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What Is So Bad About a Hemoglobin Level of 12 to 13 g/dL for Chronic Kidney Disease Patients Anyway?

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What Is So Bad About a Hemoglobin Level of 12 to 13 g/dL for Chronic Kidney Disease Patients Anyway?

Anatole Besarab, Stanley Frinak, and Jerry Yee

Randomized controlled trials (RCTs) clearly indicate a possible cardiovascular morbidity and mortality risk when deliberately targeting a normal hemoglobin (Hb) concentration of 13 to 15 g/dL. By contrast, observational studies point to greater hospitalization and mortality at Hb levels <11 g/dL. There are no direct data to help us determine where, within this broad range, the optimal Hb lies. In RCTs and observational studies, significant confounding from the interrelationships of anemia and epoetin resistance occurs in patients with a serious illness. Patients with comorbidities such as malnutrition and inflammatory processes are more resistant to epoetin and, invariably, require greater cumulative epoetin doses. The effect of a higher erythropoiesis-stimulating agent (ESA) dose on increasing mortality has been noted repeatedly in post hoc analyses of RCTs. It is therefore too simplistic to solely attribute the outcomes achieved in RCTs to "target Hb." We discuss various mechanisms for potential harm at higher Hb levels as opposed to those that may be obtained from higher epoetin doses. For the individual patient, the therapeutic decision should center on what Hb is most appropriate at a "safe" ESA dose. Consequently, an Hb of 12 to 13 g/dL may be totally appropriate in some patient populations.

Index Words: Anemia; Chronic kidney disease; Erythropoiesis-stimulating agent; Iron deficiency

"It was the best of times. It was the worst of times." So begins the opening of Dickens' *A Tale of Two Cities*. Whether those times were good or bad depended on the observer's perspective. The same might be said about maintenance of hemoglobin (Hb) levels in the 12 to 13 g/dL range in chronic kidney disease (CKD) patients at varying stages of disease. Randomized controlled trials (RCTs) indicate that there is a strong trend for increased risk of death or adverse composite outcomes with erythropoiesis-stimulating agent (ESA) treatment in kidney disease to Hb targets higher than those currently recommended. However, the RCT results stand in stark contrast to findings from large observational, population-based studies that continue to show the association of low and not "high" hemoglobin with adverse outcomes. As a result, polarized positions have been taken. Some believe that any hemoglobin >13 g/dL is harmful and that this level must be avoided. This position has also been taken by the United States Food and Drug Administration who simply will not permit any study examining anemia management to exceed an Hb of 13 g/dL while advocating for a target Hb range of 10 to 12 g/dL. Others contend that there is no additional risk as long as the dose producing the Hb of 13 or greater is "low." The purpose of this review was to summarize the conflicting results and provide a balanced perspective regarding the target Hb range.

Target Hemoglobin: The History

When epoetin alfa was first approved for use in 1989, the recommended treatment was for partial correction of anemia to an Hb of 9 to 10 g/dL, with the primary objective of avoiding transfusion,[1] despite the fact that initial clinical trials targeted a higher Hb range

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with mean maintenance Hb values >11 g/dL.[2,3] Because of a variety of external pressures, chiefly reimbursement, the main question was not the target Hb, but rather the quantity of ESA, its frequency,[4,5] and its route[6] that provided the highest mean Hb among dialysis patients. Two years after the introduction of epoetin in the United States, Hb levels averaged less than 10 g/dL and the average dose less than 8,500 U/wk.[7] Six years later when the first National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) anemia guidelines were released,[8] the mean Hb had increased to nearly 11 g/dL (with a proportional increase in epoetin alfa dose to nearly 16,500 U/wk) and, most recently, to a mean of approximately 12 g/dL with an average weekly epoetin dose of 22,000 U. Although the Hb target was widened by the updated NKF KDOQI anemia guidelines to 11 to 13 g/dL,[9] there was coincident adoption by the Centers for Medicare and Medicaid Services (CMS) of the clinical performance measure (CPM) quality indicator of achieving an Hb of 11 g/dL or greater in 80% of patients.[10]

As shown in Figure 1, the target Hb adopted in Canada[11] and worldwide tended to parallel those of the United States. However, European Best Practices Guidelines[12] had the same lower but no upper limit on Hb. The Australian-New Zealand (Caring for Australians with Renal Impairment) guidelines for its upper limit depended on the presence or absence of cardiovascular disease.[13] In the United Kingdom, the lower limit was less at 10 g/dL. Until the pure red cell aplasia scare of the early 2000,[14,15] the most common route of administration outside the United States was subcutaneous because of the increased cost-effectiveness of this route.[16,17]

These guidelines for higher Hb evolved as evidence accumulated, and a better understanding was reached regarding the benefits of correcting Hb. These were chiefly in quality of life[3] and persistent observational findings of lower mortality and hospitalization at higher as compared with lower achieved Hb values.[18]

