The new FDA label for erythropoietin treatment: How does it affect hemoglobin target?

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The erythropoietin analogs have been an important advance for the treatment of the anemia of kidney disease, resulting in reduced need for blood transfusion and improved quality of life. Recent studies, however, have indicated risks associated with targeting higher levels of hemoglobin (Hb). As a result, in March 2007, the US Food and Drug Administration (FDA) substantially changed prescribing information for these drugs to alert clinicians to these risks. In this review, we consider the recent literature, the change in FDA warnings, and new National Kidney Foundation Anemia Guidelines. Suggestions for new Hb targets during erythropoiesis-stimulating agent treatment are presented.

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The availability of erythropoietin analogs (the current preferred terminology is erythropoiesis-stimulating agents or ESAs) has been one of the most important medical advances in the treatment of patients with kidney disease. Before the availability of ESAs, severe anemia was common in uremic individuals,[1] resulting in disabling fatigue, substantially diminished quality of life, and the need for frequent blood transfusions. Partial correction of anemia with ESA treatment results in reduced need for blood transfusions, and significantly improved functional health and well being.[2,3]

The accumulated experience with the use of ESAs in end-stage renal disease, non-dialysis chronic kidney disease (CKD), and other anemic states spans over two decades. As the use of these agents has expanded and matured, interest in optimization of therapy has intensified. In recent years, much of this interest has centered on the extent of hemoglobin (Hb) correction, in particular, the magnitude of Hb correction required to achieve the greatest improvement in outcomes and quality of life.

After Food and Drug Administration (FDA) approval of epoetin alfa in 1989, the goal for treatment of anemia in kidney disease was generally to increase Hb to greater than 10 g/dl. This was consistent with FDA labeling, which specified a target range of 10–12 g/dl. It should be noted that this labeling was based on safety concerns by the FDA, as the registration trials with epoetin alfa targeted a hematocrit of 32–38% and achieved an average hematocrit of 36.5%. The lower limit treatment goal of 10 g/dl remained the usual practice until publication of the National Kidney Foundation's Dialysis Outcomes Quality Initiative (NKF-KDOQI) Anemia Guidelines in 1997, which recommended an Hb target range of 11–12 g/dl.[4] Between 1991 and 2005, the mean Hb of US hemodialysis patients increased from 9.7 to 12 g/dl.[5] In 2006, the KDOQI guidelines were updated, recommending maintaining Hb > 11 g/dl while noting a lack of evidence for ESA treatment to target Hb > 13 g/dl.[6] These statements were misinterpreted by many as a recommendation to increase the target range to 11–13 g/dl. Similarly, in 2005–2006, the Centers for Medicare and Medicaid Services modified its reimbursement policies for ESAs, requiring a dose reduction only when Hb was greater than 13 g/dl in order to avoid a post-payment audit of claims. These events appeared to set

the stage for a new era of higher targets for Hb during ESA therapy.

A major tipping point in the history of ESA therapy took place in November 2006. The pivotal event was the publication of two key studies, correction of hemoglobin and outcomes in renal insufficiency (CHOIR) and cardio-vascular risk reduction by early anemia treatment with epoetin beta (CREATE), both of which indicated a trend toward an increased risk of death with targeting of higher Hb concentrations[7,8] (these studies are often incorrectly referred to as the first studies to demonstrate possible harm). In fact, Besarab *et al.* in a study in hemodialysis reported very similar findings 8 years earlier (see below). This was followed, in early 2007, by reports from two studies conducted in patients with cancer that indicated safety concerns associated with ESA treatment in this population (http://www.healthsentinel. com/news.php?id=1740&title=Studies+Show+Anemia+Drugs+ May+Harm+Cancer+Patients&event=news_print_list_item). Subsequently, on 9 March 2007, the US FDA drastically changed labeling for ESAs. The agency inserted a boxed warning, stating that providers should avoid Hb targets greater than 12 g/dl because of increased risk of death and serious cardiac events. In addition, the labeling noted that ESAs should be used to increase Hb only to the lowest level necessary to avoid transfusion. These recommendations created considerable confusion and concern within the provider and patient communities regarding the available data and the most effective and safe Hb levels for individual patients.

