

CLINICAL UPDATE

Angiotensin-II–receptor blockers and nephropathy in patients with type 2 diabetes

Brenner BM, Cooper ME, De Zeeuw D, Keane WF, Mitch WE, Parving HH, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;345:861-9.

Background: Interference with the renin–angiotensin–aldosterone (RAA) axis through the use of angiotensin-converting-enzyme (ACE) inhibitors has been shown to retard the progress of renal disease in patients with type 1 diabetes mellitus and in those with nephropathy of nondiabetic origin.^{1,2} Although it has become standard practice to use ACE inhibitors in patients with type 2 diabetes, there is a paucity of direct evidence of clinical benefit. Moreover, it is unknown whether comparable renoprotective effects can be achieved by using angiotensin-receptor blockers (ARBs).

Question: Does the ARB losartan, alone or in combination with other antihypertensive medication, confer renal and cardiovascular protection in patients with type 2 diabetes?

Methods: In the RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) study³ subjects aged 31–70 years with type 2 diabetes and nephropathy were randomly assigned to either treatment with losartan, 50–100 mg once daily, or placebo. Nephropathy was defined by the presence of a ratio of urinary albumin (in milligrams per litre) to creatinine (in grams per litre) of at least 300, urinary protein excretion of at least 0.5 g/d or a serum creatinine level of 115–265 µmol/L. Subjects were excluded if they had type 1 diabetes, nondiabetic renal disease, congestive heart failure, a recent coronary event or a cerebrovascular event. Use of other antihypertensive medications (apart from ACE inhibitors and other ARBs) was permitted in order to achieve target blood pressures below 140/90 mm Hg.

Patients were followed up every 3 months, or more often if necessitated by clinical circumstances. The study's primary end point was the time elapsed to a composite outcome of a doubling in serum creatinine level, end-stage renal disease (ESRD) or death. Secondary end points included progression of renal disease, change in level of proteinuria and a composite index of cardiovascular morbidity and mortality. Analysis was performed on an intention-to-treat basis, yielding hazard ratios for the primary and secondary end points.

Results: Of 1513 patients enrolled, 751 received losartan and 762 placebo. Baseline characteristics were comparable. The proportion of patients taking antihypertensive therapy at baseline was 93.5%.

Although the intended duration of observation was 4.5 years, the study was ended after a mean of 3.4 years, when evidence emerged that ACE inhibitors had a beneficial effect on cardiovascular outcome in patients with renal impairment of both diabetic and nondiabetic origin.⁴ By this time, the study had achieved a relative risk reduction (RRR) of 16% (95% confidence interval [CI] 2%–28%) in its primary end point (327 [43.5%] of patients taking losartan v. 359 [47.1%] of those given placebo, $p = 0.02$). Most of the benefit was achieved through losartan's doubling of the serum creatinine level (RRR 25%, 95% CI 8%–39%, $p = 0.006$) and the occurrence of ESRD (RRR 28%, 95% CI 11%–42%, $p = 0.002$). Although no significant difference was observed in cardiovascular morbidity or mortality, losartan was found to reduce the level of proteinuria by 35% ($p < 0.001$) and to slow the rate of decline in renal function by 18% ($p = 0.01$). Adjustment for blood pressure did not alter any of these results significantly. The maximum dose of losartan (100 mg) was required in 79% of patients in the treatment group. Use of the study drug was stopped because of side effects in 17.2% and 21.7% of patients taking losartan and placebo respectively.

Commentary: This study confirms that, in patients with type 2 diabetes and nephropathy, ARBs bestow a renoprotective effect that is independent of their antihypertensive effect. Moreover, these agents appear to be well tolerated, as evidenced by the comparable rates of study drug discontinuation in the 2 groups of the trial. The investigators' decision to omit an ACE-inhibitor arm in their trial has sparked controversy⁵ and makes it impossible to know whether the specific pharmacologic route of intervention in the RAA axis is important in achieving the desired clinical outcome in this patient population. Physiologic considerations and indirect comparison of trial results would suggest that the magnitude of effect is probably comparable.

Practice implications: In patients with type 2 diabetes and nephropathy, losartan slows the progression of renal disease and delays the onset of ESRD, independent of its effect on blood pressure. This agent can now be viewed as an effective and well-tolerated alternative for diabetic patients in whom the use of ACE inhibitors has been limited by side effects. — Donald Farquhar

The Clinical Update section is edited by Dr. Donald Farquhar, head of the Division of Internal Medicine, Queen's University, Kingston, Ont. The updates are written by members of the division.

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