

Angiotensin Receptor Blockers Versus Angiotensin-Converting Enzyme Inhibitors in Type 2 Diabetes for the Prevention of Nephropathy

Barnett AH, Bain SC, Bouter P, et al. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. *N Engl J Med* 2004;351:1952–61.

Study Overview

Objective. To compare the renoprotective effects of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in patients with type 2 diabetes.

Design. Multicenter, double-blind, 5-year trial designed to show noninferiority of telmisartan compared with enalapril.

Setting and participants. 250 subjects with type 2 diabetes and early nephropathy were recruited from 39 centers in northern Europe. Patients aged 35 to 80 years were eligible if they had type 2 diabetes treated with diet, oral hypoglycemics, or insulin; mild to moderate hypertension; normal renal morphology; glomerular filtration rate (GFR) greater than 70 mL/min per 1.73 m² of body surface area; and microalbuminuria (measured by overnight urinary albumin excretion rates between 11–999 µg/min).

Intervention. Patients were randomized to receive either an ACE inhibitor (enalapril 20 mg/day; *n* = 130) or ARB (telmisartan 80 mg/day; *n* = 120). All patients started at half the dose (enalapril 10 mg/day or telmisartan 40 mg/day) and underwent a forced titration after taking study drug for 4 weeks.

Main outcome measures. Change in GFR (determined by iohexol plasma clearance) after 5 years. Secondary endpoints were annual changes in GFR, urinary albumin excretion, serum creatinine, blood pressure, and rates of clinical events (ie, heart failure, end-stage renal disease [ESRD], stroke, myocardial infarction). A clinically significant difference between the 2 groups was predefined as a GFR difference of –10 mL/min. If the lower boundary of the 95% confidence interval (CI) of the difference between the groups was greater than –10 mL/min in favor of enalapril, then telmisartan was judged to be noninferior to the ACE inhibitor.

Main results. After 5 years, the decrement change in GFR was –17.9 mL/min with telmisartan (in 103 subjects) as compared with –14.9 mL/min with enalapril (in 113 subjects), resulting

in a treatment difference of –3.0 mL/min (95% CI, –7.6–1.6). The lower boundary of the CI in favor of enalapril was greater than the predefined margin of –10.0 mL/min, indicating that telmisartan was not inferior to enalapril. The effects of the 2 agents on the secondary endpoints were not significantly different after 5 years.

Conclusion. Telmisartan is not inferior to enalapril in providing renal protection in type 2 diabetes patients, and this finding supports the clinical equivalence of ARB and ACE inhibitor in this setting.

Commentary

Type 2 diabetes mellitus is the leading cause of renal disease, blindness, and nontraumatic amputations and remains the leading cause of dialysis-requiring renal disease in African Americans. In 2001, a total of 142,963 patients with ESRD due to diabetes were living on chronic dialysis or with a kidney transplant. The worldwide incidence of ESRD among patients with type 2 diabetes is expected to double by 2010.

Barnett et al try to answer the question: which drug should be used for treating people with type 2 diabetes and nephropathy? They demonstrate that there was no difference in GFR between those being treated with an ACE inhibitor or those treated with an ARB. They also found no difference in the level of blood pressure control or rate of adverse events between the 2 groups. A limitation noted by the authors is that available GFR data points were carried forward for patients who dropped out of the study after the first year, which would have a tendency to raise the mean GFR over time.

Clinical trials to date have supported the use of either an ACE inhibitor or an ARB in patients with diabetes; however, as the literature shows, the care of patients with type 2 diabetes involves much more than administering these agents. According to data from the National Ambulatory Medical Care Survey, the length of the average office visit to the primary care physician is 15 minutes, where there is an increasing array of preventive care priorities as well as management of acute and chronic medical issues for the primary provider

to address, including management of diabetes [1]. Providers are expected to monitor blood pressure, albuminuria, and blood glucose levels. Patients are counseled to lose excess weight and engage in regular exercise. Lowering blood pressure to less than 130/80 mm Hg and blocking the renin-angiotensin system can have an important effect on nephropathy and possibly other complications of type 2 diabetes [2].

Applications for Clinical Practice

The study by Barnett et al provides evidence that there is a progression of renal dysfunction that can be limited through the use of either an ACE inhibitor or an ARB in patients with type 2 diabetes and microalbuminuria. Given the clinical

equivalence in this population and the expense of telmisartan (3 times more expensive than enalapril), patients should probably still be given an ACE inhibitor as first-line therapy for the treatment of nephropathy.

—Review by Christianne L. Roumie, MD

References

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2. Mitch WE. Treating diabetic nephropathy—are there only economic issues? *N Engl J Med* 2004;351:1934–6.

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