The purpose of this paper is to review the recent literature and consider the application of current scientific knowledge to clinical guidelines for target Hb. We will focus on the two major outcomes most clearly associated with ESA therapy, quality of life and mortality risk.

PROBLEMS WITH CLINICAL GUIDELINES FOR TARGET Hb

The US Agency for Healthcare Research and Quality defines a treatment practice guideline as 'a guideline that recommends procedures or practices that are intended to relieve physical or mental illness or injury.[9]' Such guidelines are not intended to define standards of care, but rather to be tools to assist clinicians and patients make the best decisions in individual cases. The need for practice guidelines derives from a number of factors. First, medical knowledge often progresses rapidly, exceeding the ability of busy practicing clinicians to keep pace. Second, the sheer number of new medical publications is daunting, and no clinician can hope to read even a small percentage of relevant, published studies. Third, the process of synthesizing medical literature while weighing the relative interaction of benefit and risk requires a broad knowledge of the literature, the relevant medical science and related health systems. It is highly sensible to use multidisciplinary panels of experts, with broad knowledge of a specific medical problem, to review the literature and use it to design specific guideline statements for clinical practice.

The process of development of practice guidelines for binary treatment decisions is simpler than that for decisions involving continuous variables such as target Hb. It should be clear that no treatment decision is fully binary. However, many, such as whether or not to use warfarin to prevent stroke in atrial fibrillation or aspirin after myocardial infarction or angiotensin converting enzyme inhibitors in diabetic kidney disease are to a great extent simple, dichotomous decisions. For treatment decisions of this type, it is relatively straightforward to use the literature to develop practice guidelines. Published studies generally indicate with reasonable clarity whether the treatment works and is safe.

For a continuous variable like target Hb, translating the literature into practice guidelines can be very difficult. As an example of why this is true, we will consider the CHOIR study. In this trial, patients were randomized to Hb targets of 11.3 and 13.5 g/dl. The primary results were that for the group randomized to the higher Hb target there was increased risk as measured by a composite end point. Taken in isolation, the study indicates that an 11.3 g/dl Hb target is preferred to a 13.5 g/dl target.[7] However, in no way do the results demonstrate that an 11.3 g/dl Hb target would be ideal or optimal. As no Hb targets between 11.3 and 13.5 g/dl were studied, the possibility of increased risk at interim Hb values cannot be excluded. In fact, as Hb levels below 11.3 g/dl were not studied, the possibility remains, however unlikely, that even the Hb target of 11.3 g/dl might be associated with greater risk than some lower Hb target. In isolation, the CHOIR study does not point to any specific optimal Hb target; it simply indicates that the target should be some value less than 13.5 g/dl. Therefore, the process of guideline development must attempt to interpolate the results of different Hb target studies, comparing the various Hb targets and results to yield relative boundaries of benefit and risk. Unfortunately, there is great overlap in target Hb levels and substantial heterogeneity among the published studies. As a result, it is nearly impossible to specify with any degree of certainty what a truly optimal target Hb range should be.

Another difficulty with Hb target studies is that both the benefit (quality of life improvement) and risk (increased mortality rate) are affected by the Hb target selected. In contrast, another familiar treatment decision that is a continuous variable is target cholesterol level. The benefit for cholesterol lowering is closely related to the achieved cholesterol concentration, whereas the risks (liver and muscle toxicity) are more idiosyncratic. Therefore, the cholesterol target is more 'one-tailed' than Hb target, studies are easier to design and power and results are simpler to translate into practice guidelines. Hb target is characteristically 'two-tailed,' both risk and benefit are influenced by the target chosen. Therefore, the most useful information on target Hb requires a study in which a very large group of patients would be randomized to multiple different Hb targets, such as 9,10,11,12, and 13 g/dl. The level at which quality of life was maximized, whereas risk was minimized would be the optimal target. The study would require such a large sample size that it

would likely never occur. Without such a study, and given the limitations of the current literature, there is insufficient evidence for any strong Hb target recommendation.

