Uncertainty in the Treatment of Anemia in Chronic Kidney Disease

Marc A. Pfeffer, MD, PhD, FACC,* Scott D. Solomon, MD,*
Peter Ivanovich, MD,† Ajay K. Singh, MD,* John J. V. McMurray, MD‡

*Department of Medicine, Brigham and Women's Hospital, Boston, MA; †Department of Medicine, Jesse Brown Veterans Administration and Northwestern University, Chicago, IL; ‡Department of Cardiology, Western Infirmary, Glasgow, UK

The practice of medicine requires that the assimilation of today's best available data be directed toward individual patient-care decisions. In the absence of definitive data, surrogate measures are adopted to anticipate how therapeutic strategies would influence clinical outcomes and prognosis. Unfortunately, randomized controlled clinical trials (RCTs) have not always found these estimates of outcome to be reliable. Anemia is a clear marker of adverse prognosis, which can be modified by erythropoietic stimulating proteins (ESP). At present, there is sufficient uncertainty regarding the risks and benefits of ESP treatment in patients with chronic kidney disease and anemia to warrant major RCTs. This article reviews the rationale and design features for these trials. [Rev Cardiovasc Med. *2005;6(suppl. 3):S35-S41*]

Key Words: Anemia • Chronic kidney disease • Erythropoietin • Randomized controlled clinical trials

A delicate balance exists between providing optimal, up-to-date treatment for today's patients and probing investigative frontiers that may lead to improvements in patient healthcare tomorrow. There is comfort and satisfaction in providing what are considered state-of-the-art therapies. However, unless the bases for these approaches have been firmly proven in a rigorous fashion, what is currently considered optimal might not be effective or as beneficial as initially anticipated. Moreover, if inadequately proven therapeutic

approaches are readily adopted and implemented as standardized care, the incentive to seek more efficacious discoveries may be diminished.

The Importance of Randomized Trials

Randomized controlled clinical trials (RCTs) examining important clinical outcomes have emerged as the premier tool with which to evaluate the risks and benefits of prospective therapies.[1] Under the light generated from major RCTs, prior therapeutic approaches, which may have been considered "state-of-the-art" based on strong epidemiological associations or surrogate endpoints from smaller RCTs, have all too often been exposed as ineffective.[2] Indeed, in a novel analysis of the 49 most prominently cited articles about medical therapies published between 1990 and 2003, 5 of the 6 therapeutic approaches that were based on nonrandomized case series or large prospective cohort studies were contradicted by subsequent RCTs.[3] As important as the efficacy information (positive, negative, or neutral), these large outcome trials have generated equally important quantitative data concerning the risks that can be anticipated from the therapy.

Recent experiences with supplemental hormone replacement therapy (HRT) for postmenopausal women offer one of the most illustrative examples of a well accepted and widely utilized clinical therapy that was considered state-of-the-art, only to be found ineffective and potentially harmful when studied in a major placebo controlled RCT. The linkages of HRT to a strongly held belief of cardiovascular benefits were based on multiple large, observational databases, as well as a smaller RCT with such surrogate outcomes as lipid levels and vascular reactivity.[4] Based on those best available data, use of HRT was endorsed for both primary and secondary prevention of cardiovascular events in post-menopausal women. The unexpected but definitive negative findings came from the Women's Health Initiative, which randomized over 40,000 postmenopausal women to either an estrogen and progestin combination or placebo. The results stunned the medical community with the recognition that what was considered state-of-the-art therapy might actually have been harmful.[5] Indeed, in addition to delineating benefits, if any, the most important contribution of the Women's Health Initiative was to provide sufficient placebo-controlled exposure to generate the firmest data quantifying the risks of this commonly prescribed therapy.

Cardiovascular physicians and investigators have been repeatedly exposed to the possibility that accepted therapies may not deliver their presumed benefits when properly scrutinized in RCTs. The Cardiac Arrhythmia Suppression Trial (CAST) offered 1 of the earlier major lessons concerning the unreliability of surrogates.[6] The presence of ventricular ectopic activity has long been recognized as a marker of augmented risk. Although the antiarrhythmic therapies in CAST were effective in reducing this marker of risk, their use resulted in significant reductions, rather than the anticipated prolongation, in survival rates.

