

# Benazepril Is Safe and Effective in the Treatment of Advanced Renal Insufficiency

Hou FF, Zhang X, Zhang GH, et al. Efficacy and safety of benazepril for advanced chronic renal insufficiency. *N Engl J Med* 2006;354:131–40.

## Study Overview

**Objective.** To evaluate the efficacy and safety of angiotensin-converting enzyme (ACE) inhibitors in patients with advanced renal insufficiency.

**Design.** Randomized, double-blind study.

**Setting and participants.** 422 nondiabetic patients in China with a serum creatinine level between 1.5 and 5 mg/dL, a creatinine clearance (CrCl) between 20 and 70 mL/min/1.73 m<sup>2</sup>, and proteinuria greater than 0.3 g/day were enrolled. After an 8-week run-in period, patients with a serum creatinine level of 1.5 to 3 mg/dL (group 1) received benazepril; those with a serum creatinine level of 3.1 to 5 mg/dL (group 2) were randomized to receive benazepril or placebo. The average follow-up was 3.4 years. In all groups, antihypertensive regimens that excluded ACE inhibitors and angiotensin II receptor blockers were used as needed to maintain blood pressures below 130/80 mm Hg. Etiologies of renal disease were glomerular (60%), hypertensive (20%), polycystic kidney disease (10%), interstitial disease (3%), and other (7%).

**Main outcome measures.** The primary endpoint was a composite of the doubling of the serum creatinine, end-stage renal disease (long-term dialysis or renal transplantation), or death. Secondary endpoints included changes in proteinuria level and progression of renal disease, the latter measured by the reciprocal of the serum creatinine, CrCl, and the Modification of Diet in Renal Disease (MDRD) equation for glomerular filtration rate (GFR).

**Main results.** In group 1, 22 patients (22%) reached the primary endpoint. In group 2, 44 benazepril-treated patients (41%) versus 65 placebo-treated patients (60%) reached the primary endpoint. In group 2, benazepril-treated patients also had statistically significant reductions in proteinuria level ( $P < 0.001$ ) as well as rate of decline of renal function as measured by the reciprocal of the serum creatinine ( $P = 0.02$ ) and the MDRD GFR ( $P = 0.006$ ). Blood pressure was similar in both subgroups with group 2. Benazepril was not associated with an increased likelihood of hyperkalemia.

**Conclusion.** In nondiabetic patients with advanced renal insufficiency, benazepril treatment proved to be effective at slowing the progression of renal disease and was safe.

## Commentary

ACE inhibitors have been shown to slow the progression of chronic renal insufficiency. In 1993, Lewis et al [1] showed that captopril slowed deterioration of renal function in patients with type 1 diabetes, high-level proteinuria (> 500 mg/d), and serum creatinine levels less than 2.5 mg/dL. In 1996, Maschio et al [2] showed that benazepril also slowed the progression of renal insufficiency in patients with mild (CrCl, 46–60 mL/min) to moderate (CrCl, 30–45 mL/min) renal insufficiency due to multiple etiologies. Until now, however, large prospective trials assessing the efficacy and safety of ACE inhibitors in patients with advanced renal insufficiency have been lacking. Physicians have been hesitant to use ACE inhibitors in this subset of patients due to perceived lack of benefit and concerns regarding hyperkalemia.

Hou et al studied the efficacy and safety of the ACE inhibitor benazepril in nondiabetic patients with a serum creatinine level greater than 3 mg/dL. Over a follow-up period averaging 3.4 years, benazepril decreased the composite risk of doubling of serum creatinine, occurrence of end-stage renal disease (long-term dialysis or renal transplantation), and death by 43%. This is equal to an absolute risk reduction of 19% and number needed to treat of 5.

This study was well designed, primary outcomes were relevant, important adverse events were measured, and few patients were lost to follow-up. However, the generalizability of the findings is limited. Patients in this study had low levels of hyperkalemia, but as the accompanying editorial pointed out [3], the initial run-in period excluded those with early evidence of this, and Chinese diets (lower in potassium) and concomitant diuretics may further explain the surprisingly low rates of hyperkalemia despite twice-daily benazepril dosing. Furthermore, the trial's population is clinically different from the U.S. population, where the large majority of chronic renal insufficiency is due to diabetes. Finally, this study was conducted under highly controlled and somewhat artificial conditions. As is the case with so many clinical trials,

the next step is an effectiveness study—real-world experience with patients with multiple comorbidities and varying levels of compliance; in such a situation, the balance between number needed to treat and number needed to harm (ie, extra cases of hyperkalemia) will be quite different [4].

### Applications for Clinical Practice

If doctors can ensure close monitoring for hyperkalemia, nondiabetic patients with advanced chronic kidney disease (stage IV, GFR 15–29 mL/min) can be treated with ACE inhibitors. Whether or not these findings apply to diabetic patients with advanced renal insufficiency, the most common cause of end-stage renal disease in the United States, still needs to be determined.

—Review by Natalie K. Levy, MD (New York University School of Medicine), and Nirav R. Shah, MD, MPH

### References

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