With these cautions in mind, we shall next explore the major treatment effects that inform the scientific balancing of benefit and risk for Hb target; the tradeoff of quality of life benefit against safety risk. Other factors such as cost will not be considered in this article. The cost of ESAs and reimbursement systems change over time and are by their nature artificial constructs. There is great need for formal cost benefit analyses, but this is not the purpose of this article.

THE RELATIONSHIP OF QUALITY OF LIFE TO TARGET Hb

The World Health Organization (WHO) defines health as 'A state of complete physical, mental, and social well-being not merely the absence of disease'.[10] WHO has developed instruments to be used worldwide to assess health-related quality of life (HRQOL) and assist clinicians and patients in medical practice to improve the doctor–patient relationship, to assess the effectiveness and relative merits of different treatments, to be used in health service evaluation, in research, and in policy-making.[10] In its landmark publication, *Crossing the Quality Chasm*, the Institute of Medicine recommended six attributes of healthcare that were needed to optimize outcomes, including patient-centeredness – 'providing care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions'.[11] Patient-reported outcomes such as HRQOL are often devalued by scientists and clinicians, and labeled as 'subjective' or 'non-rigorous'. It is now clear, however, that HRQOL can be measured rigorously, and available instruments can be evaluated for reliability and validity.[12] Hahn *et al.*[12] recently have developed a conceptual model for linking biological and physiological variables to HRQOL. Such variables, one example of which is the Hb level, impact symptom status, which in turn impacts functional status. Functional status has a major influence on general health perceptions and the latter affect HRQOL. Considering this chain of causality, it is remarkable that the change in any physiological variable, such as Hb, can be shown to significantly correlate with a change in HRQOL, but this is the case.

Quality of life of dialysis patients was dismal before the availability of recombinant human erythropoietin. In the phase III trials, quality of life was measured before and after correction of anemia, from an hematocrit level typical at that time of 22.3–35% at 12 weeks and 34% at 40 weeks.[13] 'A statistically significant improvement was established between baseline and second follow-up on most objective and subjective quality of life parameters…'[14] In a follow-up phase IV study following FDA approval of recombinant human erythropoietin, the quality of life impact of anemia treatment in the general dialysis population was evaluated using the SF-36, a validated tool to assess HRQOL.[15] In addition, aspects of QOL were compared for the dialysis patients before and after anemia correction and individuals in the general population as well as non-renal patients with clinical depression or congestive heart failure. At baseline, before receiving recombinant human erythropoietin, dialysis patients had SF-36 scores consistently below those of the general population as well as patients with congestive heart failure or depression. Following partial correction of anemia (hematocrit at baseline 25.5%, and at follow-up 29.9%), statistically significant improvements were seen in multiple domains of the SF-36 including physical functioning, vitality, social functioning, mental health, mental component summary score, and percent reporting improvement in health status over 1 year. The improvement in vitality seen was not only statistically significant but was similar to the difference in this domain reported between patients with chronic back pain and the general population, and over half the improvement in vitality observed at a 6-month follow-up of patients who receive a new heart valve.

Although a recent meta-analysis of evidence for Hb targets for the anemia of CKD concluded that '…it was not possible to perform a pooled analysis [of quality of life studies] given the wide variability of the assessment of these outcomes and uncertainties regarding the validity of the instruments used…', this should be viewed as a statement about statistical methodology, not necessarily the evidence regarding Hb level and quality of life.[16] Jones *et al.*,[17] in fact, did perform a meta-analysis looking at quality of life impact of anemia treatment with recombinant human erythropoietin. Sixteen published studies were utilized for the analysis, five of which were randomized, controlled trials. Baseline Hb was quite low, around 8 g/dl, and quality of life at baseline, assessed using one of several valid instruments, was low. Average Hb increased 3.4 g/dl after treatment and significant improvement in quality of life domains occurred including 15–30% improvement from baseline in the physical and fatigue dimensions of the instruments. When sensitivity analysis was performed only including the randomized, controlled trials, the results remained the same.

