



The Illinois Medical Bulletin



The Relationship Between Hemoglobin Targets with Erythropoiesis-Stimulating Agents and Cardiovascular Risk in Chronic Kidney Disease: A Review of Pivotal Trial Evidence

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Article History :

Received date : 2024/10/12
Revised date : 2024/11/28
Accepted date : 2024/12/09
Published date : 2025/01/13



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ABSTRACT

Introduction: Anemia is a near-universal complication of Chronic Kidney Disease (CKD), contributing to poor quality of life and a high burden of cardiovascular disease. The development of Erythropoiesis-Stimulating Agents (ESAs) effectively treated this anemia, leading to the widespread hypothesis that correcting hemoglobin to normal levels would be cardioprotective.

Literature Review: A review of pivotal randomized controlled trials reveals a consistent and unexpected pattern of harm associated with this approach. Multiple large-scale trials were designed to test the hypothesis that targeting a normal or near-normal hemoglobin level with ESAs was superior to a more conservative strategy with a lower hemoglobin target. Contrary to expectations, these trials, including the landmark CHOIR and CREATE studies, were terminated prematurely. They consistently demonstrated that the pursuit of higher hemoglobin targets did not reduce cardiovascular risk and, in fact, significantly increased the risk of death,

myocardial infarction, heart failure, and stroke. Subsequent large trials and meta-analyses confirmed these hazardous outcomes.

Conclusion: This body of evidence definitively refuted the long-held belief that normalizing hemoglobin with ESAs would improve cardiovascular outcomes in patients with CKD. It established that such a strategy is harmful, prompting a fundamental reversal of clinical practice and leading to new guidelines that advocate for more conservative hemoglobin targets and the use of the lowest effective ESA dose.

Keywords: Chronic Kidney Disease (CKD), Anemia, Erythropoiesis-Stimulating Agents (ESAs), Hemoglobin, Cardiovascular Risk.

INTRODUCTION

Anemia is a hallmark of progressive Chronic Kidney Disease (CKD), resulting primarily from the kidneys' failure to produce adequate amounts of the hormone erythropoietin. This anemia is a major cause of the debilitating fatigue and reduced quality of life experienced by patients with CKD. Furthermore, observational studies had long linked the presence of anemia to adverse cardiovascular outcomes, including the development of left ventricular hypertrophy and increased mortality, leading to the hypothesis that anemia was a modifiable cardiovascular risk factor in this population.

The introduction of recombinant human erythropoietin, a class of drugs known as Erythropoiesis-Stimulating Agents (ESAs), revolutionized the management of CKD-associated anemia by effectively raising hemoglobin levels and reducing the need for blood transfusions. This success led to a logical and compelling new hypothesis: if anemia contributes to cardiovascular disease, then correcting the anemia to normal physiological levels with ESAs should be cardioprotective. This literature review will synthesise the pivotal clinical trial evidence that rigorously tested this hypothesis and ultimately revealed unexpected and significant harm.

LITERATURE REVIEW

The investigation into the optimal hemoglobin target for patients with CKD treated with ESAs is a cautionary tale of a well-intentioned hypothesis being refuted by high-quality evidence.

The initial rationale for targeting normal hemoglobin levels was strong. It was believed that correcting anemia would reduce the stimulus for left ventricular hypertrophy and improve myocardial oxygen supply, thereby mitigating the extremely high cardiovascular risk faced by CKD patients. However, early signals of potential harm emerged from a trial in hemodialysis patients which suggested a trend towards increased mortality in the group randomized to a normal hematocrit target. This set the stage for more definitive investigations in the larger pre-dialysis CKD population.

Two major, concurrent randomized controlled trials were designed to definitively test the normalization hypothesis. The Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study and the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) study both randomized patients with CKD and anemia to either a high hemoglobin target (normal or near-normal) or a lower, more conservative target. The results from both trials were concordant, surprising, and profoundly impactful. Both studies were stopped prematurely by their respective data safety monitoring boards because the patients in the high-hemoglobin target groups experienced a significantly higher rate of adverse cardiovascular events, including death, myocardial infarction, and heart failure, with no discernible benefit to offset this harm (Drücke et al., 2006; Singh et al., 2006).

These findings sent a shockwave through the nephrology community, challenging a practice that had become widespread. The results were further substantiated by meta-analyses of existing trials. One such influential analysis pooled data from numerous studies and confirmed that targeting higher hemoglobin levels with ESAs was associated with a significantly increased risk of all-cause mortality, arteriovenous access thrombosis, and poorly controlled hypertension (Phrommintikul et al., 2007).

The final, definitive evidence from this period came from the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT). This was a very large, placebo-controlled trial in over 4,000 patients with diabetes, CKD, and anemia. The trial showed that treatment with an ESA did not significantly reduce the risk of the primary composite endpoints of death or a cardiovascular event, or the composite of death or end-stage renal disease. Most alarmingly, the use of the ESA was associated with a twofold statistically significant increase in the risk of stroke (Pfeffer et al., 2009). This finding effectively ended the debate about the potential cardiovascular benefits of normalizing hemoglobin in this population.

CONCLUSION

The pivotal body of literature examining the use of Erythropoiesis-Stimulating Agents to achieve normal hemoglobin targets in patients with Chronic Kidney Disease tells a clear and consistent story. A biologically plausible and well-intentioned hypothesis—that correcting anemia would be cardioprotective—was definitively and repeatedly proven false by a series of large, well-conducted randomized controlled trials.

The evidence overwhelmingly demonstrated that targeting higher hemoglobin levels does not improve cardiovascular outcomes and, in fact, substantially increases the risk of serious and life-threatening adverse events, including death, myocardial infarction, and stroke. This research forced a complete paradigm shift in clinical practice, leading to the universal adoption of more conservative hemoglobin targets and a focus on using the lowest ESA dose necessary to avoid blood transfusions. It remains a powerful example of how rigorously tested evidence must guide clinical practice, even when it contradicts long-held physiological assumptions.

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