

Primary care

Effects of angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists on mortality and renal outcomes in diabetic nephropathy: systematic review

Giovanni F M Strippoli, Maria Craig, Jonathan J Deeks, Francesco P Schena, Jonathan C Craig

NHMRC Centre for Clinical Research Excellence in Renal Medicine, Cochrane Renal Group, Children's Hospital at Westmead, Westmead, NSW 2145, Australia
Giovanni F M Strippoli
editor of Cochrane Renal Group
Maria Craig
endocrinologist
Jonathan J Deeks
senior research biostatistician
Jonathan C Craig
associate professor of clinical epidemiology

Department of Emergency and Organ Transplantation, Section of Nephrology, University of Bari, Italy
Francesco P Schena
chief

Correspondence to: G F M Strippoli
gfmstrippoli@katamail.com

BMJ 2004;329:828-31

Abstract

Objective To evaluate the effects of angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists (AIIRAs) on renal outcomes and all cause mortality in patients with diabetic nephropathy.

Data sources Medline, Embase, the Cochrane controlled trials register, conference proceedings, and contact with investigators.

Study selection Trials comparing ACE inhibitors or AIIRAs with placebo or with each other in patients with diabetic nephropathy.

Data extraction Mortality, renal outcomes (end stage renal disease, doubling of serum creatinine concentration, prevention of progression of microalbuminuria to macroalbuminuria, remission of microalbuminuria), and quality of trials.

Data synthesis 36 of 43 identified trials compared ACE inhibitors with placebo (4008 patients), four compared AIIRAs with placebo (3331 patients), and three compared ACE inhibitors with AIIRAs (206 patients). We obtained unpublished data for 11 trials. ACE inhibitors significantly reduced all cause mortality (relative risk 0.79, 95% confidence interval 0.63 to 0.99) compared with placebo but AIIRAs did not (0.99, 0.85 to 1.17), although baseline mortality was similar in the trials. Both agents had similar effects on renal outcomes. Reliable estimates of the unconfounded relative effects of ACE inhibitors compared with AIIRAs could not be obtained owing to small sample sizes.

Conclusion Although the survival benefits of ACE inhibitors for patients with diabetic nephropathy are known, the relative effects of ACE inhibitors and AIIRAs on survival are unknown owing to the lack of adequate head to head trials.

Introduction

Large randomised controlled trials have shown that angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists (AIIRAs) delay the progression of diabetic nephropathy by slowing the deterioration of renal function and reducing proteinuria. For this reason they are the most widely used agents in patients with diabetic nephropathy.¹⁻⁵

Nephropathy has been shown to be an independent risk factor for early death due to cardiovascular diseases in diabetic patients.⁶ Microalbuminuria is associated with a twofold to fourfold increase in the risk of death, whereas overt proteinuria and hypertension are associated with an even higher risk when present together.

The Joint National Committee on Prevention, Diagnosis and Management of Hypertension and the American Diabetes Association recommend that hypertensive and normotensive patients with diabetic nephropathy should receive ACE inhibitors or AIIRAs as first line treatment.^{7,8} We searched for evidence from randomised controlled trials of the effects of ACE inhibitors and AIIRAs on renal outcomes and mortality in patients with diabetic nephropathy.

Methods

We included randomised controlled trials of at least six months duration in which ACE inhibitors or AIIRAs were compared with placebo or no treatment or in which the relative effects of the agents were compared directly, in patients with diabetic nephropathy. Any stage of diabetic nephropathy was included.

We searched Medline (1966-September 2003), Embase (1988-September 2003), the Cochrane Renal Group trial register, and the Cochrane central registry of randomised controlled trials. See bmj.com for search terms. Two authors (GFMS, MC) analysed the titles and abstracts of identified trials according to the inclusion criteria, searched the reference lists, and sought information about unpublished or additional trials.