Positive inotropic agents for the treatment of patients with heart failure attributed to systolic dysfunction provide other vivid examples of strongly held views, which directly influenced patient care, but were reversed by unexpected data from RCTs powered to address clinical outcomes. Impaired pump function and inotropic incompetence are the hallmarks and central pathophysiologic defect in these forms of heart failure. In numerous small surrogate endpoint-directed RCTs, positive inotropic agents were shown to ameliorate the hemodynamic derangements of heart failure, resulting in lower filling pressure and higher cardiac output and ejection fraction. In initial studies, several of these agents were considered quite promising, based on their effects on hemodynamics measurements.

Following extensive basic and clinical data demonstrating positive inotropic properties and initial tolerability in patients with heart failure, flosequinan was shown in relatively small, placebo-controlled RCTs to significantly improve exercise duration, functional status, and quality of life in patients with heart failure.[7,8] The cumulative information from these studies and other nonclinical outcomes trials was consistent and sufficiently convincing for the US Food and Drug Administration (FDA) to approve flosequinan for treatment of patients with heart failure (FDA web site).[9] Though not definitive, the flosequinan package insert included a specific mention of a potential worrisome signal from the cumulative experiences of these small trials, suggestive of higher mortality rates in those treated with the inotropic agent. Fortunately, a properly powered, placebo-controlled

Cardiovascular physicians and investigators have been exposed repeatedly to the possibility that accepted therapies may not deliver their presumed benefits when properly scrutinized in RCTs.

RCT with a primary outcome measure of mortality was conducted. This study demonstrated that administration of flosequinan, which had been shown to improve many surrogates of heart failure severity, resulted in an approximately 40% higher risk of death compared to placebo.[10] The dissociation between the effects of flosequinan and indeed other orally active, positive inotropic agents that improved symptoms and quality of life but produced a significant increase in the risk of death,[11] may be germane when considering the use of erythropoietic agents for the treatment of anemia in patients with chronic kidney disease (CKD).

Obviously, RCTs cannot be available to answer all the myriad clinical questions facing the practitioner.[12] Expert guidelines are commonly available to assist clinicians in navigating and prioritizing among therapeutic options.[13] These guidelines generally provide recommendations along with supporting documentation based on the strength of the currently available evidence (Figure 1). Guidelines intended to summarize contemporary data should also serve to identify areas where more definitive future information is needed. As such, guidelines should be considered as time-sensitive documents ready to be revised in response to new relevant data. Indeed, progress in a particular field can be tracked by the need to update guidelines whenever new, more robust data becomes available.

Anemia

The presence of anemia, defined as a hemoglobin level of less than 12 g/dL in women (hematocrit less than 36%) and less than 13 g/dL in men (hematocrit less than 39%), has been demonstrated in multiple epidemiologic databases to be associated with greater risk for subsequent cardiovascular events.[14,15] This negative impact of the presence and indeed the degree of anemia on prognosis persists after adjustment for other known risk factors and can be considered additive or even synergistic with more established classical risk factors.[16,17] These and multiple other studies designate the degree of anemia as a readily quantifiable marker of risk. The development of erythropoietic therapies that are effective in raising hematocrit levels makes low hemoglobin a particularly attractive therapeutic target. Because it is possible to correct anemia with pharmacological agents, it is important to design appropriate RCTs to determine whether the risk associated with the presence of anemia can be modified by therapies directed to raise hematocrit levels and result in safe and favorable outcomes.

Currently, there is no question that erythropoietic stimulating proteins (ESPs) can raise hematocrit. The cumulative results from multiple studies supports the conclusion that in patients on renal replacement therapies with severe anemia, treatment with ESPs will increase hemoglobin, improve quality of life, and decrease transfusion requirements. In the much larger population of patients with CKD and anemia, ESPs have also been shown to increase hemoglobin and improve quality of life.[18] These conclusions are based on the findings of generally small trials that were not designed or intended to accurately identify possible alterations (either positive or negative) in clinical outcomes.

