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Perspective: Will We Ever Know the Optimal Hgb Level in ESRD?

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The determination of an optimal hemoglobin (Hgb) level in patients with ESRD requires a thorough assessment of the risks and benefits of the Hgb level itself and the therapy required to achieve it. The 1997 Dialysis Outcomes Quality Initiative anemia treatment guideline[1] recommended against normalizing hematocrit/Hgb levels with recombinant human erythropoietin, and rather, it recommended a target hematocrit level of 33%–36%, which corresponds to a target Hgb level of 11–12 g/dl. Three large randomized, controlled trials (RCTs) of higher versus lower target Hgb levels in patients with CKD in the United States treated with erythropoiesis-stimulating agents (ESAs) were published between 1998 and 2009, and they are summarized in Table 1. Although two of these three studies were conducted in patients with nondialysis CKD, it is not unreasonable to extrapolate their outcomes to the ESKD population. These RCTs have shown that higher target Hgb levels with ESA therapy are associated with increased vascular access thrombosis in patients on hemodialysis, increased major cardiovascular events (MACEs), and increased mortality from preexisting solid tumors. It is intuitive that increased vascular access thrombosis might be due to increased blood viscosity from the high Hgb levels themselves and that the increased mortality from preexisting solid tumors might be due to the trophic effects of ESAs. The increased MACE at higher target Hgb levels is more problematic and could be due to increased blood viscosity, larger ESA doses required to achieve the higher target Hgb levels, or a combination of the two. Retrospective analyses

loses of ESAs had better MACE outcomes than those randomized to lower target Hgb levels who required high doses of ESAs,[6] although these analyses are highly confounded by comorbidities that may lead to both ESA resistance and adverse outcomes. The Food and Drug Administration (FDA), in its 2011 labels for ESAs,[5] implies a target Hgb range of 10–11 g/dl for patients receiving ESA therapy. The FDA cautions that no RCT has identified a target Hgb level, ESA dose, or dosing strategy that does not increase the risks of ESA therapy and recommends that the lowest ESA dose be used to reduce the need for red blood cell transfusions. Improved outcomes after the new FDA ESA labels and dialysis reimbursement changes in 2011 that led to both lower ESA use and lower Hgb targets cannot differentiate between the two variables.[7,8]

It is clear from published RCTs that higher target Hgb levels do not decrease MACEs and actually increase

them. What would be the rationale for targeting Hgb levels with ESAs higher than the 10–11 g/dl that the FDA seems to recommend? One would be transfusion avoidance, which is the only benefit of ESAs that the FDA acknowledges since 2007.[9] Because transfusions carry their own risk of allergic reactions, sensitization for future transplant, infection, and iron overload, it would seem prudent to maintain Hgb levels away from a patient's transfusion threshold, whatever that might be. Another rationale for targeting higher Hgb levels is improved quality of life (QOL). In ESA labels before November 2007, the FDA acknowledged a QOL benefit of therapy on the basis of phase 3 studies that used pre-/post-treatment QOL questionnaires.[10] Because RCTs examining high versus low target Hgb levels failed to showed any consistent QOL benefit at higher Hgb levels, the FDA removed the QOL claim from ESA labels.[9,10] It is notable that the QOL benefit of higher target Hgb levels in the Normal Hematocrit Study[3] was refuted by a subsequent analysis.[11]

The most recent 2012 Kidney Disease Improving Global Outcomes (KDIGO) anemia guidelines[12] recommend initiating ESA therapy when the Hgb falls below 10 g/dl and not maintaining the Hgb level above 11.5 g/dl. KDIGO acknowledges in a nongraded recommendation that individualization of therapy will be necessary, because some patients may have improvements in QOL at Hgb concentration above 11.5 g/dl and will be prepared to accept the risks. This recommendation seems to leave the door open for higher target Hgb levels in an individualized risk versus benefit proposition. Target Hgb levels in selected guidelines and regulations are summarized in Table 2.

The answer to the question posed in the title of this perspective is that we will probably not know any more about the optimal target Hgb level in the future than we do now. It is highly unlikely that there will be any additional RCTs comparing higher versus lower Hgb targets in patients treated with ESAs. Because targeting a Hgb level is not an exact science in clinical practice, a change in the target Hgb level results in moving a wide Hgb distribution curve to the right or the left. A move to the left means that more patients will be transfused on the low Hgb end; a move to the right means that more patients will have MACEs and/or vascular access thrombosis on the high Hgb end. The goal is to place the Hgb distribution curve in a position that minimizes the combination of these adverse outcomes. Understanding that evidence-based recommendations derived from a risk versus benefit analysis are on the basis of population studies is fundamental to the application of such recommendations to individual patients who may have unique risk and benefit attributes. Such recommendations are designed as decision-making tools and not as a standard of care or "one size fits all" approach.