Data extraction and quality assessment

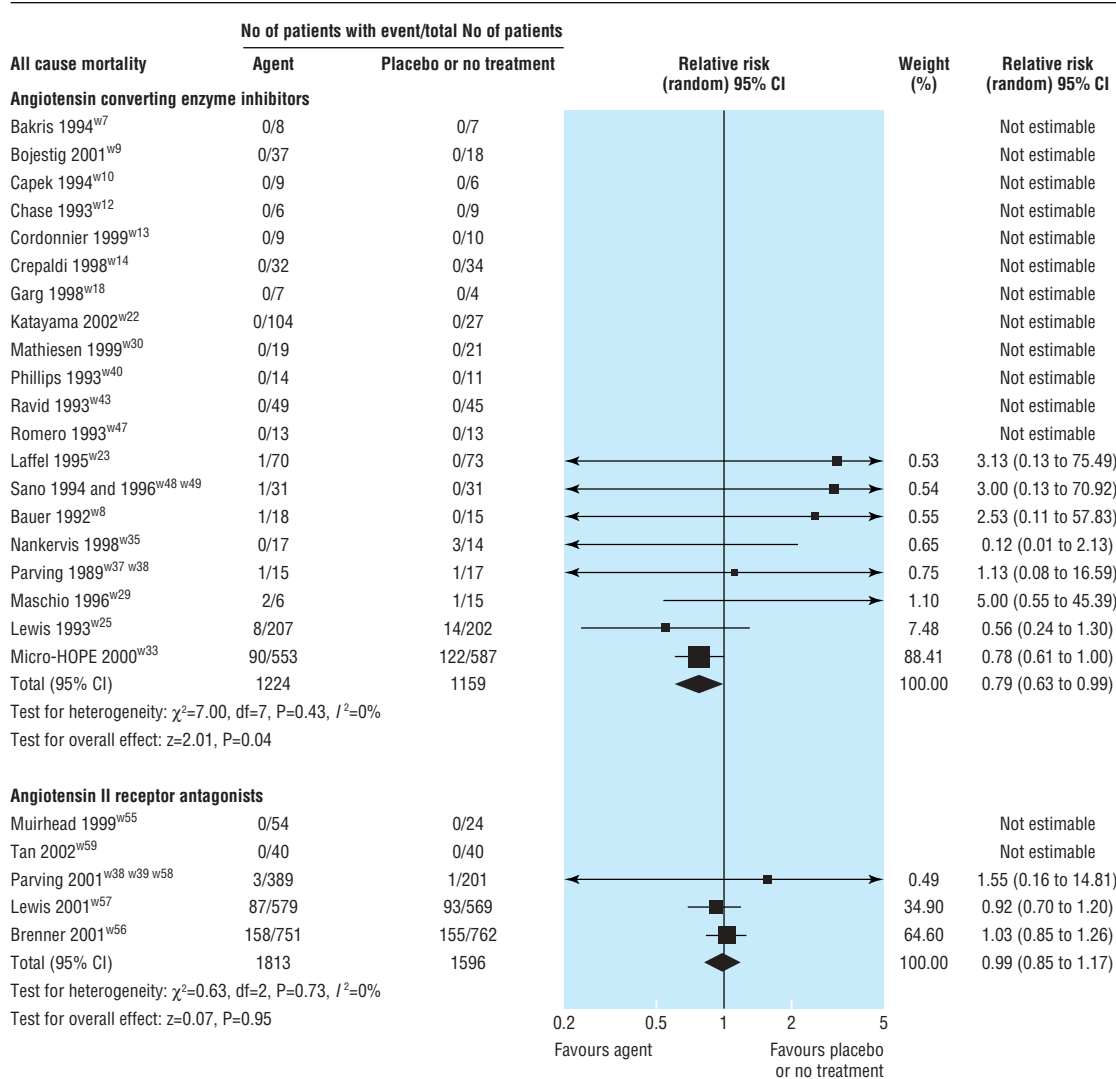
GFMS and MC assessed each trial independently. They extracted data on the characteristics of the participants, interventions, comparisons, and outcomes (all cause mortality, end stage renal disease, doubling of



References w1-w59 are on bmj.com



This is the abridged version of an article that was posted on bmj.com on 30 September 2004: <http://bmj.com/cgi/doi/10.1136/bmj.38237.585000.7C>



Effect of angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists compared with placebo or no treatment on overall mortality

serum creatinine concentration, progression from microalbuminuria to macroalbuminuria, regression from microalbuminuria to normoalbuminuria, cough, headache, hyperkalaemia, and impotence). Whenever these were not reported, the authors were contacted at least twice for the data.