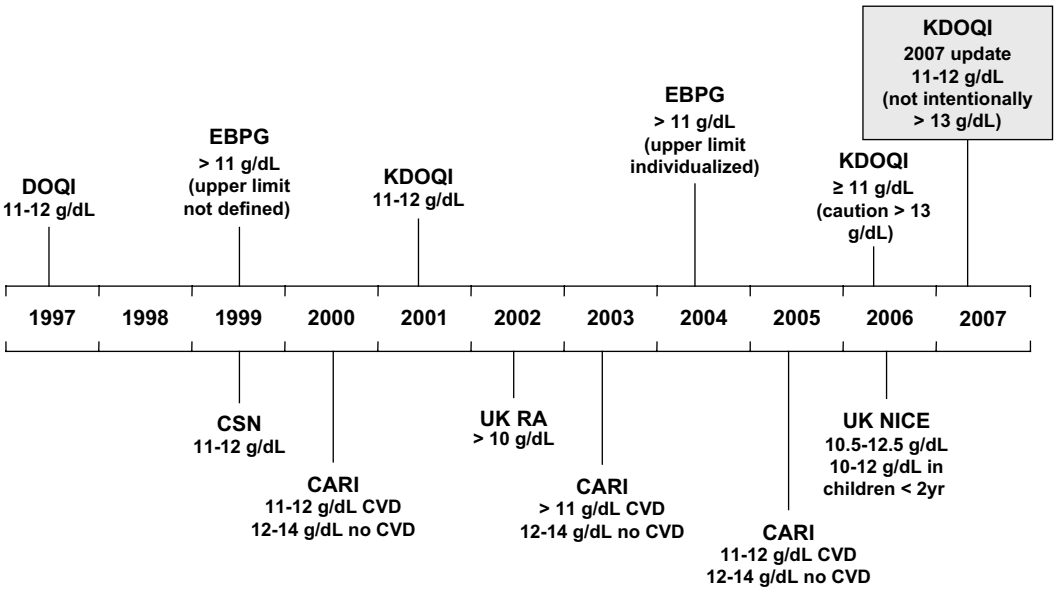

Figure 1. Anemia management guidelines and target Hb. Since 1997, a number of clinical guidelines for the management of anemia have been developed. Guidelines have evolved as evidence has accumulated. Improved understanding of the benefits of correcting Hb in specific patient groups has also been attained (eg, patients with comorbid conditions such as CVD and diabetes). CVD, cardiovascular disease; DOQI, dialysis outcomes quality initiative; EBPG, European Best Practice Guidelines; CSN, Canadian Society of Nephrology, CARI, Caring for Australians with Renal Impairment: KDOQI, Kidney Disease Outcomes Quality Initiative; UK NICE, United Kingdom National Institute for Clinical Excellence.[9-13]

However, the interest in normalizing Hb to 13 g/dL or greater was initially dampened by the first large randomized controlled trial (RCT) of Hb normalization in hemodialysis patients (Normal Hematocrit Cardiac Trial [NHCT]) that found a trend toward increased mortality risk with treatment to an Hct target of 42%.[19] Subsequently, 4 randomized controlled trials[19-22] in ESRD dialysis-dependent patients and eight trials in non–dialysis-dependent CKD patients compared treatment with 2 different Hb targets,[23-30] one target being 12 to 14 g/dL and the other target several grams lower. Most of the studies found improved quality of life at the higher Hb targets. However, none showed a significant improvement in mortality or cardiovascular endpoints. Rather, it has been the inverse; targeting higher hemoglobin may produce harm.

Informative Clinical Trials

Figure 2 depicts the major clinical trials that have been conducted over the past 2 decades. The earliest trials (dotted box) compared a level of anemia (usually <9 g/dL) with a moderate level of correction (usually 10.5-12.5 g/dL). However, the most common mean Hb target was between 11 and 12 g/dL (solid box); RCTs since 1998 have mostly compared 2 different levels of correction, a lower range of 9 to 11 (dashed lines) with a higher range >12 and usually >13 g/dL.

Early meta-analyses of RCTs of kidney disease patients treated with ESAs that suggested that Hb targets >13 g/dL compared with <12 g/dL were associated with higher risk of mortality[31] were dominated by the NHCT. This study of hemodialysis patients had a sample size of over 620 patients in each of the 2 groups[19] and did not show a statistically significant increase in death rate when the study was stopped for safety reasons (increased morbidity from vascular access thrombosis in the higher 13-15 g/dL group), but it did not show benefit either. In addition, in the Canadian study on cardiac

