Benazepril was effective and safe for advanced chronic kidney disease without diabetes

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.

Clinical impact ratings: GIM/FP/GP ★★★★★★☆ Nephrology ★★★★★☆☆

QUESTION

In patients with advanced chronic kidney disease (CKD) without diabetes, does benazepril delay the progression of renal dysfunction?

METHODS

Design: Randomized placebo-controlled trial.

Allocation: {Concealed}†.*

Blinding: Blinded (patients, outcome assessors, monitoring committee, {data collectors, and data analysts}†).*

Follow-up period: Mean 3.4 years.

Setting: A hospital in Guangzhou, China.

Patients: 224 patients 18 to 70 years of age (mean age 45 y, 50% men) who had a serum creatinine level 3.1 to 5.0 mg/dL (274 to 442 µmol/L) with < 30% change in the previous 3 months, nondiabetic renal disease, and persistent proteinuria and had not received angiotensin-converting enzyme (ACE) inhibitors in the past 6 weeks. Exclusion criteria included immediate need for dialysis; current treatment with corticosteroids, nonsteroidal antiinflammatory drugs, or immunosuppressive drugs; renovascular disease; myocardial infarction or cerebrovascular events within the previous year; connective tissue disease; and obstructive uropathy.

Intervention: Benazepril, 10 mg twice daily (n = 112), or placebo (n = 112). All patients had an 8-week run-in phase (benazepril, 10 mg/d for 4 wk; then 10 mg twice daily for 4 wk) and a 3-week treatment wash-out period before the trial started. All patients received open-label antihypertensive drugs to maintain systolic blood pressure < 130 mm Hg and diastolic blood pressure < 80 mm Hg and were advised to restrict intake of sodium chloride (5 to 7 g/d), protein (0.5 to 0.7 g/kg per d), and foods rich in potassium.

Outcomes: A composite endpoint of doubling of serum creatinine level from baseline, end-stage renal disease, or death. Secondary outcomes included urinary protein excretion, renal function, glomerular filtration rate (GFR), and adverse events.

Patient follow-up: 96% (intention-to-treat analysis).

MAIN RESULTS

Fewer patients in the benazepril group had the primary composite endpoint than did those in the placebo group (Table). Benazepril led to a greater reduction in proteinuria (52% vs 20%, P < 0.001) and delayed rates of decline in renal function (median slope –0.09 vs –0.11 dL/mg per y, P = 0.02) and GFR (6.8 vs 8.8 mL/min per 1.73 m^2, P = 0.006) more than placebo. Groups did not differ for adverse events (death, nonfatal cardiovascular events, hyperkalemia, acute decline in renal function, dry cough, and hypotension).

CONCLUSION

In patients with advanced chronic kidney disease without diabetes, benazepril delayed the progression of renal dysfunction.

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*See Glossary.

†Information provided by author.

Benazepril vs placebo for advanced chronic kidney disease without diabetes at mean 3.4 years‡

Outcome	Benazepril	Placebo	RRR (95% CI)	NNT (CI)
Composite endpoint§	41%	61%	31% (7.0 to 68)	6 (3 to 24)

‡Abbreviations defined in Glossary; RRR, NNT, and CI calculated from control event rate in article and hazard ratio provided by author.

§Doubling of serum creatinine level from baseline (12% vs 20%), end-stage renal disease (29% vs 40%), or death (0.9% vs 0.0%). Event rates for creatinine and end-stage renal disease provided by author.

COMMENTARY

Use of ACE inhibitors or angiotensin-receptor blockers (ARBs) is 1 of the few interventions proven to retard CKD progression. However, these agents are underutilized among patients with advanced CKD (1), perhaps because of an exaggerated fear of an increase in serum creatinine and hyperkalemia associated with angiotensin blockade. Many physicians fail to distinguish between an acute increase in serum creatinine because of a hemodynamically induced decrease in glomerular filtration and an increase in serum creatinine caused by progressive renal parenchymal damage. The former is reversible and reflects a beneficial reduction in glomerular hypertension. Hyperkalemia can often be managed with diuretics, a low-potassium diet, and avoidance of nonsteroidal antiinflammatory drugs.

The study by Hou and colleagues is important because it shows that ACE inhibitors are safe and effective in advanced CKD, at least in a trial. These results are consistent with a post hoc analysis from an earlier Italian trial (2). They are also consistent with clinical experience whereby some patients can be treated with ACE inhibitors or ARBs until they commence dialysis therapy.

The trial by Hou and colleagues was done in China. Most patients with CKD do not live in North America or Europe (3), and provision of renal replacement therapy would be expensive in many developing countries. Hence, appropriate application of proven effective therapies to retard progression of CKD will be critical and literally life-saving.

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