We used standard criteria to assess the quality of the trials. Differences were resolved by discussion.

Statistical analysis

We summarised the treatment effects as relative risks, used random effects model to pool the data, and examined heterogeneity of treatment effects between studies. We used subgroup analysis and random effects metaregression to explore the influence of possible sources of heterogeneity on treatment effect (follow up, type of diabetes, type of drug, presence or absence of hypertension at baseline, stage of diabetic nephropathy, and specific quality items).

For trials that did not compare ACE inhibitors with AIIAs directly, we computed indirect comparisons of treatment effects on all outcomes by using the control group as a common comparator (from trials that com-

pared the agents with placebo or with no treatment). Analysis was performed as a metaregression using the trial intervention as the explanatory variable.

Results

We identified 4723 articles, and after exclusions there were 43 eligible randomised controlled trials (59 publications), which enrolled 7545 patients.^{w1-w59} We obtained supplemental data from the authors of nine trials or from publications relating to the primary trial. (See bmj.com for table of study characteristics.)

ACE inhibitors compared with placebo

Of the 36 trials (4008 patients) comparing ACE inhibitors with placebo, 20 enrolled patients with type 1 diabetes, 11 enrolled patients with type 2 diabetes, and five enrolled mixed populations. Sixteen trials included patients with hypertension at baseline. In 18 trials, other antihypertensives were given to equalise blood pressure in both groups and to minimise the confounding effect of blood pressure. Twenty three trials enrolled patients with microalbuminuria, eight

enrolled patients with macroalbuminuria, and five enrolled mixed populations. Three trials also enrolled a few patients with normoalbuminuria.^{w2 w16 w53}

AIIRAs compared with placebo

The four trials (3331 patients) that compared AIIRAs with placebo enrolled hypertensive patients with type 2 diabetes. Antihypertensive cointerventions were given in all four trials. Two trials enrolled patients with microalbuminuria and the other two trials enrolled patients with macroalbuminuria.

ACE inhibitors compared with AIIRAs

The three trials (206 patients) that compared ACE inhibitors with AIIRAs enrolled microalbuminuric patients with type 2 diabetes. Two trials enrolled hypertensive patients and one trial enrolled normotensive participants. Antihypertensive cointerventions were given in two trials.

Study quality

Trial quality was variable. Allocation concealment was unclear in 36 (84%) trials, inadequate in one (2%) trial, and adequate in six (14%) trials. Blinding occurred in the participants in 33 (77%) trials, investigators in 29 (66%) trials, and outcome assessors in four (9%) trials. Thirteen (30%) trials used an intention to treat analysis. Between 0% and 20% of patients were lost to follow up in 40 (93%) trials and between 21% and 40% were lost to follow up in three (7%) trials.

All cause mortality and renal outcomes

In 20 trials (2838 patients), all cause mortality was lower with ACE inhibitors than with placebo or no treatment (relative risk 0.79, 95% confidence interval 0.63 to 0.99; figure). This analysis was dominated by two trials, which contributed 88.4% and 7.5% of the weight to the summary estimate.^{w25 w33}

No statistically significant reduction in all cause mortality was found in the four trials (3329 patients) of AIIRAs compared with placebo or no treatment (relative risk 0.99, 0.85 to 1.17). This analysis was dominated by two trials, which contributed 64.6% and 34.9% of the weight to the summary estimate.^{w56 w57}

Nine of the trials (1907 patients) comparing ACE inhibitors with placebo showed weak evidence for a reduced risk of end stage renal disease (relative risk 0.64, 0.40 to 1.03), and eight of the trials (1868 patients) showed weak evidence for a doubling of serum creatinine concentration (0.60, 0.34 to 1.05). In 16 trials (2010 patients) ACE inhibitors significantly reduced the risk of progression from microalbuminuria to macroalbuminuria (0.45, 0.28 to 0.71), and in 15 trials (1888 patients) ACE inhibitors significantly increased the rate of regression from microalbuminuria to normoalbuminuria (3.42, 1.95 to 5.99).

