The treatment of anemia in patients with chronic kidney disease (CKD) has been predicated on a large body of evidence from large observational studies and small clinical trials suggesting that patients with the lowest hemoglobin values have worse outcomes than those with higher hemoglobin values. The apparent robust nature of this association, supported by known physiologic consequences of anemia (including fatigue, exercise intolerance, cognitive impairment, and cardiovascular disease exacerbation), has led most clinicians to insist on the need for treatment of anemia.

However, it is important to note that these observational studies were conducted in different populations (both dialysis and nondialysis patients with CKD) and during a significant time, some of which predated the use of erythropoiesis-stimulating agents (ESAs). The initial clinical trials, performed in hemodialysis patients, tested the hypothesis that ESA therapy was effective in increasing hemoglobin levels in those with hemoglobin levels <7.0 g/dL, which, until 1989, was the “usual” hemoglobin level for dialysis populations.1,2 The remarkable clinical transformations seen in patients for whom hemoglobin values increased to >9 g/dL from these previously very low values were touted as revolutionary. However, that initial Canadian study did not find a benefit in quality of life or other parameters in those with hemoglobin values that increased to >11 g/dL.

After the new “norm” in hemoglobin values was established at around 11 g/dL, the question arose about the value of higher levels in patients with CKD. This line of research reflected the continued realization that outcomes continued to be poor in patients with CKD and lower hemoglobin levels consistently were associated with poor outcomes. A series of randomized controlled trials were developed and executed, evaluating the use of ESAs to achieve normalization of hemoglobin levels in both dialysis and nondialysis CKD populations.3-5 Interestingly, despite different populations, dosing regimens, and slightly different targets, no subsequent study was able to show a benefit to higher hemoglobin levels in patients with CKD. Ironically, the reluctance to even enter into placebo-controlled studies because of the clinical conviction that withholding anemia therapy was unethical ultimately stalled our ability to examine the serious question of whether ESA therapy was good and what was the appropriate target hemoglobin level.

Clinical guidelines have been developed based on a combination of evidence and expert judgment; perhaps the latter was tainted by the clinical conviction that anemia marks for poor outcomes and therefore must be treated.6,7 In the face of new evidence, guidelines are updated and modified; this occurred multiple times in the US National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (KDOQI) process with regard to anemia, reflecting results of landmark studies during the past decade. Using robust processes, the new international guideline group KDIGO (Kidney Disease: Improving Global Outcomes) will need to address anemia guidelines, reflecting the recent evidence provided by TREAT (Trial to Reduce Cardiovascular Events With Aranesp Therapy), published in 2009 in the New England Journal of Medicine.8

WHAT DOES THIS IMPORTANT STUDY SHOW?

The recently published TREAT, which examined the effect of darbepoetin alfa therapy in patients with type 2 diabetes, CKD, and anemia, has received a substantial amount of attention from clinicians and researchers alike. This robust study, which examined the impact of darbepoetin
therapy versus placebo in more than 4,000 patients, did not show a decrease in the primary outcome of death, nonfatal cardiovascular event, or end-stage renal disease and was associated with increased risk of stroke in the treatment group.

The achieved hemoglobin level in the treatment group was 12.5 g/dL versus 10.6 g/dL in the placebo group. The average darbepoetin dosage used in TREAT was 176 μg/mo in the treatment group, far exceeding typical doses used in clinical practice. The primary outcomes, a composite end point of time to death from any cause, cardiovascular events (nonfatal myocardial infarction, congestive heart failure, stroke, or hospitalization for myocardial infarction), and a composite of time to death or end-stage renal disease treatment, were adjudicated by a clinical end point committee in which the members were unaware of treatment assignment and hemoglobin values.

The incidence of stroke was almost 2 times higher in the treatment group (5.0% vs 2.6%) and statistically significant, thus raising the very real question of the safety of treatment to this higher target. For the first time in nephrology, a large, appropriately powered, and well-executed study describes not only a lack of treatment benefit, but also a suggestion of harm in a group of patients with diabetes, nondialysis CKD, and anemia. The importance of this study cannot be underestimated with respect to its impact on care.

As an interesting aside, the study also showed that patients with CKD and anemia are iron deplete and respond well to iron supplementation. This latter point perhaps may be missed by many, but has important implications for clinical care, research, and guideline development.

**HOW DOES THIS STUDY COMPARE WITH PRIOR STUDIES?**

Several other studies published, especially within the last 5 years, have shown similar trends, albeit using different study designs, populations, agents, and dosing regimens. A series of similarly designed smaller clinical trials in Australia, Canada, and the United Kingdom using erythropoetin were unable to show differences in left ventricular mass growth during a 2-year period in patients with CKD.\(^9\)\(^{11}\) Each study enrolled 150 patients randomly assigned to ESA therapy or no therapy, resulting in a collective total of 450 patients exposed to this study design. Harm or adverse events were not reported. Interestingly, in each study, participants were iron replete and patients randomly assigned to the control group had relatively stable hemoglobin values during the study.