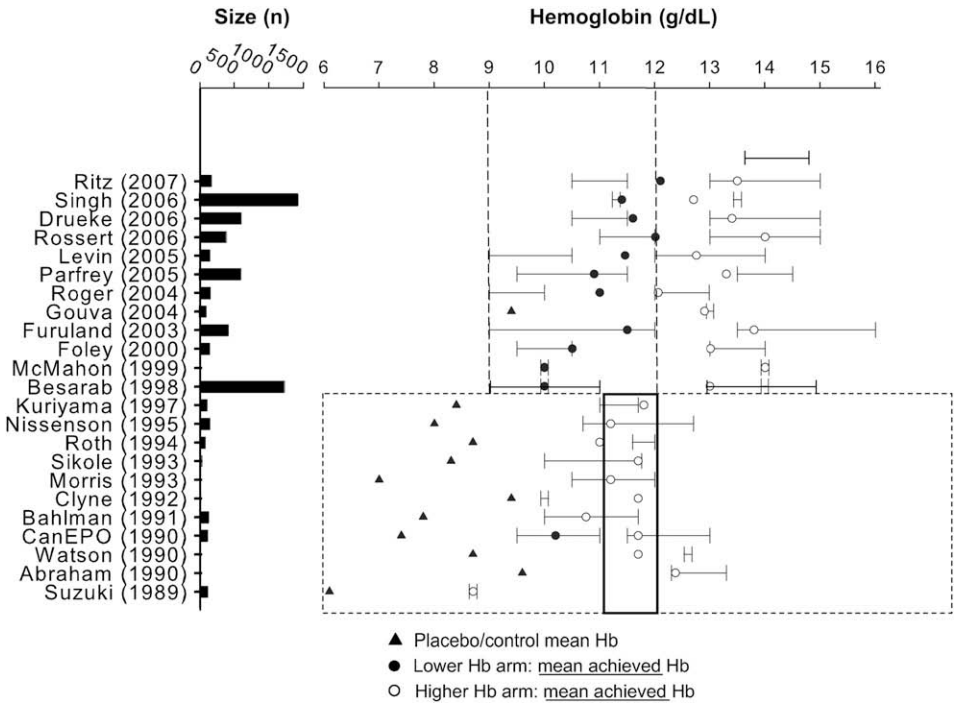

Figure 2. Clinical trials on anemia management. The dashed box includes trials before 1998, which were generally small (ie, N < 100) and compared an Hb level <9 g/dL to an Hb level of 11 to 12 g/dL, depicted by the solid vertical box (incomplete correction of anemia). After 1998, larger trials compared effects of moderate levels of correction (range between dashed vertical lines) and more complete anemia correction (Hb >12 g/dL). (Adapted from NKF-K/DOQI Clinical Practice Guidelines for Anemia in Chronic Kidney Disease.[9])

remodeling in incident patients, increased stroke was found in the higher target (13.5-14.5 g/dL) compared with the lower target (9.5-11.5 g/dL). All other studies in the meta-analysis were by themselves grossly underpowered to evaluate mortality or morbidity risk.

However, the potential "danger" of higher Hb levels was rekindled with the November 2006 publication of 2 large studies, the Cardiovascular risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) trial[23] and the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial,[24] in nondialysis CKD patients. Both studies found trends toward increased mortality risk and for other adverse outcomes as well.

In the CHOIR study by Singh et al,[24] a composite endpoint assessing multiple events was used. These included death, hospitalization, hospitalization for congestive heart failure, cerebrovascular accident, and residual renal decline assessed as the need to initiate dialysis. Before the study was scheduled for completion, the "DSMB recommended…study be terminated…even though neither the efficacy or futility boundaries had been crossed, because the conditional power of benefit for the high-hemoglobin group by the scheduled end of study was less than 5%." When the final data were collated and analyzed, the composite endpoint was significantly higher in the group randomized to the higher Hb target of 13.3 g/dL compared with the group randomized to an Hb of 11.3 g/dL even though the Hb target in the higher Hb group fell short by 0.5 g/dL. None of the individual components of the composite including mortality risk in these nondialysis kidney patients was significantly different in the higher Hb target group.

In the CREATE study,[23] a composite of 8 cardiovascular events was used to assess hazard. This study was completed as designed, with data collected for 2 more years after final patient enrollment. A trend toward harm was also noted in CREATE in the group targeted to attain/maintain an Hb of 13.5 g/dL by early epoetin beta therapy, but the hazard rate again did not reach significance because the event rate was only half that expected. The event rate used to calculate the sample size for CREATE was based on data collected almost a decade earlier in British Columbia, Canada, and did not factor in the improvements in care of CKD nondialysis patients that had accrued in the previous decade. Thus, it, like many other previous studies, was underpowered to evaluate mortality risk or a composite endpoint measuring death, cardiovascular events, or the need for renal replacement therapy.

Despite the fact that both studies individually failed to show definitive proof of harm because of unforeseen methodologic flaws, the addition of these large studies allowed the performance of a more powerful meta-analysis of the available studies totaling ~5,000 patients. Such an analysis was reported by Phrommintikul et al[32] in February 2007. Indeed, the 3 largest RCTs published, the CHOIR (n = 1,433),[24] NHCT (n = 1,232),[19] and CREATE (n = 600)[23] trials, all found trends toward increased mortality risk. The results of these 3 studies are consistent: an increase in all-cause mortality of about 20% at higher Hb targets is seen in each of the 3 studies but in none of them individually. Only when all the studies are combined does a statistically significant effect emerge. Although all 3 studies have design or execution flaws, like all RCTs, and these have recently been elucidated for the CHOIR and CREATE trials,[33] the consistent thread of evidence in the direction of increased risk of death must be taken seriously.[34]

Vascular access thrombosis also increases at higher Hb levels,[19,20] and blood pressure control often worsens. With this in mind and with similar adverse findings reported from studies of ESA treatment in cancer,[35] 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,[36] in effect placing a "black box" warning and narrowing the "recommended" Hb target range to 10 to 12 g/dL.

