

4. Sandham JD, Hull RD, Brant RF, et al. A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. *N Engl J Med* 2003;348:5-14.
5. Richard C, Warszawski J, Anguel N, et al. Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2003;290:2713-20.
6. Cooper DJ, Rosenfeld JV, Murray L, et al. Decompressive craniectomy in diffuse traumatic brain injury. *N Engl J Med* 2011;364:1493-502. [Erratum, *N Engl J Med* 2011;365:2040.]

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Trials in Kidney Disease — Time to EVOLVE

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Patients with kidney disease face a substantially increased risk of cardiovascular events and death¹ — one in five patients who are undergoing dialysis die each year in the United States.² Elevated parathyroid hormone levels are almost universal in persons with advanced kidney failure and have been associated with these risks.³ Cinacalcet is an oral calcimimetic agent approved by the Food and Drug Administration (FDA) in 2004 for the treatment of secondary hyperparathyroidism in patients with dialysis-dependent kidney failure. Early reports^{4,5} supported the possibility that cinacalcet conferred cardiovascular protection and reduced fracture risk, although the statistical power of these studies was limited.

In the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial, now reported in the *Journal*, Chertow et al.⁶ tested the hypothesis that cinacalcet, as compared with placebo, would reduce the risk of death and cardiovascular events in dialysis-dependent patients with hyperparathyroidism. The trial enrolled 3883 participants from many countries and followed them for up to 5 years.

Among patients in the cinacalcet group, the nonsignificant relative reduction in the primary outcome of 7% (odds ratio, 0.93; 95% confidence interval, 0.85 to 1.02) was disappointing, particularly given the huge effort involved in conducting the study. It is also disappointing that a number of prespecified secondary analyses hint that the trial may have missed the detection of a real benefit. Thus, the results point to a missed opportunity to identify or exclude a protective therapy for patients undergoing dialysis.

No clear effect on fracture was identified, although a reduced risk of calciphylaxis was observed, with low overall rates in both groups (6 vs. 18 events, $P=0.009$). The need for parathyroidectomy was also reduced, although this finding is a matter of indeterminate importance. The sub-

stantially elevated risk of adverse events in the cinacalcet group, including an increased number of neoplastic events, is a cause for concern that requires further analysis.

Why was the primary result of the trial negative? The surprising imbalance in baseline characteristics between the two groups may well have had an effect — and probably represents simple bad luck but illustrates the importance of stratification for key prognostic factors. More important were the high rates of treatment crossover during the trial: almost two thirds of patients in the cinacalcet group discontinued active therapy, and one fifth of those in the placebo group started taking commercially available cinacalcet before trial completion. The resultant reduction in the between-group separation in parathyroid hormone levels substantially reduced the power of the trial to test its hypotheses.

The main reasons for early therapy discontinuation were adverse events (18.1% in the cinacalcet group and 13.0% in the placebo group) and administrative decisions or patient requests (21% and 31%, respectively). These rates highlight the challenges of maintaining the involvement of both site investigators and study participants who have multiple coexisting conditions in a long-term trial, suggesting that better models are required.

The large proportion of patients in the placebo group who started taking commercially available cinacalcet is also striking, since although the drug had been approved for use, there has been no clearly demonstrated benefit for patient-level outcomes.⁴ A regulatory process that allowed the agent to be registered and widely used without stronger evidence of efficacy suggests a system failure. It is even more troubling that this system also had a serious effect on the capacity of the EVOLVE trial to define the effects of the drug on definitive clinical outcomes.

Equally problematic is the willingness of the clinical nephrology community to prescribe an unproven agent to large numbers of patients, including those participating in this trial. A better regulatory strategy is needed. A version of the model that has been used in diabetes therapies, in which the FDA has defined the hard outcome-data requirements before and immediately after drug registration,^{7,8} may be worthy of broader consideration.

Where do the EVOLVE results leave the clinician? The trial does not provide clear evidence that cinacalcet provides protection against cardiovascular events and raises questions about the drug's side-effect profile and safety, with a potential underestimation of both effects owing to high crossover rates. Physicians will no doubt continue to prescribe this drug, and patients will continue to take it. Yet neither group will have a clear, objective understanding of the balance between risks and benefits.

The real insights from this study are for clinical trialists and regulators. We need to change the way we study the effects of new drugs and integrate these changes into regulatory processes, guideline development, and clinical practice. If such goals can be achieved, even a negative result from the EVOLVE trial will have had a very positive effect.

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1. Chronic Kidney Disease Prognosis Consortium. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010;375:2073-81.
2. U.S. Renal Data System. USRDS 2012 annual data report. Bethesda, MD: National Institutes of Health, 2012.
3. Palmer SC, Hayen A, Macaskill P, et al. Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with chronic kidney disease: a systematic review and meta-analysis. *JAMA* 2011;305:1119-27.
4. Strippoli GF, Palmer S, Tong A, Elder G, Messa P, Craig JC. Meta-analysis of biochemical and patient-level effects of calcimimetic therapy. *Am J Kidney Dis* 2006;47:715-26.
5. Garside R, Pitt M, Anderson R, et al. The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end-stage renal disease patients on dialysis: a systematic review and economic evaluation. *Health Technol Assess* 2007;11:iii, xi-xiii, 1-167.
6. The EVOLVE Trial Investigators. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. *N Engl J Med* 2012;367:2482-94.
7. Joffe HV, Parks MH, Temple R. Impact of cardiovascular outcomes on the development and approval of medications for the treatment of diabetes mellitus. *Rev Endocr Metab Disord* 2010;11:21-30.
8. Guidance for industry: diabetes mellitus — evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. Silver Spring, MD: Food and Drug Administration, 2008.

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