Combination ACE inhbitor and angiotensin-receptor blocker therapy was better than monotherapy in nondiabetic renal disease

Nakao N, Yoshimura A, Morita H, et al. **Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomised controlled trial.** Lancet. 2003;361:117-24.

QUESTION

In patients with nondiabetic renal disease, what is the effectiveness of the angiotensin II–receptor blocker (ARB) losartan, the angiotensin-converting enzyme (ACE) inhibitor trandolapril, or the 2 drugs combined for delaying disease progression?

DESIGN

Randomized (unclear allocation concealment*), blinded (clinicians, patients, data collectors, and monitoring committee),* controlled trial with 3-year follow-up.

SETTING

Hospital outpatient renal clinic serving 3 cities in Japan.

PATIENTS

301 patients 18 to 70 years of age who had chronic nondiabetic renal insufficiency, persistent proteinuria, and no history of allergic reaction to drugs. Exclusion criteria included immediate need for renal replacement therapy; need for corticosteroids, nonsteroidal antiinflammatory drugs, or immunosuppressive drugs; proteinuria > 10 g/d and hypoalbuminemia < 28 g/L; other serious disease; and pregnancy or breastfeeding. 263 patients (mean age 45 y, 54% men) completed an 18-week run-in period and were randomized. Follow-up of these patients was 97%.

INTERVENTION

Patients were allocated to losartan, 100 mg/d plus placebo (n = 89); trandolapril, 3 mg/d plus placebo (n = 86); or a combination of losartan, 100 mg, and trandolapril, 3 mg/d (n = 88).

MAIN OUTCOME MEASURES

A combined endpoint of time to doubling of serum creatinine level or end-stage renal disease (ESRD) (glomerular filtration rate < 7 mL/min per 1.73 m^2 or implementation of dialysis). Secondary outcomes were changes in blood pressure and urinary protein excretion, and adverse effects.

MAIN RESULTS

Analysis was by intention to treat. At 3 years, fewer patients who received combination treatment reached the combined endpoint than did patients who received either drug with placebo (Table). Blood pressure did not differ between groups. Patients in the combination treatment group had the greatest decrease in urinary protein excretion rate (maximum decrease 75%) compared with losartan alone (42%) and trandolapril alone (44%). Groups did not differ for adverse effects, and no patient had an acute decline in renal function.

CONCLUSION

In patients with nondiabetic renal disease, losartan and trandolapril combined were better than either drug alone for delaying disease progression.

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*See Glossary.

Combination therapy vs losartan or trandolapril alone for nondiabetic renal disease at 3 years†

Outcome	Comparisons	Event rates	RRR (95% CI)	NNT (CI)
Combined endpoint	Combination therapy vs losartan	11% vs 23%	49% (0.5 to 75)	9 (5 to 1722)
	Combination therapy vs trandolapril	11% vs 23%	50% (1.7 to 75)	9 (5 to 359)

†Combined endpoint = time to doubling of serum creatinine level or end-stage renal disease. Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

COMMENTARY

ACE inhibitors are standard therapy for slowing the progression of nondiabetic renal disease, and this benefit is mediated by factors in addition to lowering blood pressure and urinary protein excretion (1). The possibility that additional reductions in the rate of progression are achievable has led to consideration of the combination of an ACE inhibitor with an ARB. Several small short-term studies have shown an improved antiproteinuric effect and the safety of this combination therapy.

The COOPERATE study confirms these findings and reports a remarkable reduction of the long-term combined outcome of doubling of serum creatinine or ESRD with combination therapy compared with either drug alone. Only 1 of 85 patients in the combination therapy group reached ESRD at 3 years. These results were achieved with excellent blood pressure control (125/72 mm Hg during the trial), marked dietary protein restriction, and the use of maximum doses of both classes of drugs.

Previous studies of ACE inhibitors (2, 3) were designed to achieve diastolic blood pressures < 90 mm Hg with submaximal doses and showed less compliance with low-protein diets than did the COOPERATE trial. The generalizability of this study is hampered by the relatively young age of the patients (mean age 45 y) and the preponderance of glomerular renal disease, primarily IgA nephropathy, an uncommon cause of ESRD in Europe and North America. Future studies evaluating combination therapy need to include older patients with underlying nephrosclerosis before this promising approach can be recommended as a safe and effective therapy for nondiabetic renal disease.

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References

1. **Jafar TH, Schmid CH, Landa M, et al.** Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. Ann Intern Med. 2001;135:73-87.
2. **Ruggenenti P, Perna A, Gherardi G, et al.** Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. Lancet. 1999;354:359-64.
3. **Maschio G, Alberti D, Janin G, et al.** Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group. N Engl J Med. 1996;334:939-45.