Three trials (3251 patients) comparing AIIRAs with placebo or no treatment showed a significantly reduced risk of end stage renal disease (relative risk 0.78, 0.67 to 0.91) and doubling of serum creatinine concentration (0.79, 0.67 to 0.93). AIIRAs also significantly decreased the risk of progression from microalbuminuria to macroalbuminuria (three trials, 761 patients; 0.49, 0.32 to 0.75) and increased the rate of regression from microalbuminuria to normoalbuminuria (two trials, 670 patients; 1.42, 1.05 to 1.93).

ACE inhibitors compared with AIIRAs

The three trials that compared ACE inhibitors with AIIRAs did not report on all cause mortality, end stage renal disease, and doubling of serum creatinine concentration, and we were unable to obtain these data from the authors. Progression from microalbuminuria to macroalbuminuria was reported in one trial (92 patients) and there was no significant difference in risk, with the point estimate favouring ACE inhibitors (relative risk 0.16, 0.02 to 1.44).^{w53} Regression from microalbuminuria to normoalbuminuria in one trial showed a non-significant difference in the risk.^{w54}

Indirect comparison of treatment effects

Regression analysis of treatment effects of ACE inhibitors compared with AIIRAs using active treatment as the explanatory variable showed no significant difference between these two agents for the risk of any outcome (death: relative risk 0.79, 0.60 to 1.05; end stage renal disease: 0.82, 0.50 to 1.36; doubling of serum creatinine concentration: 0.83, 0.58 to 1.20; progression from microalbuminuria to macroalbuminuria: 1.14, 0.31 to 4.22; regression from microalbuminuria to normoalbuminuria: 0.76, 0.56 to 1.05).

The ACEI and AIIRA trials had potentially important differences in study design, particularly the two pairs of trials that dominate the summary estimates of effects (see bmj.com).

Side effects and investigations for sources of heterogeneity

Reports of side effects were few in the smaller trials. See bmj.com for summary estimates of the effects of ACE inhibitors and AIIRAs on cough, hyperkalaemia, headache, and impotence. We found no significant heterogeneity across all trials.

Metaregression and subgroup analyses were possible only in trials comparing ACE inhibitors with placebo or no treatment, given the small number of trials evaluating AIIRAs. We found no evidence that the effect of ACE inhibitors on all cause mortality varied according to type of diabetes, presence or absence of hypertension, or microalbuminuria compared with macroalbuminuria at baseline. Differences in the risk of other outcomes according to type of diabetes, hypertension, and study design are all explained by the results of the micro-HOPE trial.¹ When we excluded this trial from our analyses, results were homogeneous for all outcomes (see bmj.com).

Discussion

Trials have shown a survival benefit with angiotensin converting enzyme (ACE) inhibitors but not with angiotensin II receptor antagonists (AIIRAs), in patients with diabetic nephropathy. Both agents prevent progression of nephropathy and promote regression to normoalbuminuria. The relative survival advantage of one class of antihypertensives over the other in this population is, however, still unknown because only indirect comparisons based on small studies are available.

Three potential explanations for these apparent different effects between the two classes of antihypertensives are chance, confounding, and true differences. The usual 5% level for statistical significance was reached for all renal outcomes for AIIRAs, compared with ACE inhibitors, where this threshold was reached

What is already known on this topic

Diabetic nephropathy is managed by angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists (AIIRAs)

ACE inhibitors and AIIRAs may be used interchangeably

What this study adds

Evidence exists that ACE inhibitors prevent early death in patients with diabetic nephropathy, but there is no such evidence for AIIRAs

The two classes of drugs have equivalent effects on renal outcomes

The relative effects of ACE inhibitors and AIIRAs on survival are unknown owing to the lack of adequate head to head trials

for the prevention of progression from microalbuminuria to macroalbuminuria, and regression of microalbuminuria to normoalbuminuria, but not end stage renal disease or doubling of serum creatinine concentration. The point estimates of effect for all renal outcomes favoured ACE inhibitors compared with AIIRAs, but there was considerable imprecision surrounding these summary point estimates for ACE inhibitors. For all cause mortality, the absence of benefit shown by AIIRAs is unlikely to be due to chance alone because the summary point estimate is close to unity and the 95% confidence intervals are relatively narrow. Formal tests of differences in ACE inhibitors and AIIRAs did not show any differences in the risk of the outcomes beyond those expected by chance. The design and conduct of the ACEI and AIIRA trials have clear differences, which may explain apparent differences in results.

