

Ramipril reduced the rate of progression to end-stage renal disease and overt proteinuria in nondiabetic nephropathy

Ruggenenti P, Perna A, Gherardi G, et al. Renoprotective properties of ACE-inhibition in nondiabetic nephropathies with non-nephrotic proteinuria. *Lancet*. 1999 Jul 31;354:359-64.

QUESTION

In patients with nondiabetic chronic nephropathy and nonnephrotic proteinuria (1 to 2.9 g/24 h), does ramipril reduce the rate of disease progression?

DESIGN

Randomized (unclear allocation concealment*), blinded (patients and clinicians),* placebo-controlled trial with median follow-up of 31 months (Ramipril Efficacy in Nephropathy [REIN] trial).

SETTING

14 clinical centers in Italy.

PATIENTS

186 adults (mean age 50 y, 74% men) with chronic nephropathy and persistent proteinuria (1 to 2.9 g/24 h). Exclusion criteria were use of angiotensin-converting enzyme (ACE) inhibitors in the previous 2 months and use of corticosteroids, nonsteroidal anti-inflammatory drugs, or immunosuppressive drugs in the previous 6 months; urinary tract infections; or overt heart failure. Follow-up was 94%.

INTERVENTION

After a 1-month run-in period, patients were allocated to increasing doses of

ramipril, starting with 1.25 mg/d ($n = 99$) or placebo ($n = 87$). Study drugs were increased or other antihypertensive drugs were added or increased every 2 weeks to achieve a diastolic blood pressure (BP) < 90 mm Hg. All patients were asked to limit sodium intake and to eat 0.6 to 0.8 g protein/kg of body weight per day.

MAIN OUTCOME MEASURES

Change in glomerular filtration rate (GFR) and time to end-stage renal failure. Secondary outcomes were degree of proteinuria, major cardiovascular complications, and mortality.

MAIN RESULTS

Analysis was by intention to treat. Fewer patients in the ramipril group reached end-stage renal failure ($P = 0.01$) or overt proteinuria ($P = 0.005$) than did patients in the placebo group (Table). The groups did not differ for change in GFR (0.26 for ramipril group vs 0.29 mL/min per mo in

the placebo group, $P = 0.6$), mortality, nonfatal cardiovascular events, BP, or adverse effects (12% for ramipril vs 7% for placebo [$P = 0.3$]†).

CONCLUSION

Ramipril reduced the rate of end-stage renal failure and overt proteinuria in patients who had nondiabetic nephropathy with nonnephrotic proteinuria.

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*See Glossary.

† P value calculated from data in article.

Ramipril vs placebo for nondiabetic nephropathy with nonnephrotic proteinuria†

Outcomes at median 31 mo	Ramipril	Placebo	RRR (95% CI)	NNT (CI)
End-stage renal failure	9.1%	20.7%	56.1% (9 to 79)	9 (5 to 69)
> 3 g/24 h proteinuria	15.1%	31.0%	51.2% (15 to 72)	6 (4 to 27)

‡Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

COMMENTARY

Urinary protein excretion is a marker of progressive renal disease and predicts the effect of BP control on the decline of GFR in patients with proteinuria > 1 g/d. ACE inhibitors have shown benefits in patients with chronic nephropathies and hypertension (1, 2). But in most of the early trials, BP was lower in ACE-inhibitor groups than in control groups.

The REIN study was designed to explore the effect of ramipril on progressive renal disease in patients with treated hypertension or normal BP compared with patients with equally controlled BP. Patients were stratified by level of proteinuria because a previous trial that studied ramipril had shown a decrease in the slope of GFR decline for patients with proteinuria > 3 g/d (3). The results for the second stratum of patients (proteinuria 1 to 2.9 g/d) are now available. Despite the lack of significant changes in the slope of GFR decline, ramipril halved the risk for end-stage renal disease without substantial adverse effects. These results support the overall conclusions that, first, ACE inhibition is beneficial in patients with chronic nephropathies and proteinuria and that, second, the extent of the benefit on progressive renal disease is proportional to the

protein excretion rate. These converging results should help to convince specialists as well as general practitioners that strict control of BP is a major therapeutic goal in chronic renal disease and that ACE inhibitors are the drugs of choice in patients with proteinuria.

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