Soon thereafter, 2 very large randomized clinical trials, CREATE (Cardiovascular Risk Reduction by Early Anemia Treatment With Epoetin beta) and CHOIR (Correction of Hemoglobin and Outcomes in Renal Insufficiency), were reported.\(^4\)\(^5\) CREATE included an international non–US-based cohort of nondialysis patients (n = 600) and, similar to the trials reported previously, could not show a benefit of higher target hemoglobin levels (>12 g/dl) on cardiovascular outcomes or death. CHOIR, a study with an initial enrollment of 1,200 patients but significant dropout of almost 50%, was stopped early because of futility and a suggestion of harm. Patients enrolled in CHOIR were from the United States, received relatively high doses of ESAs, and were not balanced with respect to cardiovascular history despite randomization. Furthermore, with adjustment for these baseline demographic imbalances, differences in adverse outcomes were no longer statistically significant. Most importantly and consistent with previous studies, CHOIR did not show a benefit to targeting higher hemoglobin levels in CKD populations.

Clinical trials in hemodialysis patients of similar design and with targets in the high-hemoglobin group of >12.5 g/dL also have not shown benefit to the higher hemoglobin target. In addition, signals for higher vascular access thrombosis rates and a suggestion of greater incidence of stroke have been seen in these studies, whether examining incident or prevalent patients with varying degrees of cardiac disease.\(^12\)\(^{13}\)

TREAT is the largest, best conducted, and only placebo-controlled trial in patients with CKD to date. It essentially consolidates many findings of the earlier studies and answers a very specific question: in patients with diabetes, CKD, and anemia, is there a survival, cardiovascular, or renal preservation benefit to targeting and achieving higher hemoglobin values (of 12.5 g/dL) using ESA therapies? The answer is no.
Although there may be a minor improvement in quality-of-life, fatigue, and energy scores, which is important for individuals, this small benefit may come at a cost of increased risk of stroke.

**WHAT SHOULD CLINICIANS, RESEARCHERS, AND GUIDELINE GROUPS DO?**

Clinicians need to re-evaluate their present thresholds and paradigms regarding anemia treatment. Specifically, the need to start ESA therapy in the absence of symptoms and in the context of relatively “arbitrary” thresholds, such as 11 g/dL, should be reassessed. Patients need to be informed of the potential risk and benefit of the medication so that the full impact of treating anemia in CKD is understood.

Researchers now need to define a new set of questions for clinical trials, including understanding of the physiologic consequences of anemia and its treatment with respect to different CKD populations. Relationships among hemoglobin level, estimated glomerular filtration rate, vascular health, and other nontraditional risk factors (such as vitamin D, parathyroid hormone, phosphate, and fibroblast growth factor 23 levels) need to be explored before single-intervention studies are undertaken again. We need to re-explore the risk-benefit of iron therapy, ESA therapy, and the combination so that we truly understand the consequences of treating anemia. Most importantly, we need to re-examine the issue of target hemoglobin level and ESA dose and the notion that one size fits all irrespective of vascular health, age, comorbid conditions, and treatment modality. Perhaps the concept of targeting a single value of a continuous physiologic variable for all patients is erroneous, and we need to better understand the implications of changes in these variables and their underlying causes. Furthermore, focus on “hemoglobin variability” as a new therapeutic target, which has been recommended by some, is likely to lead to problems similar to targeting single values, so we would advise against this. In general, the importance of supplementing or repleting hormone deficiencies and the complexity of the interplay among nontraditional risk factors, such as anemia, phosphate level, vitamin D level, and other factors, on patient outcomes in CKD require better understanding.

Clinical practice guideline groups now need to review the best set of evidence available to date and incorporate that information into recommendations. The challenge is to go against current practice, refraining from the rhetoric that there is “only” one study and that perhaps “on balance” we can still recommend the higher hemoglobin targets. Guideline groups, such as KDIGO, should ensure that patient-centered outcomes remain the focus of the guideline commentary: messages for the updates need to be clear and succinct, refraining from too much conjecture. The data are clearer now than they have been for decades: anemia therapy aimed at high hemoglobin targets does not change clinically meaningful outcomes, such as cardiovascular events, death, or time to dialysis therapy. Although therapy may impact positively on specific aspects of quality of life, it also may confer risks.

**Adeera Levin, MD, FRCPC**

**Monica Carol Beaulieu, MD, FRCPC**

University of British Columbia

Vancouver, Canada

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