The real issue is not whether treatment of severe anemia in CKD patients improves quality of life, but at what Hb level is quality of life maximized? There is clearly conflicting data in this regard, but a brief review of the available studies is of some value to put this in perspective. The Canadian Erythropoietin Study Group reported the results of a randomized, double-masked placebo-controlled trial with three groups: placebo (mean Hb 7.4 g/dl, $n = 32$); group 2 (mean Hb 10.2 g/dl, $n = 34$); group 3 (mean Hb 11.7 g/dl, $n = 33$).[18] Marked improvement in QOL was reported in group 2, but no further improvement statistically in group 3. No mention of power analysis is given here and the small numbers of patients studied make interpretation difficult. On the other hand, the normal hemoglobin cardiac trial (randomized controlled trial (RCT)),[19] as well as studies from Sweden (RCT)[20] and Spain,[21] demonstrated quality of life improvements in dialysis patients when Hb was targeted at normal, compared to 10–11 g/dl. In CKD patients not yet

on dialysis, targeting an Hb of 13.5 g/dl in the CHOIR did not result in quality of life benefits compared to targeting an Hb of 11.3 g/dl,[7] but this finding is in marked contrast to other recent studies. In the CREATE trial, CKD patients randomized to a target Hb of 13–15 g/dl, compared to those randomized to 10.5–11.5 g/dl, had significant improvements in general health and physical function on the SF-36.[8] Ritz et al.[22] reported the results of the Anemia Correction in Diabetes (ACORD) study, involving CKD patients with diabetes. Those randomized to a target Hb of 13–15 g/dl, compared to 10.5–11.5 g/dl, had significantly better quality of life as determined by SF-36. It should be noted that in the latter two studies there were no excessive adverse events in the high Hb groups, suggesting that on balance, benefit (quality of life) outweighed potential harm. Finally, the use of the SF-36 in these and many other studies is important, as it has been shown to be highly valid and reliable.[12]

THE RELATIONSHIP OF SAFETY TO TARGET Hb

The benefit of ESA treatment for improving quality of life must be balanced against the potential risk for adverse outcomes with higher Hb targets. We will consider safety primarily with respect to risk for mortality, as this is a highly objective and, obviously, negatively valued outcome. Ultimately, the tradeoff of quality of life benefit against risk for mortality is the fulcrum that balances Hb target decisions for individual patients.

Risk for mortality with various Hb targets has been the subject of a number of observational studies. The approach is usually to analyze a large administrative or clinical database of end-stage renal disease patients, with collection of data on Hb (either at a point in time or averaged over time), outcomes, and available covariates. All observational studies have found that there is an association between lower Hb level and increased risk for death. From the initial work of Lowrie and Lew, a series of studies by Collins and co-workers, and through the recent analysis of Regidor et al., the findings are highly consistent.[23–29] In the latter study, Regidor et al.[26] evaluated 58 058 subjects undergoing treatment at Da Vita Inc. dialysis facilities. The risk for mortality increased progressively at Hb concentrations below 12 g/dl, and the best survival was seen when the Hb was 12–13 g/dl (interestingly, mortality showed a trend to increase at Hb above 13 g/dl).[26]

Observational research is an important scientific process that identifies trends and relationships. The results of these studies can never, however, define causality in relationships. This form of research is most valuable when used to generate hypotheses that can be tested by RCTs. The subsequent performance of RCTs may confirm the findings of observational studies, or conversely may fail to confirm or may even find the opposite of the observational findings. A striking recent example of the latter is the literature on the value of estrogen to reduce cardiovascular risk for postmenopausal women. Observational studies consistently found estrogen to be beneficial, and a generation of women was offered

treatment as a result. When RCTs were subsequently performed, most notably the Women's Health Initiative, estrogen was found not only not to be protective, but to actually increase risk.[30] This is a dramatic example of how observational research can mislead as to causality. As one considers the literature on Hb target, it is becoming apparent that for the outcome of mortality risk there are parallels to the literature on estrogen treatment. The observational studies indicate benefit, whereas RCTs have generally found no benefit or even harm with higher Hb targets.

