

Review: Angiotensin-converting enzyme inhibitors reduce the progression of nondiabetic renal disease

Jafar TH, Schmid CH, Landa M, et al., for the ACE Inhibition in Progressive Renal Disease Study Group. Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. *Ann Intern Med.* 2001 Jul 17;135:73-87.

QUESTION

In patients with nondiabetic renal disease, are antihypertensive regimens with angiotensin-converting enzyme (ACE) inhibitors effective for slowing the progression of disease?

DATA SOURCES

Studies were identified by searching MEDLINE (May 1977 to September 1997), scanning abstracts in the proceedings of U.S. and international conferences, scrutinizing bibliographies from relevant articles, and contacting investigators for unpublished data.

STUDY SELECTION

English-language randomized controlled trials were selected if they compared the effectiveness of antihypertensive regimens containing ACE inhibitors (enalapril, captopril, benazepril, cilazapril, and ramipril) with that of antihypertensive regimens not containing ACE inhibitors (control group) in patients with nondiabetic renal disease and if they had ≥ 1 year of follow-up.

DATA EXTRACTION

Data were extracted on sample size, patient characteristics, key components of the intervention, and outcomes. Main outcomes included end-stage renal disease (ESRD), defined as the initiation of long-term dialysis therapy, and a composite outcome of a 2-fold increase in serum creatinine levels from

baseline values or ESRD. Secondary outcomes included death and a composite outcome of ESRD or death.

MAIN RESULTS

11 studies (1860 patients; 941 in the ACE-inhibitor group and 919 in the control group) were included in the meta-analysis. The incidence rates of ESRD and the combined end point of doubling of baseline serum creatinine levels or ESRD were lower in the ACE-inhibitor group than in the control group (Table). Groups did not differ for death rates or the composite outcome of ESRD or death (Table).

CONCLUSION

In patients with nondiabetic renal disease, antihypertensive regimens containing angio-

tensin-converting enzyme (ACE) inhibitors are more effective than regimens without ACE inhibitors for slowing the progression of disease.

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For correspondence: Dr. A.S. Levey, Division of Nephrology, New England Medical Center, 750 Washington Street, Box 391, Boston, MA 02111, USA. FAX 617-636-8329. ■

Antihypertensive regimens with angiotensin-converting enzyme (ACE) inhibitors (treatment) vs regimens without ACE inhibitors (control)*

Outcomes at 2 to 4 y	Weighted event rates		RRR (95% CI)	NNT (CI)
	Treatment	Control		
ESRD	10.5%	11.5%	34% (14 to 50)	102 (36 to 114)
Doubling of serum creatinine or ESRD	15.7%	20.3%	34% (18 to 47)	22 (11 to 257)
ESRD or death	11.1%	12.7%	23% (-7 to 45)	Not significant
			RRI (CI)	NNH
Death†	2.4%	1.2%	63% (-219 to 16)	Not significant

*ESRD = end-stage renal disease. Other abbreviations defined in Glossary; RRR, RRI, NNT, NNH, and CI calculated from data provided by author using a random-effects model.

†A fixed-effects model was used.

COMMENTARY

ACE inhibitors slow the progression of renal disease in type 1 diabetes mellitus independent of the effects on blood pressure (BP). Mounting evidence exists that the same is true in type 2 diabetes mellitus. The benefits of ACE inhibitors may result from lowering BP and reducing proteinuria (effects not specific to ACE inhibitors) and by mitigating the direct effects of angiotensin II on glomerular hemodynamics, inflammation, fibrosis, and sclerosis.

Whether ACE inhibitors benefit patients more than do other antihypertensives in nondiabetic renal disease has not been as convincingly shown. In 5 of the 11 trials included in the meta-analysis by Jafar and colleagues, no benefit from ACE inhibitors was seen. The achieved systolic BP and diastolic BP in many of the studies were lower in the ACE-inhibitor-treated groups. Therefore, it could not be concluded that ACE inhibitors were more effective than other antihypertensives, except in their effect on BP.

Patients with greater degrees of proteinuria are at greater risk for progressive renal disease and ESRD. This study and a related meta-analysis by the same authors (1) suggest that ACE inhibitors lower

urinary protein excretion more than other antihypertensive therapies even after controlling for antihypertensive effects. The reduction in proteinuria with ACE inhibitors is greater in patients with higher levels of urinary protein excretion. This probably explains the observation that in nondiabetic renal disease, the ability of ACE inhibitors to slow progression of renal disease is most apparent for patients with heavier proteinuria (≥ 2 to 3 g/d). The same benefit has not yet been shown for patients with urine protein levels < 0.5 g/d.

Sentiment is growing that ACE inhibitors should be the drugs of choice in many hypertensive patients with nondiabetic renal disease and proteinuria. But one important caveat exists: In all but 2 of the studies (both of which are unpublished), 99% to 100% of the patients were white; further studies are needed to determine whether a renoprotective effect of ACE inhibitors is also seen in other populations.

*Jeffrey S. Berns, MD
Presbyterian Medical Center
Philadelphia, Pennsylvania, USA*

Reference

- Jafar TH, Stark PC, Schmid CH, et al. *Kidney Int.* 2001;60:1131-40.