inverse probability weighting was used to adjust for time-dependent confounding by indication. This is essentially a propensity-score-based method that is described in de-

tail elsewhere.³² These investigators used a United States Renal Data System dataset comprising patients ≥ 65 yrs of age that had started hemodialysis in 2003 and survived 3 mo on dialysis. The sample comprised 18,454 patients who met these criteria. The association between cumulative average erythropoietin dosage and survival was then explored over the subsequent 9-mo period. Unlike the prior observational analyses (including their own earlier paper) using propensity scoring, Zhang *et al.* reported that survival was similar throughout the entire follow-up period for the three hypothetical erythropoietin treatment regimens selected: low dosage 15,000 units/wk, medium dosage 30,000 units/wk, and high dosage 45,000 units/wk. Compared with a cumulative average dosage of 20,000 to 30,000 units/wk, the estimated HR (95% CI) was 0.90 (0.52 to 1.54) for $< 10,000$ units/wk, 0.84 (0.67 to 1.05) for 10,000 to $< 20,000$ units/wk, 0.96 (0.76 to 1.21) for 20,000 to $< 40,000$ units/wk, and 0.91 (0.67 to 1.22) for $> 40,000$ units/wk. The lack of an association between erythropoietin exposure and adverse outcome may reflect the lack of adequate adjustment for time-dependent confounding by indication.

Collectively, one sees a synthesis of the observational data points to the fundamental problem of confounding as a potential source of error in arriving at a precise estimate of risk. Until optimal statistical techniques are used to examine the complex relationship among erythropoietin exposure, hemoglobin level, patient comorbidities, and outcome, forming an opinion regarding the toxicity of erythropoietin is probably ill-advised.

To further examine the relationship among erythropoietin dose, patient comorbidities, and outcome, Szczech *et al.* performed a secondary analysis of the CHOIR study³³ where I was a co-author. The details on the methodology and the rationale behind the statistical technique used in the paper are published elsewhere.^{6,33,34} The landmark analysis was applied to subjects enrolled in the CHOIR study. However, to be included in the analysis, subjects needed to survive to the landmark, receive erythropoietin, and have at least one postbaseline hemoglobin measurement. Of the 1,432 subjects randomized in CHOIR, 25 (1.75%) subjects were excluded because they had not received a dose of epoetin or did not have a hemoglobin measurement after baseline. In the 4-mo landmark analysis, 1,260 subjects were included. In the 9-mo landmark analysis, 1,057 subjects comprised the analysis population. The relationship between erythropoietin dose and two outcome measures was explored: the primary composite endpoint of death, CHF hospitalization, stroke, and MI as well as death alone. The conclusions were similar using both outcomes. In the 4-mo landmark analysis, more subjects in the high-hemoglobin *versus* low-hemoglobin arm were unable to achieve target hemoglobin concentrations (37.5% *versus* 4.7%, $P < 0.001$) and required high-dose erythropoietin (35.4% *versus* 9.6%, $P < 0.001$). In unadjusted analyses, both inability to achieve target hemoglobin concentrations and requirement of high-dose erythropoietin were significantly associated with an increased hazard of the primary endpoint ($P = 0.05$ and 0.003 , respectively). In adjusted models, the increased hazard associated with randomization to the high-hemoglobin arm from the primary trial was no

longer significant ($P = 0.49$), whereas high-dose erythropoietin was associated with a 57% increased hazard of the primary endpoint (HR 1.57, CI 1.04 to 2.36, $P = 0.03$). Hence, this study was compatible with the results of the other observational studies in suggesting that erythropoietin dose rather than the hemoglobin level is associated with adverse outcome. However, the results were “hypothesis testing” and did not prove causality. Indeed, although the landmark methodology reduces biases that might have resulted from differential dropout of patients and intervening events between the time of randomization and the inception time for the outcome measurement, it does not entirely exclude them. Patients were excluded if they did not receive erythropoietin or if the hemoglobin level was not measured. In intention-to-treat analyses, as in the original CHOIR publication,⁶ all patients are included in the analysis regardless of whether they actually received the intervention. The landmark methodology tested the effect of dose on outcomes, whereas the underlying trial tested the effect of target hemoglobin. In other words, the underlying intervention was different. As well, the impact of later hemoglobin levels and doses received after the landmark time cannot be examined using this methodology. Lastly, the choice of the landmark point—at 4 and 9 mo—was chosen in a *post hoc* fashion.