The insurmountable problem with observational research on Hb level and mortality risk is the fact that sicker patients, whether patients with kidney failure or with other chronic diseases, or among individuals admitted to hospitals, tend to have lower Hb levels.[31–33] Indeed, Hb concentration tends to decrease as illness develops and progresses.[34] As a result, there is an inherent intertwining between Hb level and health status. Even the most sophisticated statistical methods cannot separate the two, leaving completely unclear the question of which causes which, between anemia and the associated illness and health outcome. As RCTs have increasingly failed to confirm the observational finding of a relationship between lower Hb and increased mortality risk, the meaning of results from the observational studies has become less clear.

None of the published RCTs have found a significant reduction in mortality risk with ESA treatment to higher Hb targets. There have been eight published studies with reasonable rigor in non-dialysis CKD[7,8,35–40] and four in hemodialysis.[19,20,41,42] If all of these trials are included, then the relative risk for mortality for the higher Hb target groups is not significantly different than for the lower target groups; in non-dialysis CKD relative risk is 1.01 (95% confidence interval (CI) 0.63–1.61) and in hemodialysis it is 1.12 (95% CI 0.91–1.37).[43] However, two of the studies, with more than 500 non-dialysis patients, were stopped prematurely because of institution of a European contraindication to subcutaneous administration of epoetin alfa.[39,40] Importantly, the early termination resulted in short follow-up, only 7–8 months in one study.[39] In both trials, the follow-up was probably inadequate to allow for any meaningful conclusions on mortality risk. Without inclusion of these two studies, the trend toward increased mortality risk is more apparent. A recent meta-analysis reported by Phrommintikul et al. was rigorous in terms of studies included for analysis.[44] A total of nine studies were included, four in hemodialysis, five in non-dialysis CKD. The primary finding was a 17% increased risk of death in patients with kidney disease treated with ESAs to target higher Hbs ($P = 0.03$). In addition, there were significant increases in risk for higher blood pressure and vascular access thrombosis in the higher target groups.[44]

The most troubling finding from the literature is that the three largest trials have all found substantial trends toward increased mortality risk. The largest of these, the CHOIR study, was a study of 1432 patients with non-dialysis CKD. Patients were randomized to Hb targets of 11.3 and 13.5 g/dl.

Risk for death was found to be increased in the higher Hb target group with a hazard ratio of 1.48 and a *P*-value of 0.07. The CHOIR study found a statistically significant increased risk of a composite of death, stroke, myocardial infarction, and hospitalization for congestive heart failure with the higher Hb target.[7]

The second largest published RCT is the Normal Hematocrit Cardiac Trial (NHCT), a study of 1233 hemodialysis patients. Subjects were randomized to hematocrit targets of 30 or 42%. The primary finding was a 1.21 risk ratio for death in the higher hematocrit group. The 95% CI was 0.9–1.9, indicating that statistical significance was nearly achieved.[19] Although the study was of hemodialysis patients with cardiac disease, the entry criteria were loose enough to apply to a substantial proportion of the current hemodialysis population.

The third largest trial, the CREATE study, randomized 603 subjects with non-dialysis CKD to ESA treatment to target Hb 13–15 g/dl or delayed ESA treatment to target Hb 10.5–11.5 g/dl. In this study, there was a 48% increased risk for death, with a *P*-value of 0.14. In addition, there was a trend toward increased risk based on the composite end point in the higher Hb target group and a significantly increased risk for reaching dialysis, as well as higher blood pressure.[8]

