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Correction of Anemia — Payoffs and Problems

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Anemia develops in most patients with chronic kidney disease, historically often requiring transfusion, with obvious risks. With the advent of recombinant erythropoietin in the late 1980s, it became possible to treat anemia without transfusion, ushering in a new era. It soon became clear that additional considerations were important, such as ensuring adequate iron stores, providing sufficient folate and vitamin B₁₂, and identifying other conditions affecting the hemoglobin level. How best to administer erythropoietin — as well as how best to produce it, given cases of pure red-cell aplasia related to production and administration — were also identified as important issues. Yet, despite years of use of erythropoietin, the hemoglobin levels at which this therapy should be initiated, as well as its target hemoglobin level, remain controversial.

Although current recommendations for treating anemia resulting from chronic kidney disease are to initiate recombinant human erythropoietin when the hemoglobin value falls below 9.0 g per deciliter, many patients are not treated before they need renal-replacement therapy.^{1,2} The recent recommendations of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) panel on anemia suggest that the target hemoglobin level should be 11.0 g per deciliter or greater, with caution urged if a hemoglobin value of more than 13.0 g per deciliter is intentionally maintained.¹ However, these recommendations are not based on persuasive randomized, controlled trials.¹

In this issue of the *Journal*, two trials address the optimal target level for hemoglobin in patients with chronic kidney disease who do not yet need renal-replacement therapy: the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) trial by Drüeke et al.³ and the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial by Singh et al.⁴ The CREATE trial showed that, in patients with an estimated glomerular filtration rate of 15.0 to 35.0 ml per minute, early complete correction of anemia (to a target hemoglobin value in the

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normal range, 13.0 to 15.0 g per deciliter) does not decrease the incidence of cardiovascular events, as compared with partial correction of anemia (to a target hemoglobin value of 10.5 to 11.5 g per deciliter). In the CHOIR trial, a higher target hemoglobin value (13.5 g per deciliter, as compared with 11.3 g per deciliter) was associated with increased risks of death, myocardial infarction, hospitalization for congestive heart failure (without renal-replacement therapy), and stroke without improvement in the quality of life. Singh et al. conclude that correction of anemia in patients with chronic kidney disease should use a target hemoglobin value of 11.0 to 12.0 g per deciliter. It is of interest that the data and safety monitoring board recommended that the CHOIR trial be terminated after the second of four planned interim analyses because of the extremely low likelihood of detecting a true benefit in the high-hemoglobin group by the end of the study.

Thus, neither of these studies of chronic kidney disease had the anticipated result — that normalization of the hemoglobin level would be beneficial. Randomized studies in patients receiving dialysis have previously shown that normalization of hemoglobin levels did not improve left ventricular indexes or reduce the mortality rate.^{5,6} A recent Canadian trial that examined the effect of maintaining a hemoglobin level of 12.0 to 14.0 g per deciliter on preventing or delaying left ventricular hypertrophy in patients with chronic kidney disease showed no effect.⁷ In a study by Rossert et al. that compared treatments with a high target hemoglobin level (13.0 to 15.0 g per deciliter) to a lower target level (11.0 to 12.0 g per deciliter), the authors found no cardiovascular benefit, though the study was halted early because of concerns about pure red-cell aplasia.⁸

Why doesn't complete correction of anemia favor better cardiovascular outcomes in randomized, controlled trials? A higher hematocrit level should improve oxygen delivery to tissues. Indeed, tissue hypoxia and oxidative stress, as seen in patients with anemia, are both linked to inflammation and the progression of chronic kidney disease. However, complete correction of anemia might increase both blood pressure and the risk of thrombosis and accentuate vasoconstriction.

In the CREATE and CHOIR studies, the prevalence of hypertension was similar in the low-hemoglobin group and the high-hemoglobin group at baseline. In the CREATE study, patients with the higher target hemoglobin level had higher systolic and diastolic blood pressures (by 1 to 2 mm Hg) at the end of the study, and had uncontrolled hypertension more frequently, than did patients with the lower hemoglobin target level. Such differences, though small, could contribute to an excess cardiovascular risk that is clinically appreciable.⁹

Anemia, chronic kidney disease, and heart failure are a risky combination. The rheology of blood may be important in chronic kidney disease, and it has been known for decades that bleeding time is prolonged in patients with renal dysfunction and hematocrit levels of less than 30%.¹⁰ Raising the hematocrit level above 30% decreases bleeding time and, in patients with uremia, the tendency to bleed. However, raising hemoglobin levels substantially also increases platelet adhesiveness. One study¹¹ reported increased blood viscosity in patients with chronic kidney disease, as compared with healthy subjects, at all levels of shear stress and concluded that the increased viscosity in patients with kidney disease might relate to the altered shape of red cells and their decreased deformability.

In the CREATE trial, the mean time to dialysis was significantly shorter among patients with the normal hemoglobin target range than among those with a lower target range. These findings are consistent with data from earlier studies¹²

showing that chronic moderate anemia reduces glomerular injury in different experimental models of chronic renal disease, whereas raising hemoglobin values by administering recombinant human erythropoietin resulted in accelerated glomerulosclerosis.

In both the CREATE and CHOIR studies, patients in the high-hemoglobin groups received more iron supplementation than did those in the low-hemoglobin groups. Iron is bound to transferrin, which undergoes ultrafiltration through the glomerular barrier into the urinary space, where it dissociates from transferrin in the relatively acidic tubular fluid and catalyzes the formation of hydroxyl radicals.¹³ Thus, iron overload might accelerate renal injury through oxidative stress and chronic interstitial inflammation. Reduction of iron levels in the body through a low-iron diet and iron-absorption inhibitors resulted in a decreased incidence of progression to end-stage renal disease and a decreased rate of death from any cause in humans, without appreciably affecting hemoglobin levels.¹⁴ Furthermore, patients with diabetes receiving low-iron diets have a 20 to 30% lower mortality rate from coronary artery disease than those receiving high-iron diets.¹⁵ Subjects assigned a high target hemoglobin value in previous studies might have had a relative iron overload, which could have increased the overall renal and cardiovascular risks.

There was no significant difference in mortality rates between the high-hemoglobin and low-hemoglobin groups in either the CREATE or the CHOIR study, though the absolute number of deaths was higher in the high-hemoglobin group in each study. In the high-hemoglobin groups, increased blood viscosity might have increased the risk of thrombosis,¹⁶ consistent with the trend toward arteriovenous fistula thrombosis among patients in the CREATE study (12 patients in the high-hemoglobin group and 8 in the low-hemoglobin group). However, in the CHOIR study, the incidences of major thrombotic events (acute myocardial infarction and stroke) were similar between the two groups.

The most surprising finding is that high target hemoglobin levels did not ameliorate left ventricular hypertrophy in the CREATE study and, indeed, they increased the risk of congestive heart failure in both trials. Secondary fluid retention and higher blood pressure, related to worsening renal function, might explain this finding, at least in part. Increased hematocrit value, associated with increased blood viscosity, may increase the impedance of the systemic circulation and the ventricular afterload. All these changes might contribute to accelerated left ventricular dysfunction or hypertrophy and might offset the benefits of improved myocardial and peripheral oxygenation.

Taken together, these two studies suggest caution in the full correction of anemia in patients with chronic kidney disease. Currently, there are several additional multicenter trials of complete as compared with partial correction of anemia in patients with chronic kidney disease; Dr. Remuzzi is participating in one of them. Although we need more information about the ideal target level and should consider the present guidelines incomplete, it seems wisest to refrain from complete correction of anemia in persons with chronic kidney disease.

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Source Information

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