Reflections on Observational Data

In contrast to the RCT, observational studies have shown a totally different effect of Hb levels on mortality. As stated previously, Hb

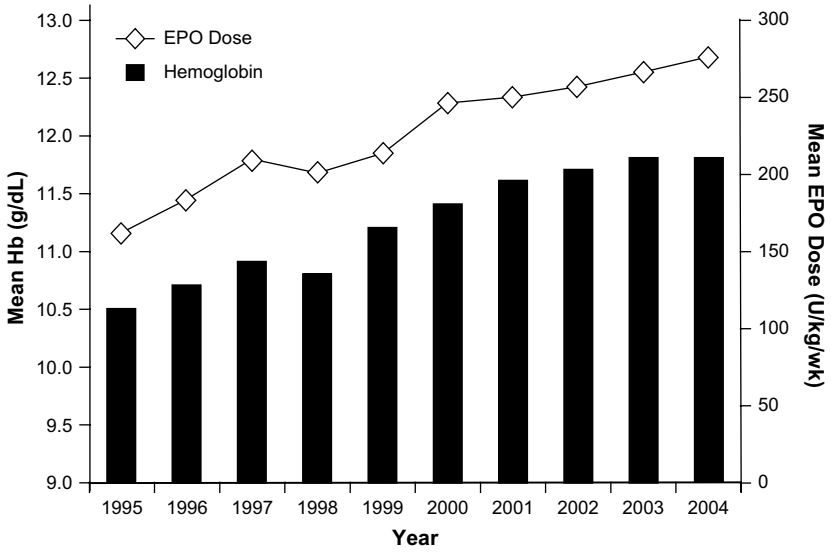

Figure 3. Increasing erythropoietin alfa doses produce higher Hb levels. The relationship between administered erythropoietin dose and Hb is shown from 1995 to 2004. The mean achieved Hb of approximately 7,500 subjects, from annually derived Centers for Medicare and Medicaid Services data of the Clinical Performance Measures anemia project, is shown from a 3-month interval of data collection from months October through December (Adapted from Besarab A, Frankenfield D, Johnson C, et al: Trends in anemia management in HD patients: Observations from the Centers for Medicare & Medicaid (CMS) Clinical Performance Measures (CPM) Project. Presented at the American Society of Nephrology, Nov 2007).

targets and the Hb achieved have evolved since epoetin alfa was introduced in 1989.

As shown by the data from the CMS-CPM project in Figure 3, Hb levels and epoetin dose increased in parallel[37] in the decade from 1995 to 2004. In this decade, NKF-DOQI guidelines put pressure on providers to achieve an Hb >11 g/dL in 80% of patients receiving maintenance hemodialysis. The ratio of the change in epoetin alfa that produced a change in Hb, as noted by Figure 3, was 100 U/kg/wk epoetin alfa per +1.0 g/dL Hb change.

Large databases have been analyzed to assess the consequences of raising the Hb level during this period. Data from the USRDS have repeatedly noted that higher Hb levels correlate with lower hospitalization rates, fewer cardiovascular events, and better survival in dialysis patients.[38,39] Utilization of epoetin is higher among for-profit dialysis facilities, which frequently achieve higher mean Hb levels than not-for-profit ones[40] and achieve higher Hb levels in their patients. In the for-profit, large dialysis organization, DaVita, Regidor et al[41] noted a lower mortality rate among hemodialysis patients who maintained hemoglobin levels between 12 and 13 g/dL as opposed to lower Hb values. After adjustments for demographic and laboratory information in this study, a time-averaged hemoglobin level of 12 to 12.9 g/dL was associated with approximately half the mortality rate compared with a hemoglobin level of 10 to 10.4 g/dL. No adverse effect of Hb up to a value of 13 g/dL was noted in this study, increasing only when Hb exceeded 13.5 g/dL. In a similar vein, Szczech et al[42] recently showed by post hoc analysis of the CHOIR trial that patients who achieved their target Hb had better outcomes than those who did not. Among subjects who achieved their randomized target, there was no discernible increased risk associated with the higher Hb goal.

In assessing the results from these observational analyses, one must be aware of serious confounding from the interrelationship of anemia and epoetin resistance with illness in patients with CKD. Patients with comorbidities such as malnutrition and inflammatory processes are more resistant to epoetin and invariably require greater cumulative epoetin

dose to achieve the target hemoglobin level. The sickest patients rarely achieve target hemoglobin levels and are the more likely to die than healthier patients who achieve target hemoglobin levels easily and persistently and require much less epoetin in doing so.[39,43] Therefore, the time-averaged hemoglobin level may reflect both the targeted hemoglobin level and the health of the patient.