Collectively, those invoking the erythropoietin-toxicity hypothesis suggest that erythropoietin hyporesponsiveness precipitated by a state of inflammation plays an important, albeit undefined, role in priming patients for erythropoietin toxicity.^{19,35,36} Data from observational analyses lend credence to this hypothesis.^{20–23} In preliminary studies, we suggest that there may be a role for heightened cytokine activity³⁷ and activation of endothelial cells,³⁸ whereas others suggest a potential role for thrombocytosis and iron deficiency.^{26,39}

The question is whether targeting a higher hemoglobin concentration (≈ 13 g/dl) in CKD patients is associated with increased risk. It is undeniable that the preponderance of evidence from RCTs points to the answer as, yes. However, it does seem biologically implausible that targeting a normal hemoglobin concentration should be associated with adverse consequences. Several observational studies, coupled with a recent study exploring the relationship of altitude (and hence hemoglobin concentration) with mortality,⁴⁰ support the idea that a higher hemoglobin *per se* is not causally related to adverse outcome. Some but not all recent studies implicate erythropoietin toxicity in the context of erythropoietin hyporesponsiveness. Although these alternative hypotheses are tantalizing, the evidence for a causal relationship between erythropoietin toxicity and adverse outcome is rather preliminary and fraught with the problem of confounding by indication.

Keeping an open mind is absolutely essential; as Jacob Bronowski⁴¹ has aptly put it: “There is no absolute knowledge. And those who claim it, whether they are scientists or dogmatists, open the door to tragedy. All information is imperfect. We have to treat it with humility.” However, evidence currently convincingly supports the contention that targeting a higher hemoglobin concentration in CKD patients is associated with increased risk of

cardiovascular complications and mortality. At least until the TREAT study is published.³

DISCLOSURES

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Multiple studies document a consistent relationship between lower hemoglobin concentration and poorer outcomes in managing the anemia of chronic kidney disease (CKD) or anemia in dialysis populations.^{1–3} Additionally, many studies demonstrate an association between anemia treatment and reduction of left ventricular mass index.^{4,5} Because altered left ventricular geometry is a predictor of poor outcomes among dialysis patients,⁶ these studies suggest that treatment of anemia may translate into an improvement in cardiovascular events and mortality.

However, large randomized trials of anemia correction in kidney disease using erythropoiesis-stimulating agents (ESAs) also report unexpected results.^{7–9} In particular, the Normal Hematocrit Trial and the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) studies demonstrate a trend or a statistically significant increase in the risk of cardiovascular events or death. These data have been interpreted as inconsistent with observational data, with *post hoc* suggestions that residual confounding and bias in observational datasets led to these discrepant findings.

Herein, we argue that the important messages for anemia management in kidney disease are actually consistent across the spectrum of all available randomized clinical trials, including analyses of large observational datasets. These relationships are robust across multiple studies and across a large range of achieved hemoglobin concentrations. The two important messages are: First, the higher the achieved hemoglobin concentration, the better the patient outcome, at least up to a hemoglobin concentration of 13 g/dl, and second, the higher the ESA dose, the worse the patient outcome.

The interpretation of randomized trial data and observational datasets only diverges when we introduce a third element, namely, the prescription of ESAs to a target hemoglobin concentration irrespective of patient characteristics. The con-

cept of treating to a target hemoglobin concentration derives from the landmark Phase 1 to 2 single-center erythropoietin trials conducted over 20 yrs ago, which first established efficacy for erythropoietin in treatment of the anemia of kidney disease.¹⁰ These trials demonstrate a monotonic relationship among the erythropoietin dose, the trajectory of hemoglobin increase, and the achieved hemoglobin. The observed monotonic relationship suggests that erythropoietin deficiency is a dominant driver of anemia in kidney disease and, therefore, erythropoietin could be dose-titrated similar to other endocrine deficiency diseases. The corollary assumption is that the anemia of kidney disease is a relatively simple disease state. Thus, when erythropoietin received a Food and Drug Administration (FDA) label on the basis of the available data from these highly selected trial participants, it was reasonable to rely solely on a targeted hemoglobin concentration that would enhance quality of life and provide freedom from blood transfusions. Since then, the accepted anemia management paradigm is to treat to a target range. Indeed the FDA label, virtually all clinical practice guidelines published worldwide, and current clinical performance measures in the United States all still recommend dosing to a target hemoglobin concentration range.

However, evidence that biologic response to erythropoietin is more varied in clinical practice appears as early as 1989, when results of the Phase 3 multicenter trial in hemodialysis patients were published.¹¹ The dose of erythropoietin required for maintaining the hematocrit between 32% and 38% in this study varied over 20-fold among trial subjects. In the succeeding decades, the range of ESA dosages used in clinical practice expanded, and there is now a more than 100-fold difference in ESA doses utilized across the spectrum of clinical practice in dialysis care. These findings strongly suggest that the ESA dose–response relationship is much more complex than originally conceived, with the corollary that anemia in individuals with kidney disease is far more complex and multifaceted than assumed initially.

All drugs have a therapeutic index, the ratio between the dose required for efficacy *versus* toxic effects, and biologically potent agents such as ESAs, which have pleiotropic effects, are particularly likely to have potential toxicity. Yet the current paradigm in the treatment of anemia is still solely to treat to a target range of hemoglobin concentrations irrespective of dose. With a specific range in mind, the health care provider titrates the ESAs, as needed, in attempting to reach that target. Since the only measure of success is achieving the target, there is little or no concern for potential toxicity or establishing a therapeutic index. Despite the continuing “monotonic paradigm” for ESA dosing, factors related to intercurrent illness and comorbidities that are outside of the physician’s control and are often not measurable in clinical practice frequently prevent reaching the target hemoglobin concentration.