Currently, there is no question that erythropoietic stimulating proteins can raise hematocrit.

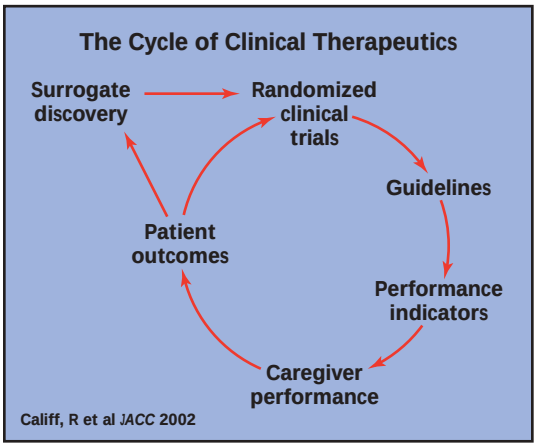

Figure 1. *The evolution of evidence-based medicine in clinical therapeutics. Clinical trials, guidelines, and physician practice all play a part in changing ideas of "state-of-the-art" care. Adapted with permission from Califf et al.*[13]

Equipoise in Theories of Anemia Treatment

Equipoise is the state in which there is balance between different influences. In a medical context, this balance relates to a "present or imminent controversy in the clinical community over the preferred treatment."[19] In clinical practice, frontline practitioners and their patients never achieve this exquisite state of balance. The basis for an RCT should be "uncertainty over the efficacy and safety of a treatment."[20] The RCT

affords the vehicle by which the potential of a therapy to improve clinical outcomes against the potential to harm is most rigorously determined. The word potential must be used in the absence of such definitive data.

Potential Benefit. Anemia is a strong independent marker of cardiovascular risk, and it is plausible that low hemoglobin, by causing reduced oxygen delivery and greater cardiac workload, may play a part in the pathophysiologic cascade precipitating cardiovascular events.[21] Moreover, sufficient studies already exist in patients on renal replacement therapy with severe anemia to indicate that raising hemoglobin with erythropoietic agents can improve patients' quality of life, principally in the physical function domain.[18] Erythropoietin therapy may slow the progression of renal disease.[22] ESP, apart from increasing red cell production, may also contribute to improved patient outcomes in other ways. Erythropoietin increases levels of bone marrow progenitor cells believed to lead to neovascularization[23] as well as cells involved that may forestall atherosclerotic lesions.[24]

Treatment of anemia presents a potential benefit in that anemia is a strong independent marker of cardiovascular risk and it is plausible that low hemoglobin, by causing reduced oxygen delivery and greater cardiac workload, may play a part in the pathophysiologic cascade precipitating cardiovascular events.

Potential Harm. The largest RCT to date that evaluated the use of recombinant human erythropoietin to either partially or totally normalize hematocrit in patients on hemodialysis with known cardiac disease did not demonstrate a benefit.[25] There was a 30%, statistically nonsignificant trend for an increase in the trial's primary outcome measure—risk of death or nonfatal myocardial infarction (MI) in patients randomized to the higher hematocrit level (risk ratio 1.3; 95% confidence interval, 0.9-1.8). A higher incidence of thrombosis of vascular access sites also occurred in the patients randomized to the higher hematocrit level. Although the study did not show a significant difference in blood pressure, the use of erythropoietic therapy has been associated with a greater need for antihypertensive agents. In a totally unrelated population of women with metastatic breast cancer, the use of erythropoietin was associated with a higher rate of death than in the placebo group.[26] Another RCT in oncology patients with head and neck cancer also produced the unanticipated and unexplained, worrisome finding of reduced survival in subjects randomized to erythropoietic therapy.[27] Although these unexpected findings can be attributed to the play of chance from RCTs lacking adequate statistical power, the potential that supplemental erythropoietin contributed to adverse outcomes must be considered. This uncertainty cannot be dismissed without further studies.