Taken together, it is remarkable that the three largest studies, involving 3268 subjects, have had a very consistent outcome, a 21–48% increased risk for mortality that in each study nearly reached statistical significance.[7,8,19] Each of these studies, like all RCTs, has design flaws that can be criticized. For example, the CHOIR study had an imbalance in baseline cardiovascular risk characteristics and censoring of subjects after reaching end-stage renal disease; CREATE was underpowered because of better than anticipated cardiovascular outcomes; and the NHCT study population may not have been representative of the general hemodialysis population. Future studies should take particular care to avoid such problems, so that the interpretation of results can be made with greater confidence. However, with the findings as consistent as they are, it would be overly optimistic to discard the remarkably consistent evidence due to flaws in the individual studies. This is particularly true when the results of these studies in kidney disease are considered together with recent findings of increased risk for death with ESA treatment to higher Hb targets in studies in cancer (http://www.healthsentinel.com/news.php?id=1740&title=Studies+Show+Anemia+Drugs+May+Harm+Cancer+Patients&event=news_print_list_item). There is a thread of consistency of findings that simply should not be ignored. The only reasonable conclusion is that treatment of populations of patients with ESAs to higher levels of Hb probably increases the risk of death, and may adversely affect other outcomes as well.

MECHANISM OF POTENTIAL HARM WITH HIGHER Hb TARGETS

The major uncertainty in the current literature is the mechanism for probable harm with achieving or targeting

of higher levels of Hb. Are there possible mechanisms of harm related to achieved level of Hb? From the perspective of physiology, a higher Hb results in increased blood oxygen carriage (beneficial) and increased blood viscosity (harmful).[45] The normal Hb concentration in healthy individuals is one that balances these two factors. One hypothesis for the risk with higher Hb levels in kidney disease is that the balance might be shifted in these patients, with increased importance for viscosity at lower than normal Hb concentrations. Greater viscosity results in increased sheer stress on the vascular endothelium. In patients with pre-existing vascular disease, and areas of vulnerable or ulcerated atherosclerotic plaque, the effect of viscosity may be to predispose to greater risk for thrombotic events. With the great burden of cardiovascular disease among patients with CKD, the optimal Hb level may be lower than for individuals without kidney disease.

A second, but related hypothesis has to do with hemoconcentration. Anemia monitoring in hemodialysis is somewhat unusual; in that, Hb levels are measured before the dialysis session. As a result, Hb levels are diluted, sometimes to a great degree. As predialysis Hb levels are used as a basis for ESA treatment, and as Hb targets tend to be the same in hemodialysis and non-dialysis CKD, true Hb values are actually raised to a higher level in hemodialysis compared to other ESA-treated populations. Furthermore, for patients who are large weight (fluid) gainers between dialysis treatments, a substantial amount of fluid is removed with the hemodialysis treatment. These patients may have extreme hemoconcentration at the end of the dialysis. It is possible that some of the adverse outcomes in hemodialysis patients targeted to higher Hb levels may relate to this phenomenon. In fact, previous studies have indicated increased risk among hemodialysis patients with larger interdialytic weight gains.[46] This, of course, would not apply in non-dialysis CKD, and would not explain the increased risk observed in the CHOIR and CREATE studies.

A third hypothesis may be that the increased blood pressure that may occur with raising Hb could increase cardiovascular risk. Worsening hypertension has been an inconsistent finding in Hb target studies, but a recent meta-analysis found a significant increase in blood pressure in the higher Hb target groups in these studies.[44] As relatively small changes in blood pressure could influence cardiovascular risk, any increase could be clinically important. Attention to blood pressure elevation during ESA treatment has probably been insufficient.