Although speculative, we hypothesize that the toxic effect of high-dose ESAs may be most concerning in the subset of ESA-resistant patients, who paradoxically receive the highest ESA doses to achieve hemoglobin concentration targets. It is now

well recognized that the high prevalence of increased inflammation and oxidative stress in patients with mild, moderate, or dialysis-dependent CKD, along with iron deficiency, are the major identifiable factors associated with ESA resistance.^{12,13} Among other operative mechanisms by which oxidative stress and inflammation influence anemia, increased oxidation of erythrocyte membrane phospholipids shortens erythrocyte lifespan, whereas inflammation induces expression of hepcidin, thereby blocking egress and mobilization of storage iron into hematopoietic precursor cells. Furthermore, increased inflammation and oxidative stress are closely associated with high rates of cardiovascular complications in CKD and dialysis patients.

It is also now clear that biologically active erythropoietin receptors exist in a variety of tissues outside the hematopoietic system, whose activation may lead to toxicity. Engagement of erythropoietin receptors in the vasculature can lead to upregulation of endothelin-1 production, increase the release of vasoconstrictive prostanoids, including thromboxane and prostaglandin F₂-alpha, and upregulate gene expression of multiple angiotensin-II-responsive genes, including TGF β , platelet-derived growth factor, and epithelial growth factor.^{14–16} Erythropoietin increases growth of vascular smooth muscle and endothelial cells in a dose-dependent manner *in vitro*, which may contribute to vascular disease progression *in vivo*.^{17,18} Several studies implicate ESAs in activating thrombogenic pathways by increasing tissue factor expression, plasma thrombomodulin levels, and platelet count and activation through transactivation of thrombopoietin receptors.^{19,20} In one study, erythropoietin increases plasma levels of asymmetric dimethylarginine, a competitive substrate for nitric oxide synthase. Higher plasma asymmetric dimethylarginine levels are associated with adverse cardiovascular outcomes in CKD. Although there are multiple mechanisms for high-dose ESAs to augment the already high cardiovascular risk in patients with kidney disease, careful studies focusing on dose-dependent toxicology are not available.

The hypothesis that use of high-dose ESAs have toxicity and are not just a surrogate for morbidity and mortality associated with erythropoietin resistance is consistent with a recent *post hoc* analysis of the CHOIR study.²¹ Here, landmark analyses assess the relationship among achieved hemoglobin concentration (≥ 13.1 g/dl in high-hemoglobin or ≥ 11.1 g/dl in low-hemoglobin arms), high-dose erythropoietin ($\geq 20,000$ units/wk), and the primary composite endpoint (death, myocardial infarction, congestive heart failure, or stroke). In the 4-mo landmark analysis, far more subjects in the high-hemoglobin *versus* low-hemoglobin arm were unable to achieve the target hemoglobin concentration (37.5% *versus* 4.7%) and required high-dose erythropoietin (35.1% *versus* 9.6%). In adjusted models, high-dose erythropoietin associates with a 57% increased hazard of the primary endpoint (hazard ratio of 1.57, confidence interval of 1.04 to 2.36), whereas the risk associated with randomization to the high-hemoglobin arm is NS ($P =$

0.49), suggesting possible mediating effects of a higher target concentration by dose. Similar results are observed in the 9-mo landmark analysis. This analysis supports the hypothesis that high-dose erythropoietin is more than a marker of inflammation and may partially explain increased risk with high-hemoglobin targets.

If the hypothesis that high-dose ESAs have direct cardiovascular toxicity is substantiated, then the problem is not “treating to a higher hemoglobin,” which is biologically beneficial, but instead “using high-dose ESAs in an effort to achieve a higher hemoglobin,” where adverse effects of ESAs outweigh benefits from a higher hemoglobin concentration. Although this may seem a subtle distinction, the clinical consequences are profound.

Where would this lead us? First, prospective studies should confirm these relationships and determine the safest dosing algorithms. Perhaps a fixed-dose strategy of ESA use should be compared with titration algorithms in a randomized trial. The biologic mechanism underlying potential toxic effects of ESAs has to be more thoroughly defined, including examination of dose-dependent, nonhematopoietic effects in subjects with different levels of ESA resistance. On an individual patient level, those who can reach higher hemoglobin levels without requiring high-dose ESAs should be allowed to enjoy this benefit. Patients feel better at higher hemoglobin concentrations, and exercise tolerance and quality of life are better. The key subgroup of ESA-resistant patients who do not respond to moderate doses of ESA will need completely different treatment goals and strategies. Novel strategies targeting a reduction in ESA resistance, thereby allowing attainment of higher hemoglobin concentrations without resorting to high-dose ESAs, should be prioritized for this group. But for those who remain ESA-resistant, the answer might be to adopt the concept of “permissive anemia,” similar to permissive hypercapnia in the management of respiratory failure. This would require changing the paradigm of benchmarks under which we have operated for nearly 20 yrs.

DISCLOSURES

None.

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