Current Trials

In addition to deterioration in renal function necessitating dialysis, patients with diabetes and CKD are at an even higher risk for a major nonfatal cardiovascular event or death. Anemia makes this risk more worrisome. The Trial to Reduce Cardiovascular Events with Aranesp® Therapy (TREAT) is a multicenter, double-blind, placebo-controlled RCT specifically designed to determine whether patients with CKD (estimated glomerular filtration rate of 20-60 mL/min/1.73 m^2), type 2 diabetes, and anemia (hemoglobin less than 11 g/dL) will experience a reduction in the risk of the composite endpoint of death or cardiovascular morbidity (nonfatal MI, hospitalization for myocardial ischemia, congestive heart failure, or stroke) when treated with darbepoetin alfa to raise hemoglobin to 13g/dL.[28] TREAT plans to enroll and follow 4000 subjects for sufficient duration so that approximately 1200 primary, centrally adjudicated endpoints are accumulated to test this hypothesis at a power of 80%, to detect a 20% reduction in the above composite cardiovascular events with randomization (intention to treat) to darbepoetin alfa. A portion of the alpha was also prespecified to address the influence of this erythropoietin therapy on the risk of progressing to dialysis or dying. The target hemoglobin for the active therapy group is 13g/dL, whereas the placebo group will receive subcutaneous injections of inactive vehicle unless their hemoglobin falls below 9 g/dL. Blinding and dose titrations (twice monthly or monthly) will be managed by using an interactive, voice-recognition-system algorithm directing usage of prefilled syringes. Endpoints will be adjudicated by an expert committee without knowledge of assignment or hemoglobin levels.

Fortunately, there will be other important sources generating data regarding the potential impact on cardiovascular disease from the treatment of anemia in patients with CKD. The Cardiovascular Risk Reduction in Early Anemia Treatment with Epoetin beta (CREATE) randomized approximately 600 patients with

Table 1
Randomized Clinical Trials of Anemia Therapy in Chronic Kidney Disease

	CREATE (n = 600)	CHOIR (n = 1350)	TREAT (n = 4000)
Primary Composite Endpoint	All-cause mortality or CV morbidity: (Change in echo LV mass)	All-cause mortality or CV morbidity: MI, Stroke, Heart Failure	All-cause mortality or CV morbidity: MI, Stroke, Heart Failure, Myocardial Ischemia
eGFR at entry ($mL/min/1.73m^2$)	15-30	15-50	20-60
DM	20% DM	~ 60% DM	100% DM
Hemoglobin (g/dL)			
Entry	11-12.5	< 11	≤ 11
Target	13-15 vs. 10.5-11.5	13.5 vs. 11.3	13 vs. Placebo unless Hb < 9
# of CV Endpoints	105	N/A	Projected: 1200

CREATE, Cardiovascular Risk Reduction by Early Anaemia Treatment with Epoetin-β; CHOIR, Correction of Hemoglobin and Outcomes in Renal Insufficiency; TREAT, Trial to Reduce Cardiovascular Events with Aranesp Therapy; CV, cardiovascular; DM, diabetes mellitus; Hb, hemoglobin; MI, myocardial infarction; LV, left ventricular, eGFR, estimated glomerular filtration rate.

anemia and CKD to either partial (hemoglobin target 10.5-11.5 g/dL) or more complete correction of anemia (hemoglobin target 13-15g/dL).[29] With 2.5 years of follow-up, there were a total of 105 cardiovascular events and no significant difference was demonstrated between groups. The higher hemoglobin group was associated with improvements in the secondary endpoint of quality of life. However, more of these patients experienced progression of renal disease to require dialysis.

The Correction of Hemoglobin and Outcomes In Renal Insufficiency (CHOIR) trial is another important RCT designed to determine whether targeting a higher hemoglobin level with an erythropoietic agent in patients with CKD (estimated glomerular filtration rate 15-50 mL/min/1.73 m^2) would favorably impact mortality and cardiovascular morbidity.[30] This trial of approximately 1350 patients also did not have a placebo arm and randomized to either partial or higher hemoglobin targets utilizing different doses of recombinant human erythropoietin (epoetin).

