

# Review: ACE inhibitors, but not angiotensin II receptor antagonists, reduce all cause mortality in diabetic nephropathy

Strippoli GF, Craig M, Deeks JJ, *et al.* Effects of angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists on mortality and renal outcomes in diabetic nephropathy: systematic review. *BMJ* 2004;**329**:828.

Clinical impact ratings GP/FP/Primary care ★★★★★☆☆ IM/Ambulatory care ★★★★★☆☆ Internal medicine ★★★★★☆☆ Nephrology ★★★★★☆☆ Endocrine ★★★★★☆☆

## Q In patients with diabetic nephropathy, what are the effects of angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists (AIIIRAs)?

### METHODS

**Data sources:** Medline (1966 to September 2003), EMBASE/Excerpta Medica (1988 to September 2003), the Cochrane Library, conference proceedings, and contact with experts.

**Study selection and assessment:** randomised controlled trials (RCTs) in any language of ≥6 months' duration comparing ACE inhibitors or AIIIRAs with placebo, no treatment, or each other in patients with any stage of diabetic nephropathy. Studies were assessed for methodological quality.

**Outcomes:** all cause mortality and renal outcomes.

### MAIN RESULTS

43 RCTs (follow up range 6–96 mo) met the selection criteria; 36 (4008 patients) compared ACE inhibitors with placebo or no treatment, 4 (3331 patients) compared AIIIRAs with placebo or no treatment, and 3 (206 patients) compared ACE inhibitors with AIIIRAs. ACE inhibitors, but not AIIIRAs, reduced all cause mortality more than placebo or no treatment (table). The table shows the effects of ACE inhibitors and AIIIRAs on renal outcomes. ACE inhibitors did not differ from placebo or no treatment for the rate of doubling of serum creatinine levels or of end stage renal disease. Data are lacking on the comparative effects of ACE inhibitors and AIIIRAs on mortality and renal outcomes.

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### CONCLUSION

In patients with diabetic nephropathy, angiotensin converting enzyme inhibitors, but not angiotensin II receptor antagonists, reduced all cause mortality compared with placebo.

### Commentary

Both ACE inhibitors and AIIIRAs have been noted for their anti-proteinuric properties.<sup>1</sup> However, it is unclear whether ACE inhibitors are more renoprotective than AIIIRAs, specifically in patients with diabetic nephropathy; and this is what Strippoli *et al* attempted to address.

In this review, the only large randomised trial to show renoprotection associated with ACE inhibitors involved patients with type 1 diabetes.<sup>2</sup> On the other hand, the only study to show renoprotection associated with ACE inhibitors in type 2 diabetes is limited by the small number of patients and the fact that the patients did not fully satisfy the criteria for diabetic nephropathy.<sup>3</sup> Furthermore, as the authors alluded to, the indirect nature of comparison between ACE inhibitors and AIIIRAs, using placebo as comparator, is a major limitation.

Much heterogeneity existed in the included studies, thus it is quite difficult to make conclusions and actual recommendations based on the data. Certainly, randomised controlled trials that directly compare ACE inhibitors and AIIIRAs in patients with diabetic nephropathy are needed to better settle the issues at hand. Until then, the only recommendations that can be derived from current published data are the use of ACE inhibitors in type 1 diabetes with nephropathy<sup>2</sup> and the use of ACE inhibitors or AIIIRAs in type 2 diabetes with nephropathy.<sup>1, 4</sup>

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- 1 Brenner BM, Cooper ME, de Zeeuw D, *et al.* *N Engl J Med* 2001;**345**:861–9.
- 2 Lewis EJ, Hunsicker LG, Bain RP, *et al.* *N Engl J Med* 1993;**329**:1456–62.
- 3 Ravid M, Savin H, Jutrin I, *et al.* *Ann Intern Med* 1993;**118**:577–81.
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Angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists (AIIIRAs) v placebo or no treatment (control)\*

Outcomes at 6–96 months	Number of trials (n)	Intervention v control	Weighted event rates	RRR (95% CI)	NNT (CI)
All cause mortality	20 (2383)	ACE inhibitors	11.5% v 12.2%	21% (1 to 37)	157 (44 to ∞)
	5 (3409)	AIIIRAs	15.4% v 15.6%	1% (-16 to 15)	NS†
Progression from microalbuminuria to macroalbuminuria	16 (2010)	ACE inhibitors	11% v 22%	54% (29 to 70)	10 (6 to 23)
	3 (761)	AIIIRAs	7.1% v 15%	51% (25 to 68)	14 (9 to 35)
Doubling of serum creatinine	3 (3251)	AIIIRAs	18% v 22%	21% (9 to 31)	32 (14 to ∞)
End stage renal disease	3 (3251)	AIIIRAs	17% v 19%	22% (9 to 33)	37 (16 to ∞)
				<b>RBI (CI)</b>	<b>NNT (CI)</b>
Regression from microalbuminuria to normoalbuminuria	15 (1888)	ACE inhibitors	28% v 10%	202% (83 to 398)	6 (4 to 10)
	2 (670)	AIIIRAs	26% v 18%	42% (5 to 93)	13 (8 to 57)

\*Abbreviations defined in glossary; weighted event rates, RRR, RBI, NNT, and CI calculated from data in article using a random effects model.  
†NS = not significant.