

Review: The renoprotective effects of ACE inhibitors and ARBs independent of blood pressure control are uncertain

Casas JP, Chua W, Loukogeorgakis S, et al. Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. *Lancet*. 2005;366:2026-33.

Clinical impact ratings: GIM/FP/GP ★★★★★☆ Endocrinology ★★★★★☆ Nephrology ★★★★★★

QUESTION

Do angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) have renoprotective effects independent of blood pressure (BP) control?

METHODS

Data sources: MEDLINE, EMBASE/Excerpta Medica, and the Cochrane Library (1960 to January 2005); and references of relevant studies and reviews.

Study selection and assessment: Randomized controlled trials (RCTs) with ≥ 1 year follow-up that examined the effect of drug treatment with a BP-lowering action on progression of renal disease. 127 RCTs (150 comparisons) with mean follow-up of 4.2 years met the selection criteria.

Outcomes: End-stage renal disease (ESRD) (need for kidney transplantation or dialysis) and doubling of serum creatinine.

MAIN RESULTS

Changes in BP were similar across the 5 outcomes; all but 1 showed no difference in the degree of change in systolic and diastolic BP between patients receiving ACE inhibitors or ARBs and those receiving other antihypertensive drugs. ACE inhibitor or ARB treatment led to a reduction in systolic BP of 1.49

mm Hg (95% CI 0.05 to 2.92) in studies with change in creatinine level as an outcome. Patients who received ACE inhibitors or ARBs compared with those who received other antihypertensive drugs had reduced risk for ESRD, and a nonsignificant trend for doubling of creatinine (Table) with smaller (compared with larger) trials showing larger benefit with ACE inhibitors or ARBs. Among placebo-controlled RCTs, ACE inhibitors and ARBs lowered risk for ESRD and doubling of creatinine, and also led to

reductions in BP (Table). Similar results occurred in patients with diabetes.

CONCLUSION

The renoprotective effects of angiotensin-converting enzymes and angiotensin-receptor blockers independent of their effect on blood pressure control are uncertain.

Source of funding: No external funding.

For correspondence: Dr. J.P. Casas, London School of Hygiene and Tropical Medicine, London, England, UK. E-mail juan.pablo-casas@lshtm.ac.uk. ■

Angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) vs other antihypertensive drugs or placebo for progression of renal disease at mean 4.2 years*

Comparisons	Outcomes	Number of trials (n)	Weighted event rates	RRR (95% CI)	NNT (CI)	Mean difference in change in SBP (mm Hg [CI])
ACE inhibitors or ARBs vs other antihypertensive drugs	ESRD	13 (37 089)	1.7% vs 2.0%	13% (1 to 25)	385 (200 to 5000)	-1.32 (-4.03 to 1.38)
	Doubling of creatinine	11 (3376)	8.0% vs 11.3%	29% (-4 to 51)	Not significant	-0.97 -3.09 to 1.14
ACE inhibitors or ARBs vs placebo	ESRD	9 (12 564)	4.8% vs 6.4%	25% (14 to 34)	63 (46 to 112)	-2.69 (-4.51 to -0.88)
	Doubling of creatinine	10 (13 082)	6.1% vs 8.6%	29% (12 to 43)	40 (27 to 97)	-2.27 (-4.02 to -0.52)

*ESRD = end-stage renal disease; SBP = systolic blood pressure. Other abbreviations defined in Glossary; RRR, NNT, and CI calculated from relative risks in article using a fixed-effects model.

COMMENTARY

A number of considerations make the results of Casas and colleagues less surprising and practice-altering than first reading would suggest. First, some of the patients in the included studies were at relatively low risk for progression of renal disease. In such patients, the therapeutic focus is on prevention of vascular events, which are common. These outcomes were not considered in this review, but have been previously summarized: No difference was found for prevention of stroke or coronary disease when ACE inhibitors were compared with diuretics or β-blockers (1). Thus, results for the prevention of ESRD are in keeping with results for vascular disease, and do not alter the currently recommended practice of using a diuretic as first-line treatment for hypertension. However, certain populations at increased risk for vascular events have been shown to benefit from renin-angiotensin system (RAS) interruption (2), and the results of the review by Casas and colleagues should not deter clinicians from using these agents to prevent vascular events in such patients.

Second, although confounded by BP control, prevention of ESRD by RAS interruption in the placebo-controlled comparisons may still be important because, from an intention-to-treat standpoint, strict BP lowering per se may not confer a benefit in preventing vascular or renal events (1, 3). The results of this meta-analysis are in keeping with placebo-controlled trials in patients with more advanced renal disease that

show that RAS interruption prevents renal events. Inhibitors of the RAS can thus still be considered beneficial to patients at risk for progression of renal disease (clearly abnormal glomerular filtration rate for their age, established progression, and proteinuria).

Finally, analyzing studies of ACEs and ARBs together is of mechanistic interest, but from a clinical perspective a selection must be made between the agents. In the prevention of vascular disease in patients with and without diabetes and renal events in patients without diabetes, the weight of evidence lies with the effectiveness of ACE inhibitors rather than ARBs (2, 4). ARBs, on the other hand, have been shown to prevent renal events and some cardiovascular events (heart failure) in patients with diabetes.

*Catherine Clase, MB, BChir
McMaster University
Hamilton, Ontario, Canada
Amit X. Garg, MD, PhD
University of Western Ontario
London, Ontario, Canada*

References

- Turnbull F, Neal B, Algert C, et al. *Arch Intern Med*. 2005;165:1410-9.
- Yusuf S, Sleight P, Pogue J, et al. *N Engl J Med*. 2000;342:145-53.
- Wright JT Jr., Bakris G, Greene T, et al. *JAMA*. 2002;288:2421-31.
- Jafar TH, Schmid CH, Landa M, et al. *Ann Intern Med*. 2001;135:73-87.