

Combined treatment with angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers to prevent end-stage kidney disease in patients who do not have diabetes

Trial: 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 randomized controlled trial. Lancet 2003; 361: 117-124.

Question

In patients without diabetes, but with impaired renal function and proteinuria, does combination treatment with the angiotensin-converting enzyme (ACE) inhibitor trandolapril and the angiotensin-receptor blocker (ARB) losartan prevent deterioration of renal function more effectively than treatment with either agent used alone?

Trial details

Design: Randomised controlled trial.

Setting: Outpatient clinics in Kisarazu, Kimitsu and Futtsu (Japan).

Participants: 263 patients (mean age about 45 years; 54% men) with non-diabetic biopsy-proven renal disease, impaired renal function (creatinine clearance rate, 20–70 mL/min), persistent proteinuria > 0.3 g/24 h, and hypertension. Patients with proteinuria > 10 g/24 h, renovascular or malignant hypertension, urinary tract infection, heart failure or myocardial infarction, connective tissue disease, chronic hepatic or pulmonary disease, cancer and those pregnant or breastfeeding were excluded.

Duration: 36 months.

Main outcome measures: Combined endpoint of end-stage kidney disease (ESRD) or doubling of serum creatinine level, death and proteinuria.

Main results: At 3 years' follow-up, 10 (11%) of 85 patients receiving combination treatment reached the combined primary endpoint, compared with 20 (23%) of 85 taking trandolapril alone (hazard ratio, 0.38; 95% CI, 0.18–0.63) and 20 (23%) of 86 taking losartan alone (hazard ratio, 0.40; 95% CI, 0.17–0.69). Proteinuria decreased significantly in all treatment groups, but the effect was greatest with combination treatment; the maximum median change in daily urinary protein excretion was –42.1% with losartan, –44.3% with trandolapril and –75.6% with the combination treatment ($P=0.01$). There was no significant difference in the mean fall in systolic blood pressure (losartan, –5.1 mmHg [standard deviation, 1.6]; trandolapril, –5.2 mmHg [SD, 1.3] mmHg; combination, –5.3 mmHg [SD, 1.4]) and diastolic blood pressure (losartan, –2.9 mmHg [SD, 0.9]; trandolapril, –2.9 mmHg [SD, 0.8]; combination, –3.0 mmHg [SD, 0.7]) among the three groups.

Conclusion: Combining ACE inhibitors and ARBs reduces the incidence of the combined end-point of ESRD or doubling of serum creatinine in non-diabetic chronic kidney disease, with moderate reduction of renal function and moderate proteinuria by at least 30% compared with treatment with either drug alone.

Commentary

Rationale for the trial

The renin–angiotensin system has been implicated in the progression of non-diabetic renal disease, and ACE inhibitors and ARBs have independently been shown in randomised controlled trials to reduce proteinuria and the risk of end-stage kidney disease (ESRD) and doubling of the serum creatinine level. Proteinuria lies in the causal pathway to ESRD; therefore, the antiproteinuric effect of these agents is a component of renoprotection.¹⁻⁶

What needed further exploration was whether the combination of ACE inhibitor and ARB was better than treatment with either agent alone. The COOPERATE trialists postulated an advantage of complete inhibition of the renin–angiotensin system with combination treatment of ACE inhibitor and ARB at maximum dosage.⁷

Trial methods

After an 18-week active run-in period, participants were randomly allocated to ACE inhibitor (trandolapril, 1–3 mg/day plus a lactose placebo), ARB (losartan, 12.5–100 mg/day plus a lactose placebo) or ACE inhibitor (trandolapril, 0.5–3 mg/day) plus ARB (losartan, 12.5–100 mg/day). Run-in was performed to establish safety, adherence and the maximum tolerable dose of ACE inhibitor. There was no run-in period for the ARB, and the maximum tolerable dose was chosen on the basis of a previous study.⁸

Information essential for assessing the quality of the trial was missing from the methods section. The trialists detailed their randomisation technique, but the methods by which the randomised intervention was allocated to the patients — such as use of sequentially labelled, sealed, opaque envelopes, or a central or pharmacy randomisation, which would guarantee concealment — was not specified. Patients and investigators were blinded by the drugs being dispensed in identical containers, but there was no mention of whether the capsules themselves were similar. There was also no indication of blinding of the outcome assessors. Analysis was reported as intention-to-treat, but six of 263 patients (who could have had outcomes measured) were actually excluded from the trial because of “protocol invalidation” or “discontinuation”, and so analysis was “per-protocol” and not intention-to-treat. Overall, seven of 301 (2.3%) patients were lost to follow-up, a small number which was unlikely to cause any differences in the final results of the trial.