Our findings are consistent with others, especially large meta-analyses in patients with congestive heart failure, which showed a significant reduction in the risk of all cause mortality with ACE inhibitors compared with placebo but not for AIIRAs.^{9,10} The main difference with our study compared to other studies in patients with diabetic nephropathy is that we included both ACEI and AIIRA trials, obtained additional data from the authors when possible, and evaluated all outcomes of interest, including all cause mortality, and not simply the traditional renal outcomes.

The major limitation of our study is the indirect nature of the comparison between ACE inhibitors and AIIRAs, by using placebo as a common comparator. Other limitations include the small number and suboptimal quality of included trials and the potential for publication bias. These issues are unlikely to be influential as the review is dominated by a few larger studies.

A possible biological rationale for the benefit of ACE inhibitors but not of AIIRAs on all cause mortality could be that bradykinin antagonism occurs with ACE inhibitors but not with AIIRAs. Although little data exist in experimental renal models, information is available from cardiac models.¹¹

The role of ACE inhibitors in the management of patients with diabetic nephropathy is well established.

Recently, equivalence of the newer and more expensive class of antihypertensive agents, AIIRAs, has been widely advocated—the Joint National Committee on Prevention, Diagnosis and Management of Hypertension and the American Diabetic Association guidelines suggest that ACE inhibitors and AIIRAs can be used interchangeably—and accepted in current practice. Our study shows that the relative effects of ACE inhibitors and AIIRAs are uncertain. Thus, outside of a comparative randomised controlled trial, the class of agent with proved survival benefit, ACE inhibitors, should be used as first line treatment. True differences in the relative effects of ACE inhibitors and AIIRAs can only be established by adequately powered trials that directly compare the two agents.

We thank Denise Campbell (medical editor) for editing the manuscript; Narelle Willis, Sham Gökalp, and Sandra Puckeridge for editorial and administrative support; Ruth Mitchell, Linda Heslop, Gail Higgins (trial search coordinators with the Cochrane Renal Group) for search strategies for this review; and Janice Pogue and the HOPE trialists, M Ravid, PJ Phillips, HH Parving, R Romero, S Katayama, ER Mathiesen, BM Brenner, and KC Tan who provided data on the trials on request.

Contributors: See bmj.com

Funding: Australia-Europe Scholarship 2003 (Department of Education, Science and Training of Australia), an NHMRC Centre for Clinical Research Excellence Grant (2003), and the Italian Society of Nephrology (Young Investigator Scholarship 2003).

Competing interests: None declared.

Ethical approval: Not required.

- Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000;355:253-9.
- Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effects of angiotensin converting enzyme inhibition to diabetic nephropathy. *N Engl J Med* 1993;329:1456-62.
- Kasiske BL, Kalil RS, Ma JZ, Liao M, Keane WF. Effect of antihypertensive therapy on the kidney in patients with diabetes: a meta-regression analysis. *Ann Intern Med* 1993;118:129-38.
- 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.
- Lewis E, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;345:851-60.
- Dinneen SF, Gerstein HC. The association of microalbuminuria and mortality in non-insulin-dependent diabetes mellitus. A systematic overview of the literature. *Arch Intern Med* 1997;157:1413-8.
- Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *JAMA* 2003;289:2560-72.
- Arauz-Pacheco C, Parrott MA, Raskin P. Treatment of hypertension in adults with diabetes. *Diabetes Care* 2003;26:S80-2.
- Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. *JAMA* 1995;273:1450-6.
- Cohn JN, Tognoni G, Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;345:1667-75.
- Klahr S, Morrissey J. Comparative effects of ACE inhibition and angiotensin II receptor blockade in the prevention of renal damage. *Kidney Int* 2002;62(Suppl 82):S23-6.

(Accepted 27 August 2004)

doi 10.1136/bmj.38237.585000.7C

*Endpiece***Bad news**

A virus is a piece of bad news wrapped in protein.

Peter Medawar (1915-87), Nobel prize winner

Fred Charatan *retired geriatric physician, Florida*