A fourth hypothesis relates not to Hb level achieved, but to targeting higher Hb and how this is carried out. Two of the changes in treatment required to increase Hb include an increase in ESA dose and increased use of iron supplementation. The increased ESA dose raises the possibility that some aspect of ESA drug treatment other than Hb level could potentially increase risk. ESA treatment results in serum erythropoietin concentrations that differ greatly from the normal biology of erythropoietin.[47] In particular, serum kinetics are notably spiky, with rapid surges in concentration

followed by a steady decline, often to very low levels.[47] The effects of the non-biologic stimulation of erythropoietin receptors, particularly in non-erythroid organs including the heart, are unknown. In the heart, erythropoietin has been demonstrated to stimulate and reset growth signals and pathways.[48] The possibility exists, and is worthy of exploration, that there may be detrimental cardiac effects of excessive and cyclical erythropoietin stimulation. A direct effect of ESA treatment on hypertension, mediated by ESA-stimulated effects on vascular smooth muscle cells including increases in cytoplasmic calcium concentration, resistance to the vaso-dilatory effects of nitric oxide, and increases in endothelin production, has also been proposed.[49] In addition, the increase in iron treatment necessary with treatment to higher Hb targets could also contribute to risk. Iron treatment has been associated with increased oxidative vascular injury and progression of atherosclerosis.[50,51] Although iron use was increased in the high hematocrit group of the Normal Hematocrit Cardiac Trial, there was no difference in iron use in the two groups of the CHOIR study.

THE MARCH, 2007 FDA PRESCRIBING INFORMATION CHANGES FOR ESA DRUGS

On 9 March 2007, the US FDA acted to increase the level of warnings for ESA drugs. The addition of a 'black box' warning was intended to heighten clinicians' attention to safety risks with these agents. Among new and intensified warnings were the following:

- 'Use the lowest dose of [Aranesp®/EPOGEN®/PRO-CRIT®] that will gradually increase the hemoglobin concentration to the lowest level sufficient to avoid the need for red blood cell transfusion.'
- 'Erythropoiesis-stimulating agents (ESAs) increased the risk for death and for serious cardiovascular events when administered to target a hemoglobin of greater than 12 g/dl.'
- A recommendation to withhold, not reduce ESA dose, when Hb is greater than 12 g/dl.

REVISED NKF KDOQI ANEMIA GUIDELINES

The May, 2006 NKF KDOQI anemia guidelines contained an evidence-based guideline recommending that Hb be maintained > 11 g/dl in patients with CKD. In addition, there was an opinion-based notation that there was insufficient evidence to recommend routine ESA treatment when Hb is greater than 13 g/dl. In early 2007, the panel reconvened to consider the implications of a series of new studies relevant to Hb target. As a result, the guidelines were amended in a more conservative direction:

2.1.1. In the opinion of the work group, selection of the Hb target and selection of the Hb level at which ESA therapy is initiated in the individual patient should include consideration of potential benefits (including improvement in quality of life and avoidance of

transfusion) and potential harms (including the risk of life-threatening adverse events) (Clinical Practice RECOMMENDATION).

2.1.2. In the opinion of the work group, in dialysis and non-dialysis CKD patients receiving ESA therapy, the selected Hb target should generally be in the range of 11.0–12.0 g/dl (Clinical Practice RECOMMENDATION).

2.1.3. In dialysis and non-dialysis CKD patients receiving ESA therapy, the Hb target should not be above 13.0 g/dl (Clinical Practice GUIDELINE – MODERATELY STRONG EVIDENCE).