Reconciliation of Discordant Results

It is important to realize that the health of the patient, the Hb targeted, the Hb level achieved, and the dose of ESA are all interrelated. It is not possible from the current literature to determine the relative importance of increased Hb itself as the primary cause of the increased risk of death with targeting higher Hb levels. In fact, a post hoc analysis of the Normal Hematocrit Cardiac Trial, the largest randomized trial on Hb target conducted to date among hemodialysis patients, found that the achieved Hct level to normal was not associated with an increased risk for death. As shown in Figure 4, in both the high Hct target group and the lower target groups, there was a trend toward an increased risk for death with a lower achieved Hct. In the more anemic group, the hazard decreased smoothly with hematocrit reaching a nadir at an Hct of 36 to 39 (Hb of 12-13 g/dL), whereas in the higher hematocrit group, there was a sharp discontinuity. Those who achieved and maintained an Hct/Hb of 39%/~13 g/dL or greater did as well as those who spontaneously drifted beyond the prespecified Hct limits of 27% to 33%. In this study, a post hoc analysis of the higher Hct/Hb target group showed that mortality was 60% lower in those who responded well to epoetin compared with those who did not.[44]

This effect of the achieved dose on mortality has repeatedly been found in post hoc analyses of the randomized clinical trials. The Food and Drug Administration also showed the influence of achieved dose in both the NHCT and CHOIR as shown in Figure 5.[45]

Whatever the stated target hemoglobin of a study that uses active therapy in both study arms, the mean target Hb value will be harder to achieve in the higher of the 2 arms. This results from the presence of subjects in the randomized population who are resistant to the administered ESA, in whom it takes longer to achieve the given goal (if at all). In clinical practice, when hemoglobin targets are 12 g/dL or less, these targets can be achieved more frequently than if the targets are set higher.

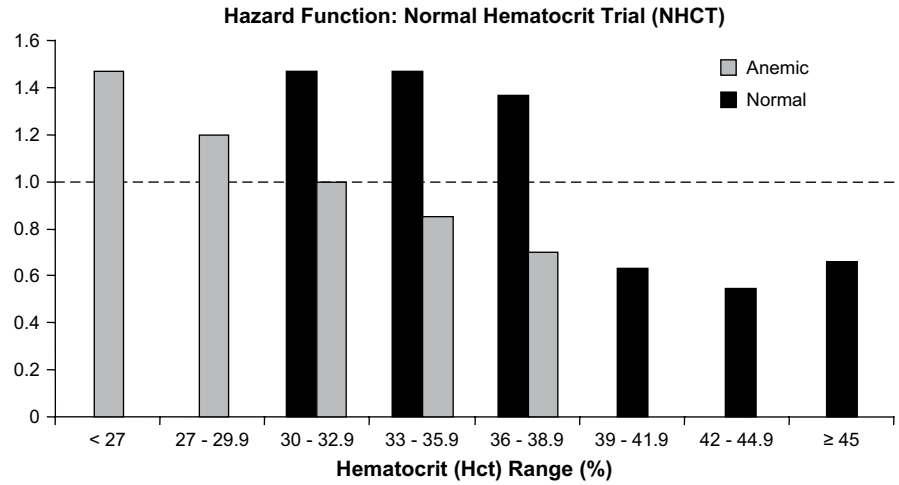

Figure 4. Hazard function (death or acute myocardial infarction [AMI]) derived from the Normal Hematocrit Trial.[19] There is a monotonic decrease in hazard ratio in the anemic group as achieved Hct increases from <27% to an Hct of 39%, despite an Hct goal of 27% to 33%. By contrast, in the normal Hct group, hazard function is increased in subjects who do not attain their Hct target, despite increasing amounts of erythropoietin. In those who attain the target Hct >39%, the hazard is equal to or lower than in the highest 2 Hct subgroups of the anemic Hc' group. The obvious question is what characteristics and therapy differentiates those with Hct levels of 30% to 39% in the 2 groups to produce this increase in mortality.