Although addressing a similar composite cardiovascular endpoint, TREAT differs in that it is placebo-controlled. TREAT is also unique in that it is an event-driven trial, with almost double the number of patients in the combined experience that will be obtained from CREATE and CHOIR (Table 1). Even more important than the number of patients is the actual number of clinical outcome events, as there are several examples in cardiovascular medicine where a larger (by endpoints) RCT did not confirm the observation of a smaller trial.[3,31] As such, TREAT should provide the most robust test of the hypothesis that raising hematocrit with an ESP in patients with CKD and anemia can favorably reduce cardiovascular as well as renal risk.

Conclusion

Patients with diabetes and CKD are a vulnerable high-risk cohort for premature death as well as major nonfatal cardiac and renal events. These patients benefit from an aggressive multidisciplinary approach to all of their currently considered, classic modifiable risk factors.[32] Anemia is a readily identifiable surrogate associated with even higher rates of adverse clinical outcomes. Because ESP can raise hematocrit, it is imperative to definitively determine the risk: benefit ratios of these available therapies in this expanding patient population. To accept a benefit based on the existing data may be exposing patients to an expensive therapy that is either ineffective or may even contributes to adverse outcomes. On the other hand, to accept harm based on existing data may deny patients the ability to improve their prognosis as well as quality of life. The public health importance of these questions should stimulate the medical community to cooperate and support adequately powered RCTs so that this current state of uncertainty can be replaced by high quality, definitive data. ■

References

1. Devereaux PJ, Yusuf S. The evolution of the randomized controlled trial and its role in evidence-based decision making. *J Intern Med*. 2003;254:105-113.
2. Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? *Ann Intern Med*. 1996;125:605-613.
3. Ioannidis JP. Contradicted and initially stronger effects in highly cited clinical research. *JAMA*. 2005;294:218-228.
4. Grodstein F, Stampfer M. The epidemiology of coronary heart disease and estrogen replacement in postmenopausal women. *Prog Cardiovasc Dis*. 1995;38:199-210.
5. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288: 321-333.
6. Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. *N Engl J Med*. 1991;324:781-788.
7. Packer M, Narahara KA, Elkayam U, et al. Double-blind, placebo-controlled study of the efficacy of flosequinan in patients with chronic heart failure. Principal Investigators of the REFLECT Study. *J Am Coll Cardiol*. 1993;22:65-72.
8. Massie BM, Berk MR, Brozena SC, et al. Can further benefit be achieved by adding flosequinan to patients with congestive heart failure who remain symptomatic on diuretic, digoxin, and an angiotensin converting enzyme inhibitor? Results of the flosequinan-ACE inhibitor trial (FACET). *Circulation*. 1993;88:492-501.
9. FDA Drug and Biologic Approvals-1992. www.fda.gov/bbs/topics/ANSWERS/ANS00463.html.
10. van Veldhuisen DJ, Poole-Wilson, PA. The underreporting of results and possible mechanisms of "negative" drug trials in patients with chronic heart failure. *Inter J Cardiol*. 2001;80:19-27.
11. Cohn JN, Goldstein SO, Greenberg BH, et al. A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure. Vesnarinone Trial Investigators. *N Engl J Med*. 1998;339:1810-1816.
12. Smith GC, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. *BMJ* 2003;327:1459-1461.
13. Califf RM, Peterson ED, Gibbons RJ, et al. Integrating quality into the cycle of therapeutic development. *J Am Coll Cardiol*. 2002;40:1895-1901.
14. Keith DS, Nichols GA, Gullion CM, et al. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med*. 2004;164:659-663.
15. Abramson JL, Jurkovitz CT, Vaccarino V, et al. Chronic kidney disease, anemia, and incident stroke in a middle-aged, community-based population: the ARIC Study. *Kidney Int*. 2003;64:610-615.
16. McCullough PA, Lepor NE. Piecing together the evidence on anemia: the link between chronic kidney disease and cardiovascular disease. *Rev Cardiovasc Med*. 2005;6:S4-S12.
17. Weiner DE, Tighiouart H, Vlagopoulos PT, et al. Effects of anemia and left ventricular hypertrophy on cardiovascular disease in patients with chronic kidney disease. *J Am Soc Nephrol*. 2005; 16:1803-1810.
18. Cody J, Daly C, Campbell M, et al. Recombinant human erythropoietin for chronic renal failure anaemia in pre-dialysis patients. *Cochrane Database Syst Rev*. 2005:CD003266.
19. Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med*. 1987;317:141-145.
20. Sackett DL. Equipoise, a term whose time (if it ever came) has surely gone. *CMAJ*. 2000;163: 835-836.
21. Anand I. Pathogenesis of anemia in cardiorenal disease. *Rev Cardiovasc Med*. 2005;6:S13-S21.
22. Gouva C, Nikolopoulos P, Ioannidis JP, Siamopoulos KC. Treating anemia early in renal failure patients slows the decline of renal function: a randomized controlled trial. *Kidney Int*. 2004;66:753-760.
23. Heeschen C, Aicher A, Lehmann R, et al. Erythropoietin is a potent physiologic stimulus for endothelial progenitor cell mobilization. *Blood*. 2003;102:1340-1346.
24. Goldschmidt-Clermont P, Diehl A. Arterial homeostasis, inflammation, and erythropoietic growth factors. *Rev Cardiovasc Med*. 2005;6: S22-S26.
25. Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med*. 1998;339:584-590.
26. Leyland-Jones B, BEST Investigators. Breast cancer trial with erythropoietin terminated unexpectedly. *Lancet Oncology*. 2003;5:206-207.
27. Henke M, Laszig R, Rube C, et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. *Lancet*. 2003;362:1255-1260.