THE TARGET Hb RANGE

The FDA prescribing instructions for ESAs and NKF KDOQI anemia guidelines are to an extent in conflict. In this section, we will consider the target Hb range in practice, and how to treat within the somewhat different parameters of FDA and KDOQI. Inevitably, the choice of Hb target range reflects the balancing of quality of life benefit against increased risk for mortality and other complications. Part of the dilemma is that guideline and regulatory recommendations are based on population management, although clinicians must treat individual patients. As recently pointed out by Clough '…the physician is the only effective advocate for the individual patient remaining in the health care system. When what is good for the individual patient is in …conflict with what is good for the population, the physician has no moral choice but to opt for the good of the individual patient…'.[52] As discussed above, it should be clear that the current literature does not, with any degree of certainty, define precisely the exact boundaries of benefit or risk. Quality of life improves as Hb is targeted to greater than 10 g/dl or even higher (a 13–15 g/dl target in the CREATE study yielded substantial quality of life benefits). Increased risk for death probably occurs with Hb targeted to greater than 13 g/dl. However, there has been no demonstration that interim targets not studied in the major trials, such as 12 or 12.5 g/dl might not increase the risk of death. With this uncertainty, choice of Hb target reflects the degree of risk sensitivity. A more conservative viewpoint would be that until safety is more clearly defined that Hb targets should be safely far from the known boundaries of risk. A different viewpoint would be that quality of life is such an important outcome for patients that the Hb range should approach an upper limit of 13 g/dl. The KDOQI recommended target range of 11–12 g/dl is a compromise. It encourages treatment to Hb levels consistent with demonstrated improvement in quality of life, while avoiding targets associated with potential harm. The implied lowering of the upper target reduces the chance of exposure to risk at higher Hb levels but may increase the likelihood of transient Hb levels less than 11 g/dl, with negative impact on the quality of life benefit. The KDOQI recommendation 2.1.1 addresses this issue by promoting individualization of treatment by considering quality of life benefit, variability in ESA responsiveness, and the potential risk of harm in
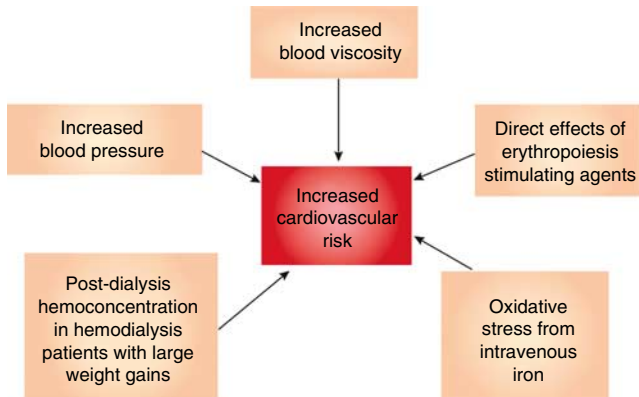
Figure 1 | Potential mechanisms of increased cardiovascular risk with targeting of higher Hb levels with erythropoiesis-stimulating agents.

choosing an Hb target for individual patients. For a patient who feels well with no decrement in quality of life, it would be reasonable to target a lower Hb level. Conversely, for the patient who suffers from fatigue and dyspnea, a higher target may be justified. There may also be room for a greater consideration of patients' health values and preferences in balancing quality of life against mortality risk. The KDOQI recommended range of 11–12 g/dl does not differentiate between hemodialysis, peritoneal dialysis, and non-dialysis CKD. Although patient characteristics, prevalence and severity of anemia, and treatment of anemia differ somewhat among these different settings, the current literature is insufficient to allow different recommendations for each.

The KDOQI generally recommended target range of 11–12 g/dl is in conflict with the FDA-revised prescribing information for these drugs. In particular, this is true for the FDA warning to use ESAs to raise Hb only to a level sufficient to avoid transfusion. Clinicians differ in their views on what Hb level indicates a need for transfusion. But few would routinely transfuse when the Hb is greater than 10 g/dl. This would imply that the FDA language asserts an Hb target of only 10 g/dl. Because this level is far from the range of demonstrated risk, and because it would deny substantial quality of life benefits, we believe that this FDA warning is overly cautious and potentially harmful to patients' well being.

CONCLUSION

Availability of ESAs has improved the lives of millions of patients with kidney disease, cancer, and other anemic states. Treatment results in reduced need for blood transfusion and improved quality of life. However, recent studies have suggested potential risk for increased mortality with treatment to higher Hb targets. The recent change in prescribing information for ESA drugs, by the FDA, was an attempt to protect patient safety in light of these studies. It is possible, however, that the language used was excessively cautious, potentially promoting insufficient anemia treatment with failure to appropriately and compassionately treat fatigue and restore compromised quality of life. During ESA treatment in kidney disease, an Hb target of 11–12 g/dl should permit

significant quality of life improvement while avoiding the risk associated with higher Hb targets (Figure 1).

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