Review: ACE inhibitors delay onset of microalbuminuria in diabetes without nephropathy and reduce mortality in diabetic nephropathy

Strippoli GF, Craig MC, Schena FP, Craig JC. **Role of blood pressure targets and specific antihypertensive agents used to prevent diabetic nephropathy and delay its progression.** J Am Soc Nephrol. 2006;17:S153-5.

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

QUESTION

Do antihypertensive agents prevent onset of microalbuminuria in patients with diabetes without nephropathy and delay progression in patients with diabetic nephropathy?

METHODS

Data sources: MEDLINE (1966 to September 2003), EMBASE/Excerpta Medica (1988 to September 2003), Cochrane Central Register of Controlled Trials (2004), reference lists, and authors in the field.

Study selection and assessment: Randomized controlled trials (RCTs) in any language comparing an antihypertensive agent with another antihypertensive agent or placebo in diabetic patients with and without nephropathy. 16 RCTs (n = 8570) in diabetic patients without nephropathy and 43 RCTs (n = 7545) in diabetic patients with nephropathy met the selection criteria. Quality assessment of individual studies was based on allocation concealment, intention-to-treat analysis, loss to follow-up, and blinding.

Outcomes: Onset of microalbuminuria, all-cause mortality, end-stage renal disease (ESRD), doubling of serum creatinine, progression from microalbuminuria to macroalbuminuria, regression from microalbuminuria to normalbuminuria, cough, headache, hyperkalemia, and impotence.

MAIN RESULTS

Meta-analysis using a random-effects model showed that angiotensin-converting enzyme (ACE) inhibitors were more effective than calcium antagonists or placebo for preventing onset of microalbuminuria (Table). ACE inhibitors and β-blockers did not differ for onset of microalbuminuria (1 RCT, n = 299; relative risk 1.01, 95% CI 0.74 to 1.37) in diabetic patients without nephropathy. In diabetic patients with nephropathy, ACE inhibitors reduced all-cause mortality more than placebo, but angiotensin-receptor blockers (ARBs) did not (Table). Both ACE inhibitors and ARBs reduced progression from micro- to macroalbuminuria, and ARBs reduced risk for ESRD and doubling of creatinine more than placebo.

CONCLUSION

Angiotensin-converting enzyme inhibitors delay onset of microalbuminuria in diabetic patients without nephropathy and reduce all-cause mortality in diabetic patients with nephropathy.

Sources of funding: Cochrane Renal Group and Australia/Europe Endeavour Scholarship.

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Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) vs calcium antagonists (CAs) or placebo for diabetes with and without nephropathy*

Outcomes	Comparisons	Number of trials (n)	Relative risk (95% CI)
Onset of microalbuminuria in diabetes without nephropathy	ACE inhibitors vs CAs	4 (1210)	0.58 (0.40 to 0.84)
	ACE inhibitors vs placebo	6 (3840)	0.60 (0.43 to 0.84)
All-cause mortality in diabetic nephropathy	ACE inhibitors vs placebo	20 (2838)	0.79 (0.63 to 0.99)
	ARBs vs placebo	4 (3329)	0.99 (0.85 to 1.17)†

*CI defined in Glossary.
†Not significant.

COMMENTARY

Choosing antihypertensive treatment can be difficult because of conflicting evidence in the literature, comorbid conditions of patients, and competing drug class benefits. Strippoli and colleagues used meta-analysis to examine whether ACE inhibitors or ARBs have advantages over other classes for cardiorenal endpoints in patients with diabetes. They concluded that the use of ACE inhibitors or ARBs protected the kidneys, and that ACE inhibitors reduced all-cause mortality. These conclusions are similar to their previous work (1, 2), but stand in stark contrast to a meta-analysis by Casas and colleagues that showed that the renal-sparing effects of ACE inhibitors and ARBs were only present in placebo-controlled trials, and vanished with active comparators or when blood pressure control was taken into account (3).

Conflicting conclusions can sometimes be resolved by applying the "face validity test"—that is, are only trials that have similar populations, interventions, and outcomes being included in the analysis? In a meta-analysis, the test for heterogeneity can determine whether the statistical properties of the trials weigh against their combination. However, trials passing this test should not automatically be combined. In the meta-analysis by Casas and colleagues (3), about 85% of the patients came from ALLHAT, a trial that excluded patients with severe renal disease and in whom ESRD was unexpected. Such a trial should not be included in an analysis of ESRD prevention. Trial selection also influenced Strippoli and colleagues' conclusion that ACE inhibitors but not ARBs reduced mortality in diabetes. The ACE inhibitor trials included the large cardiovascular-oriented HOPE study, which excluded severe renal disease. The smaller renal-oriented ARB trials only included patients with advanced renal disease—a population in which other cardioprotective therapies had failed. Both Casas' conclusions regarding the lack of efficacy of ACE inhibitors and ARBs beyond control of hypertension, and Strippoli's conclusions about the differential cardioprotective effects of ACE inhibitors and ARBs, are suspect for these reasons.

Meta-analysis is a powerful method for combining the results of clinical trials. The face validity test is more powerful than the statistical test of heterogeneity in determining whether sufficiently similar trials have been included.

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References

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3. **Casas JP, Chua W, Loukogeorgakis S, et al.** Lancet. 2005;366:2026-33.