Main Points

- Therapeutic approaches considered "state-of-the-art" based on strong epidemiological associations or surrogate endpoints from smaller trials can be exposed as ineffective when tested via randomized controlled clinical trials (RCTs).
- Recent experiences with hormone replacement therapy in post-menopausal women and the positive inotropic agent flosequinan in heart failure patients illustrate the need to test surrogate associations of benefit for all therapies with rigorous RCTs.
- In the absence of definitive RCT data, expert guidelines can be used to determine the best course of therapy. However, guidelines should be viewed as documents in a constant state of revision, based on the latest and best information.
- Multiple studies designate the degree of anemia as a readily quantifiable marker of risk in patients with chronic kidney disease (CKD) and the development of erythropoietic therapies that are effective in raising hematocrit levels makes low hemoglobin a particularly attractive therapeutic target.
- The Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) is a multicenter, double-blind, placebo-controlled RCT specifically designed to determine whether patients with CKD, type 2 diabetes, and anemia will experience a reduction in the risk of the composite endpoint of death or cardiovascular morbidity when treated with darbepoetin alfa to raise hemoglobin to 13 g/dL.
- TREAT will enroll 4000 subjects and, along with data generated from the Cardiovascular Risk Reduction by Early Anaemia Treatment with Epoetin β (CREATE) and Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) studies, should definitively answer any questions regarding the efficacy of anemia therapy with recombinant human erythropoietin in pre-dialysis CKD patients.

28. Mix TC, Brenner RM, Cooper ME, et al. Rationale—Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT): evolving the management of cardiovascular risk in patients with chronic kidney disease. *Am Heart J*. 2005;149:408-413.
29. Macdougall IC. CREATE: new strategies for early anaemia management in renal insufficiency. *Nephrol Dial Transplant*. 2003;18(Suppl 2): ii13-16.
30. Singh AK, Bhaduri S, Day B, et al. The CHOIR study: Health related quality of life (HRQOL) in patients with anemia of chronic kidney disease. *JASN*. 2003;14:456a.
31. Pitt B, Poole-Wilson PA, Segal R, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II. *Lancet*. 2000;355:1582-1587.
32. Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med*. 2003;348:383-393.