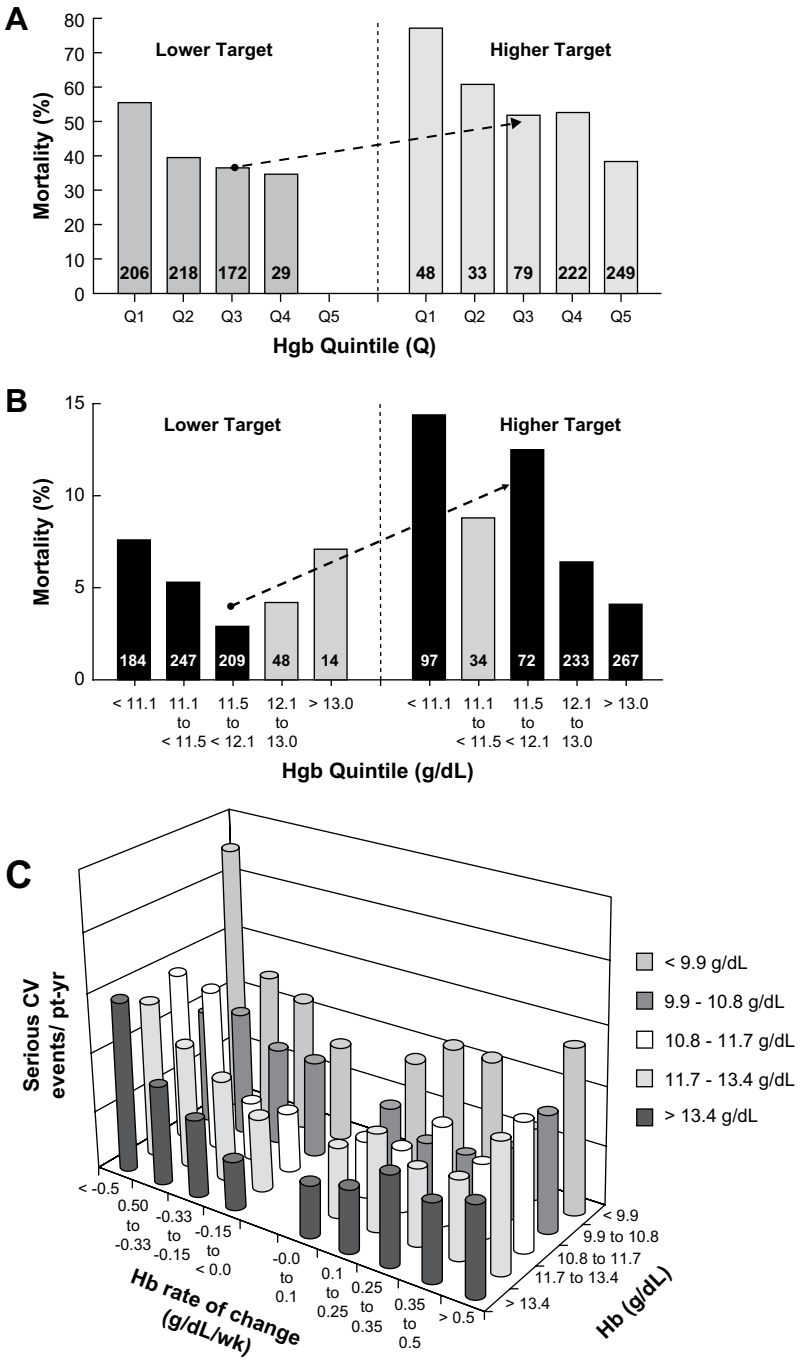

Figure 5. (A) Food and Drug Administration (FDA) analysis of the Normal Hematocrit Trial (NHCT) and the CHOIR trial. Mortality at any point in study is analyzed as a function of the attained Hb averaged over the entire duration of the trial in each individual. Quintiles were determined over both lower and higher Hb target cohorts. Quintiles (Q) in both cohorts correspond to the following ranges of Hb (g/dL): Q1, Hb $<$10.2; Q2, 10.2 $<$ Hb $<$ 10.6; Q3, 10.6 $<$ Hb $<$ 11.6; Q4, 11.6 $<$ Hb $<$ 12.8; and Q5, Hb $>$12.8. The total number of subjects in each quintile is 251 to 254 in NHCT and 281 in the CHOIR trial. Numbers in the bars represent the number of subjects. FDA analysis of data collected through July 5, 1997, from the NHCT is shown in the left panel, where the last quintile is not shown because there was a small number of subjects (n = 3). Note that the mortality decreases with increasing Hb in both cohorts. Within any quintile, mortality is greater in the higher Hb target group. (B) FDA exploratory analysis of the Correction of Hemoglobin and Outcomes in Renal Insufficiency trial (CHOIR). A negative association between mean Hb and mortality was determined. Note that the quintile ranges differ from those in Normal Hematocrit Trial (NHCT) (panel A), with Hb generally greater in CHOIR than NCHT. A U-shaped mortality curve is seen in the low Hb target group, but the mortality curve is descending in the higher target group. (C)FDA "dynamic" analysis of relations between serious cardiovascular (CV) events, prevailing Hb, and the rate of change of the preceding Hb in the Normal Hematocrit Trial. These analyses show the importance of prevailing Hb and the rate of change of Hb (decreasing or increasing) on CV event rates.

In practice, the clinicians can also compromise on the dose being used and accept a lower Hb (either voluntarily or when proscribed by the third-party payer such as CMS) for a given patient. If an Hb of 10.5 g/dL is all that can be achieved at a dose of 450 U/kg/wk, a dose frequently cited as being indicative of resistance achieved (Fig 6),[46] one does not have to continuously increase the ESA when the dose response beyond that is flat (diminishing returns). This is not true in an RCT in which dose is progressively "per protocol" increased irrespective of response.

