

Critical Missing Data on Erythropoiesis-Stimulating Agents in CKD: First Beat Placebo

Editors' Note: In this editorial, Dr Pfeffer was invited to comment on the recent controversy of efficacy and harm of erythropoietin-stimulating agents for treatment of anemia of chronic kidney disease. The editors consider the discussion by Dr Pfeffer on the conduct of these trials to be relevant to trials of other therapies in nephrology, such as those for phosphorus binding agents, for example the DCOR (Dialysis Clinical Outcomes Revisited) study presented elsewhere in this issue of *AJKD* (pp. 362 and 445).

The clinical application of erythropoiesis-stimulating agents (ESA) to patients with anemia and chronic kidney disease (CKD) has missed a vital evidence-gathering step and hence current use appears to have greatly outpaced the data. Benefits achieved in dialysis patients with severe anemia (hemoglobin < 9 g/dL [90 g/L]) have been extrapolated without sufficient data to nondialysis patients with less profound anemia. Some in the nephrology community have focused on the secondary issue of target hemoglobin for ESA, which circumvents the more critical overarching question of whether the risk-benefit ratio of these costly agents warrants use in nondialysis populations. This critical gap can only be addressed by randomized controlled trials (RCTs) comparing ESA to placebo: first beat placebo.

Most major pharmacological advances commence with the clear demonstration of meaningful clinical improvements in the highest-risk subset of patients for the new therapeutic entity. The first placebo-controlled trial proving that antihypertensive agents could improve prognosis of patients with hypertension enrolled only 143

patients with severe hypertension (diastolic blood pressure > 115 mm Hg) to definitively demonstrate the importance of blood pressure lowering.¹ Once the principle was established that lowering arterial pressure resulted in reductions in risks of cardiovascular death or major morbidity, other larger placebo-controlled trials continued to probe and, indeed, demonstrate, the benefit of antihypertensive therapies in less severely affected populations.² Although antihypertensives, by definition, effectively lower arterial blood pressure, the clinical utility across the spectrum of hypertension required multiple placebo-controlled trials. Only after proof of utility was firmly established were trials designed to uncover potential therapeutic advantages between classes of agents and levels of blood pressures.²

Similarly, the initial demonstration that an angiotensin-converting enzyme (ACE) inhibitor saved lives in patients with heart failure was achieved in the CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study) trial, which enrolled only 255 patients with a markedly impaired prognosis (median survival, 6 months).³ Rather than extrapolate or assume comparable benefits in less severely ill patients, other much larger placebo-controlled trials were then undertaken to better define the extent of the population with heart failure that would still achieve a favorable risk-benefit ratio with this therapy.⁴ When new populations such as patients with left ventricular dysfunction post-myocardial infarction were considered, superiority over placebo on clinical outcomes was again demonstrated before this therapy was more widely adopted or promoted.⁵

After the initial demonstration of reduced morbidity and mortality with the use of HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitors (statins) in high-risk patients with elevated cholesterol by the Scandinavian Simvastatin Survival Study (4S),⁶ other trials continued to test against placebo, as the effectiveness of statins was demonstrated in patients with "normal cholesterol" in the CARE (Cholesterol and Recurrent Events) and LIPID (Long-Term Intervention with Pravastatin in Ischaemic Dis-

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ease) trials and even in primary prevention in the West of Scotland Coronary Prevention Study Group as well as AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study) trials.⁷⁻¹⁰ Despite these and other impressive placebo-controlled trials demonstrating the benefits of statins, placebo was still used in probing other important patient subsets that were not well represented in previous studies.¹¹ Neutral placebo-controlled trials of statins in patients on dialysis,¹² elderly patients with vascular disease,¹³ and, most recently, heart failure,¹⁴ have provided a more accurate quantitation of benefits and risks upon which to base therapeutic decisions. Only in patient groups where the benefits of statins were well established, have other non-placebo-controlled clinical trials addressed the second-line but important question of optimal level of low-density lipoprotein cholesterol lowering.¹⁵⁻¹⁶

This pattern of establishing the benefit and risks of a therapy using placebo-controlled experiences at the severe end of the disease spectrum and continuing with placebo-controlled trials to demonstrate effectiveness in less severely ill patients has unfortunately not occurred with ESAs in kidney disease. This novel biologic therapy to raise hemoglobin was promptly applied to severely anemic patients on dialysis with favorable results on patient-reported outcomes as well as a reduction in red cell transfusions.¹⁷ Strong observational associations between anemia and increased risk of cardiovascular morbidity and mortality coupled¹⁸ with early favorable quality of life data from dialysis patients with severe anemia provided the initial impetus for use of ESAs. Zealous marketing as well as complicated economic and quality performance incentives against hemoglobin below 11 g/dL (110 g/L) have confounded the use patterns for dialysis patients.¹⁹⁻²⁰