The authors performed a subgroup analysis to assess whether the effect of combination treatment compared with single therapy with ACE inhibitor or ARB was affected by the degree of baseline proteinuria. Their methods for this subgroup analysis and report-

ing of results were incorrect and misleading, although common. They analysed the three groups separately, and showed no statistically significant benefit of combination treatment in patients with low grade (<1 g/24 h) proteinuria (hazard ratio, 0.69; 95% CI, 0.22–2.28), and statistically significant benefit in patients with moderate (1–3 g/24 h) proteinuria (hazard ratio, 0.33; 95% CI, 0.19–0.74) and heavy (>3 g/24 h) proteinuria (hazard ratio, 0.40; 95% CI, 0.21–0.84). What they should have done was a formal test of interaction (a statistical assessment of differences in the proportion of an outcome [eg, ESRD] in the three treatment groups across patients with low-grade, moderate or heavy proteinuria).⁹ Given the overlapping confidence intervals in their separate analyses, it is very likely that the test of interaction would have been negative. The absence of demonstrable effect in the lowest-risk stratum is explainable on the basis of lower event rates in this group, and therefore lack of power to detect an effect in this group separately. Urinary protein excretion on a continuous scale in grams per 24 hours (rather than groups) could also have been used as the explanatory variable. This study may also have been relatively underpowered to detect the harms of treatments because of the relatively small sample size (263) and because of the active run-in phase, which would tend to exclude patients at risk of adverse effects from the intervention. Run-in periods are common and very useful for improving the efficiency of trials by selecting patients most likely to comply with treatment and fulfil follow-up requirements. However, if there is an active run-in when patients with adverse effects are not randomised, there may be a systematic underestimation of the true harms of an intervention. Also, only the dose of ACE inhibitor, but not ARB, was established by an active run-in, and the dose of ARB in the combination treatment was not reported clearly. The potential variability of doses makes it possible that outcome differences are related to dose rather than greater efficacy. However, blood pressure — probably the most important confounder — was equalised across the two groups. Finally, in this study, no account was taken of how the effect of ACE inhibitors, ARB, or their combination, may be influenced by histological types of renal disease with different rates of progression.

New information

It is likely that there is an advantage of complete inhibition of the renin–angiotensin system with combined ACE inhibitor and ARB treatment compared with therapy with either drug alone, at maximum doses, in patients without diabetes, but with moderate (1–3 g/24 h) and heavy (>3 g/24 h) proteinuria and moderate to severe renal impairment (creatinine clearance rate, 20–70 mL/min). These findings of the COOPERATE trial are promising, but need to be further explored in light of some of the study's limitations, and the fact that comparative findings in patients with cardiovascular disease are conflicting. In chronic heart failure, combined treatment has proven to be advantageous compared with individual treatment with ACE inhibitors or ARBs.^{10,11} This has not been confirmed in studies of post-myocardial infarction.¹²



Implications for clinical practice

In patients without diabetes who have renal impairment (creatinine clearance rate, 20–70 mL/min; proteinuria, >0.3 g/24 h),

combination treatment with ACE inhibitors and ARBs at their maximum dose appears to be effective and well tolerated. Further studies are awaited to confirm the findings of the COOPERATE trial. In the meantime, combination therapy may prove a useful strategy in patients who continue to have high-grade proteinuria despite maximal doses of ACE inhibitor or ARB.

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Competing interests

None identified.

References

- Anderson S, Rennke HG, Brenner BM. Therapeutic advantage of converting enzyme inhibitors in arresting progressive renal disease associated with systemic hypertension in the rat. *J Clin Invest* 1986; 77: 1993-2000.
- The GISEN group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. *Lancet* 1997; 349: 1857-1863.
- Ruggenenti P, Perna A, Gherardi G, et al. Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. *Lancet* 1999; 354: 359-364.
- 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: 939-945.
- Locatelli F, Carbarns IRI, Maschio G, et al. Long-term progression of chronic renal insufficiency in the AIPRI Extension Study. *Kidney Int* 1997; 52 (Suppl 63): S63-S66.
- Jafar TH, Schmit 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.
- 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 randomized controlled trial. *Lancet* 2003; 361: 117-124.
- Gardman AH, Arcuri KE, Goldberg AI, et al. A randomized, placebo-controlled, double-blind, parallel study of various doses of losartan potassium compared with enalapril maleate in patients with essential hypertension. *Hypertension* 1995; 25: 1345-1350.
- Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *BMJ* 2003; 326: 219.
- McMurray JJ, Ostergren J, Swedberg K, et al for the CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003; 362: 767-771.
- McKelvie RS, Yusuf S, Pericak D, et al. Comparison of candesartan, enalapril, and their combination in congestive heart failure: randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study. The RESOLVD Pilot Study Investigators. *Circulation* 1999; 100: 1032-1034.
- Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril or both in myocardial infarction complicated by heart failure, left ventricular dysfunction or both. *New Engl J Med* 2003; 349: 1893-1906.

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