In Eschbach's original report,[46] there was considerable interpatient variability in the epoetin alfa dose required to maintain the Hb/Hct level in the target range. In this phase 3 trial, the median dose required to maintain an Hct level of 35% ± 3% in hemodialysis patients was 75 U/kg intravenously 3 times per week. A relatively broad range of required doses from 12.5 to 525 U/kg intravenous/dose was observed; however, 17% of patients required doses ≥150 U/kg 3 times per week. A decade and a half later, data from the CMS-CPM for 2005 showed virtually the same results from a national sample of >7,500 individuals; 15% of all patients still meet this definition of resistance by ESA dose. This minority of patients receives more than half of all of the epoetin administered.[3]

Finally, both the Food and Drug Administration[45] and others have found a very complex relationship between cardiovascular events/mortality and the Hb achieved and the rate of change in Hb before the events. In general, a U-shaped curve exists with a nadir for each Hb stratum for no change in Hb, with risk increasing as prevailing Hb decreases from 13 to 10 g/dL. Of course, ESA dose increases inversely with prevalent Hb and, possibly, even more so as Hb falls abruptly. Because a putative adverse effect of epoetin dose has been posited by Cotter et al,[47] it is naive to solely ascribe enhanced risk to "target" Hb in RCTs.

Potential Mechanisms of Harm

When examined carefully, the risk shown in the higher Hb target groups of the clinical trials has been related to thrombotic events, manifested as vascular occlusion, myocardial events, cerebrovascular accidents, or deep vein thrombosis. A key unknown is the mechanism for such a process. Fishbane and Besarab[48] reviewed possible mechanisms recently. One mechanism that focused on was thrombosis.

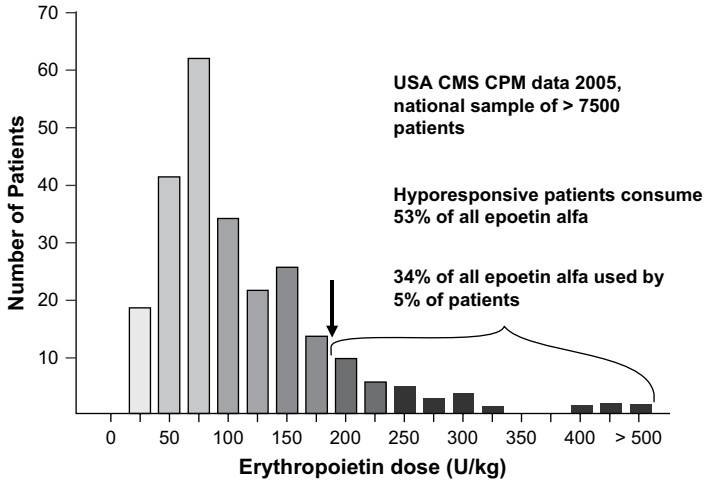

Figure 6. Interpatient variability of epoetin alfa dosing. In this phase 3 trial by Eschbach and colleagues, the median dose required to maintain a Hct level of 35%±3% in hemodialysis patients was 75 U/kg 3 times per week intravenously. A relatively broad range of required doses from 12.5 - 525 U/kg bodyweight was recorded, and 17% of patients required doses >150 U/kg 3 times per week. Data from the CPM project shows that this distribution persists more than a decade later. "Hyporesponsive" or epoetin alfa-resistant patients use the majority of the agent.[46] (Reprinted with permission from Eschbach JW, Abdulhadi MH, Browne JK, et al: Recombinant human erythropoietin in anemic patients with end-stage renal disease. Result of a phase III multicenter clinical trial. Ann Intern Med 111:992–1000, 1989). The American College of Physicians is not responsible for the accuracy of the translation.

Effects of epoetin on platelets have been documented for over 2 decades. Epoetin transiently quantitatively increases circulating platelets and improves platelet function, effects associated with a return of the bleeding time toward normal.[49] However, a restoration toward "normal" Hb will increase viscosity and wall shear stress on the vascular endothelium, which is already abnormal in advanced CKD. Changes in shear stress on endothelial cells are associated with the release of microparticles into the circulation. Circulating microparticles are associated with a variety of disorders characterized by coagulapathy (heparin-induced thrombocytopenia, thrombotic thrombocytopenic purpura, paroxysmal nocturnal hemoglobinuria, sickle cell disease) as well as vascular and cardiovascular diseases.[50] Shed membrane microparticles with procoagulant potential are produced by human atherosclerotic plaques.[51] The relationship between viscosity, shear rate, and Hb level is not linear. Shear-induced apoptosis at a higher Hb level could be a critical determinant of plaque thrombogenicity after plaque rupture. Thus, increased shear stress might produce endothelial injury or alter endothelial function increasing risk for thrombosis in some susceptible patients and the risk related to elevated Hb could be accentuated by hemodialysis-induced hemoconcentration.[52] This may partially explain evidence from previous studies of increased mortality risk among hemodialysis patients with larger interdialytic weight gains.[53]

Another contributing mechanism might be abnormal fibrin-clotting properties. In ESRD, fibrin clots derived from patient plasma are less permeable, compactible, and susceptible to fibrinolysis than control clots. Scanning electron microscopy reveals a greater fibrin fiber density in clots from patients with CKD than in clots of patients without CKD.[54] Interestingly, these fibrin structure characteristics in ESRD patients are associated primarily with the inflammatory plasma milieu rather than with the level of azotemia. It is the inflamed patient who appears most at risk for thrombosis during ESA therapy. In a follow-up study of 39 patients with such measurements of clot characteristics, mortality was significantly associated with reduced clot permeability, prolonged lysis time, faster fibrin protofibril formation, thicker fibers, and increased fibrin clot mass, suggesting that these unfavorable altered clot properties may contribute to increased CV mortality.