The risk versus benefit proposition of higher target Hgb levels has been on the basis of ESA therapy, which is associated with high blood levels of the drug and may have off-target effects detrimental to cardiovascular tissues. Hypoxia inducible factor (HIF) stabilizers, a new class of drugs to treat anemia in patients with CKD and ESRD, induce a low continuous level of endogenous erythropoietin production in the kidney and liver, and by also inhibiting hepcidin and improving iron mobilization, they are effective in raising Hgb levels comparable with those achieved by ESAs.[17] Whether HIF stabilizers are associated with fewer MACEs than ESAs at comparable target Hgb levels has yet to be shown, but a more favorable benefit/risk proposition for HIF stabilizers than for ESAs would reopen the discussion of the optimal Hgb level in ESRD.

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Footnotes

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Figures and Tables

Table 1.

Large randomized, controlled trials comparing high versus low hemoglobin targets in patients receiving erythropoiesis-stimulating agents

Study	NHS[2]	CHOIR[3]	TREAT[4]
N	1265	1432	4038
ESA	Epoetin alfa	Epoetin alfa	Darbepoetin alfa
Population	Patients on HD with coexisting HF or CAD, Hct 30%±3% on epoetin alfa	Patients with ND-CKD and Hgb<11 g/dl not previously administered ESA	Patients with ND-CKD and type 2 DM, Hgb<11 g/dl
Hgb target, g/dl	14.0 versus 10.0	13.5 versus 11.3	13.0 versus ≥9.0
Median achieved Hgb level, g/dl	12.6 versus 10.3	13.0 versus 11.4	12.5 versus 10.6
Primary end point	All-cause mortality or nonfatal MI	All-cause mortality, MI, hospitalization for HF, or stroke	All-cause mortality, MI, myocardial ischemia, HF, and stroke
Hazard ratio or relative risk (95% CI)	1.28 (1.06 to 1.56)	1.34 (1.03 to 1.74)	1.05 (0.94 to 1.17)
Adverse outcome for higher-Hgb group	All-cause mortality	All-cause mortality	Stroke
Hazard ratio or relative risk (95% CI)	1.27 (1.04 to 1.54)	1.48 (0.97 to 2.27)	1.92 (1.38 to 2.68)
QOL	Better in high-Hgb group (controversial)	No difference	No difference except less fatigue in high-Hgb group
Comment	Increased VA thrombosis in high-Hgb group		Increased cancer deaths in high-Hgb group among patients with prior history of cancer

NHS, Normal Hematocrit Study; CHOIR, Correction of Hemoglobin and Outcomes in Renal Insufficiency; TREAT, Trial to Reduce Cardiovascular Events with Aranesp Therapy; ESA, erythropoiesis-stimulating agent; HD, hemodialysis; HF, heart failure; CAD, coronary artery disease; Hct, hematocrit; ND-CKD, nondialysis CKD; Hgb, hemoglobin; DM, diabetes mellitus; MI, myocardial infarction; 95% CI, 95% confidence interval; QOL, quality of life; VA, vascular access.

Table 2.

Hemoglobin targets in selected regulations and guidelines

Source	Year	Hgb Target, g/dl
NKF-DOQI[1]	1997	11–12[a]
NKF-KDOQI	2001	11–12
NKF-KDOQI[13]	2007	11–12
CMS MAT for United States dialysis units[14]	2008	10–12
US FDA[5]	2011	10–11
KDIGO[12]	2012	10–11.5
CMS MAT for United States dialysis units[15]	2014	10–11
NICE[16]	2015	10–12

Hgb, hemoglobin; NKF, National Kidney Foundation; DOQI, Dialysis Outcomes Quality Initiative; KDOQI, Kidney Disease Outcomes Quality Initiative; CMS, Centers for Medicare and Medicaid Services; MAT, Measures Assessment Tool; FDA, Food and Drug Administration; KDIGO, Kidney Disease Improving Global Outcomes; NICE, National Institute for Health and Care Excellence (United Kingdom).

[a]Corresponds to recommended hematocrit target of 33%–36%.