The extrapolation of presumed benefits of ESAs without quantification of their risks from placebo-controlled trials to much larger populations such as patients with cancer and nondialysis CKD has created even greater uncertainties. In CKD patients with hemoglobin greater than 9 g/dL, the efficacy data for ESAs even for quality of life is rather sparse and there was a stark void in placebo-controlled clinical outcomes and safety data. Three recent RCTs (2 completed and 1 ongoing) address the important issue of correction of anemia with an ESA in CKD. The completed trials both used an

open-label design comparing 2 hemoglobin targets without testing against placebo. It is important to emphasize that this trial design—comparing 2 active dosage regimens—assumes that the therapy is warranted. In fact, with a high- versus low-target design, all scenarios of results—high superior to low, low superior to high, or no difference—would lead to an endorsement for ESA use.

The Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) trial randomized 603 patients with a hemoglobin level between 11.0 and 12.5 g/dL (110 and 125 g/L) and an estimated glomerular filtration rate (eGFR) between 15 and 35 mL/min/1.73 m² (0.25 and 0.58 mL/s/1.73 m²) to use epoetin beta to a hemoglobin target of either 13 to 15 or 10.5 to 11.5 g/dL (130 to 150 or 105 to 115 g/L).²¹ Although not significant, during 3 years, numerically more first cardiovascular events occurred in the group targeting the higher hemoglobin level (58/301 and 47/302, respectively; $P = 0.2$); however, quality of life assessments were better in the high hemoglobin arm.²¹ The CHOIR (Correction of Hemoglobin and Outcomes in Renal insufficiency) study randomized 1,432 patients with CKD (eGFR of 15 to 50 mL/min/1.73 m² [0.25 to 0.83 mL/s/1.73 m²]) and a hemoglobin less than 11.0 g/dL to a strategy to use epoetin alfa to a target of either 13.5 or 11.3 g/dL (135 or 113 g/L). More patients randomized in the higher hemoglobin target experienced the primary composite end point of death, myocardial infarction, or hospitalization for heart failure or stroke (125/715 versus 97/717, $P = 0.03$), and quality of life assessments were not different.²² Although there has been controversy about the robustness of these findings, it is nonetheless currently the largest completed RCT in this field.²³ A meta-analysis of 9 RCTs of ESAs in both dialysis and nondialysis CKD patients shows higher mortality rates across heterogeneous trials in the arm targeting higher hemoglobin concentrations.²⁴ Of interest, none of these 9 studies meeting the inclusion criteria for the meta-analysis were placebo controlled.

Other data regarding a serious safety concern about the ESA use in patients with cancer prompted the addition of a “black box warning” from the Food and Drug Administration regarding prescribing these agents.²⁵ Physicians are now instructed to use the lowest dose of an ESA to “avoid the need for blood transfusion.”²⁵ This important statement underscores that current sales appear to have greatly

exceeded proven clinical utility. This imbalance between market-driven use and data comes from extrapolations of presumed benefits in the absence of rigorous placebo-controlled clinical outcome trials.

As the only major double-blind, placebo-controlled (active therapy for hemoglobin values below 9 g/dL [90 g/L]) clinical outcomes trial, the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) is best poised to define the much-needed benefit-risk ratio of an ESA in patients with CKD.²⁶ TREAT is addressing the hypothesis that anemia therapy with darbepoetin alfa would reduce the risk of a composite cardiovascular morbidity and mortality outcomes in patients with diabetes, CKD (eGFR of 20 to 60 mL/min/1.73 m² [0.33 to 1.0 mL/s/1.73 m²) and anemia (hemoglobin \leq 11 g/dL [110 g/L]).²⁶ The target enrollment of 4,000 patients has been met and although follow-up continues as per protocol, the cumulative patient exposure and number of clinical events reported is already multifold larger than prior experiences. Of interest, at the start of TREAT some in the medical community expressed concern regarding the ethics of having a placebo group.²⁷ With the recent results of non-placebo-controlled trials, others now question the ethics of the active treatment group.²⁸ This uncertainty can and should only be addressed by quality data conducted in a responsible manner. The highly experienced TREAT Data Safety Monitoring Board has the unique perspective of being privy to the totality of both external and internal data. That they found “no cogent evidence to recommend alteration or termination of TREAT” indicates that we still do not have a reliable answer as to whether the ESA beats placebo or is associated with harm.²⁹ This more fundamental question must be squarely addressed before the secondary questions of what dose or target can or should be evaluated. The sequence of first beating placebo must be employed to provide the much needed recalibration of evidence for use of ESAs in nondialysis CKD patients with moderate anemia.

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