Recently, Dahl et al[55] have proposed a prominent role for iron deficiency in promoting thrombosis in patients on ESA therapy, the so-called iron hypothesis. An analysis of a large cohort of patients indeed confirmed that higher platelet counts were associated with lower iron stores and with higher prescribed epoetin dose.[56] The argument is as follows. Dependence on ESA to raise Hb produces functional or absolute iron deficiency. Thrombocytosis is common in iron deficiency and resolves after iron repletion. ESAs have long been known to increase platelet number,[49] perhaps not only through an effect on megakaryoctes[57] but also through this iron-deficiency pathway.[58,59]

Such relative thrombocytosis increases the risk of thrombovascular events. Concurrent provision of iron should minimize ESA-driven thrombocytosis. Data from the Dialysis Patients Response to Intravenous (IV) Iron With Elevated Ferritin (DRIVE) trial[60] in hemodialysis patients in which there was iron administration even at ferritin levels >500 ng/mL verifies this hypothesis. Platelet counts in intravenous iron-treated patients decreased by 29,000/μL, but were unchanged in patients not treated with intravenous iron.[55] Unfortunately, the major anemia trials that used ESAs reported no detailed platelet data. Lastly, relative iron deficiency has been proposed to enhance the thromboembolic rates of ESA-treated oncology patients.[61]

Another mechanism for altered coagulation may arise from altered platelet responses during ESA therapy independent of iron deficiency. Before the introduction of ESA, deep vein thrombosis/pulmonary embolism was exceedingly rare in anemic hemodialysis patients.[62] A decade after ESAs were introduced, such events began to occur with regularity[63] with an age-adjusted risk ratio of >2.[64] It is now known that recombinant erythropoietin increases platelet aggregability through a tyrosine phosphorylation–signaling pathway[65] and in fact has been used to increase

coagulation in patients with alcoholic liver disease.[66] In addition, epoetin has the following independent effects on vessels via increased endothelin-1[67]: impaired endothelium-dependent nitric oxide–induced vasorelaxation,[68] perturbed calcium homeostasis in vascular smooth muscle cells,[69] and enhanced platelet serotonin release.[70] These nonerythropoietic effects of ESA on platelet reactivity, both directly and indirectly from iron deficiency, mandate that iron sufficiency is maintained at the lowest possible ESA dose to achieve the desired Hb range in a given patient. "Harm" from "nonhemoglobin" effects of ESAs may mask a benefit from higher Hb levels.

Currently, little work has been performed to differentiate the various ESAs from each other in terms of these nonerythropoietic effects. Some of the vascular effects of epoetin develop only at supraphysiologic concentrations achieved with intravenous doses. A consistent change to the subcutaneous route or use of agents that do not need high peak levels but depend on prolonged residence time at lower concentrations might reduce these risks of thrombosis. However, no comparative data are available.

Personal Position

We currently do not know the characteristics of patients at risk for harm other than they are "ill" from inflammatory processes, use iron poorly because of reticuloendothelial blockade, and require much higher doses of epoetin than easily responsive patients in whom the issue is one of exceeding Hb >12 at relatively low doses. In the former, there is, in our opinion, definite harm from progressively increasing epoetin doses into the flat part of the dose response curve where no improvement in erythropoiesis can occur. Such patients with kidney disease and atherosclerosis can have multiple areas of unstable atherosclerotic plaque and/or ulcerations that are vulnerable to increased viscosity associated sheer stress and platelet hyperaggregability even when Hb is only 11 g/dL or less. In such patients, it is unwise to attempt to attain the CPM goal of 11 g/dL. ESRD patients may be particularly sensitive to volumetrically induced Hct changes and/or viscosity/shear stresses that occur over hours and not weeks as occurs in normals.

In contrast, we have experienced difficulty in maintaining Hb stability in highly ESA-sensitive patients. This group exhibits upward variability after minimal increases in ESA dose. Patients who drift above 13 g/dL receiving <3,000 U/wk frequently will drift below 11 g/dL over 3 months with only a 20% to 30% reduction in a weekly dose. It is extremely difficult to maintain such patients in the "desired" range, and they do note the difference in vitality at lower as compared with higher Hb levels.

Conclusion

There is nothing wrong with an Hb of 12 to 13 in the right patient treated with a low ESA dose. By contrast, there is everything wrong when administering a high ESA dose just to attain an Hb of 11 g/dL. The target Hb and ESA dose must be individualized.

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