Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis

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Summary

Background A consensus has emerged that angiotensin-converting-enzyme (ACE) inhibitors and angiotensin-II receptor blockers (ARBs) have specific renoprotective effects. Guidelines specify that these are the drugs of choice for the treatment of hypertension in patients with renal disease. We sought to determine to what extent this consensus is supported by the available evidence.

Methods Electronic databases were searched up to January, 2005, for randomised trials assessing antihypertensive drugs and progression of renal disease. Effects on primary discrete endpoints (doubling of creatinine and end-stage renal disease) and secondary continuous markers of renal outcomes (creatinine, albuminuria, and glomerular filtration rate) were calculated with random-effect models. The effects of ACE inhibitors or ARBs in placebo-controlled trials were compared with the effects seen in trials that used an active comparator drug.

Findings Comparisons of ACE inhibitors or ARBs with other antihypertensive drugs yielded a relative risk of 0·71 (95% CI 0·49–1·04) for doubling of creatinine and a small benefit on end-stage renal disease (relative risk 0·87, 0·75–0·99). Analyses of the results by study size showed a smaller benefit in large studies. In patients with diabetic nephropathy, no benefit was seen in comparative trials of ACE inhibitors or ARBs on the doubling of creatinine (1·09, 0·55–2·15), end-stage renal disease (0·89, 0·74–1·07), glomerular filtration rate, or creatinine amounts. Placebo-controlled trials of ACE inhibitors or ARBs showed greater benefits than comparative trials on all renal outcomes, but were accompanied by substantial reductions in blood pressure in favour of ACE inhibitors or ARBs.

Interpretation The benefits of ACE inhibitors or ARBs on renal outcomes in placebo-controlled trials probably result from a blood-pressure-lowering effect. In patients with diabetes, additional renoprotective actions of these substances beyond lowering blood pressure remain unproven, and there is uncertainty about the greater renoprotection seen in non-diabetic renal disease.

Introduction

National and international guidelines endorse the view that inhibition of the renin-angiotensin system with angiotensin-converting-enzyme (ACE) inhibitors should be first-line antihypertensive therapy in patients with diabetic and non-diabetic nephropathy. In the UK, the Renal Association, British Diabetic Association, British Hypertension Society, and National Institute of Clinical Excellence all encourage use of these drugs as first-line treatment to reduce proteinuria and retard the progression of renal disease.[1–4] The recommendation in diabetes has been formalised in the new General Medical Services Contract for primary care in the UK, with remuneration linked to the prescription of these drugs for this indication.[4] Similar advice is included in other European and US guidelines, which advocate that either ACE inhibitors or angiotensin-II receptor blockers (ARB) be used to delay the progression of renal disease.[5,6]

Implicit in this advice is the assumption that inhibition of the renin-angiotensin system with ACE inhibitors (and, more recently, ARBs) has specific renoprotective effects beyond those resulting from lowering blood pressure alone.[7–9] Blood-pressure-independent effects of ACE inhibitors on cardiovascular outcomes have also been proposed, based on the results of several large multicentre trials, especially the HOPE, PROGRESS, and EUROPA studies,[10–12] and similar claims have been made for ARBs.[13] However, these placebo-controlled trials have been difficult to interpret because use of the active drug reduced blood pressure compared with the control group. The log-linear association between blood pressure and the incidence of cardiovascular events[14] means that a reduction in systolic blood pressure of as little as 5 mm Hg reduces the incidence of stroke by about 40% and myocardial infarction by 20%.[15] The reduction in the occurrence of cardiovascular endpoints seen in placebo-controlled trials of ACE inhibitors or ARBs is in the range expected from the blood-pressure-lowering effect, arguing against pleiotropic effects of inhibition of the renin-angiotensin system on cardiovascular endpoints.[2,15,16] Indeed, when the cardiovascular effects in patients randomly assigned ACE inhibitors were assessed in trials with an active comparator rather than placebo, no particular advantage of ACE inhibitors was seen over other classes of blood-pressure-lowering drugs.[15]

Blood pressure is also an important risk factor for the progression of renal disease.[17–19] However, the guidelines that advocate use of ACE inhibitors and ARBs in renal

disease base their recommendations largely on the results of placebo-controlled trials, often using surrogate markers rather than clinically relevant endpoints.[20–22] To assess blood-pressure-independent renoprotection due to inhibition of the renin-angiotensin system, we undertook a systematic review and meta-analysis of randomised controlled trials investigating the effect of different classes of antihypertensive drugs on progression of renal disease. In particular, we compared the effects on renal outcomes of inhibition of the renin-angiotensin system in trials using placebo controls versus trials with active comparator drugs.

Methods

Three electronic databases (MEDLINE, EMBASE, and the Cochrane Library) were searched from 1960 to Jan 31, 2005, for randomised controlled trials investigating any antihypertensive drug and progression of human renal disease, with MeSH headings and text words (discussed in detail in search strategies, webappendix). We searched for any additional studies in the references of all identified publications, including previous relevant meta-analyses and narrative reviews.

Selection criteria

For inclusion, studies had to be randomised, controlled, parallel-design in adults, and examine the effect of any drug treatment with a blood-pressure-lowering action on progression of renal disease. Progression of renal disease was assessed by use of incident renal endpoints as primary outcomes (doubling of serum creatinine and end-stage renal disease, defined as the need for kidney transplantation or haemodialysis) and secondary continuous markers (glomerular filtration rate [GFR], serum creatinine, and urine albumin excretion). Studies had to have a minimum follow-up of 1 year. Only studies published as full-length articles or letters in peer-reviewed English-language journals were included.

Data extraction

The following information was extracted and entered into databases by three investigators (JPC, WCH, RJM): study design, type of intervention, patients' characteristics, and outcomes (webappendix). If relevant information regarding design, or renal outcomes was unavailable, or doubt existed about duplicate publications, authors were contacted to obtain the necessary information (webappendix). Uncertainties were resolved by consensus.

Statistical analysis

We compared effects of inhibition of the renin-angiotensin system, by use of ACE inhibitors or ARBs, on renal outcomes in trials that used placebo as a comparator with trials that used other antihypertensive drugs (β blockers, diuretics, calcium-channel blockers, α blockers, or combinations of these) as comparators. The trial arm with ACE-inhibitor or ARB medication was assigned as the experimental group. We used metaregression models to measure to what extent the difference in blood-pressure change (expressed as a tertile of blood-pressure reduction) between randomised groups accounted for the observed difference in renal outcomes. All trials with ACE-inhibitor or ARB treatment were included for these analyses. We excluded trials that did not provide information on achieved blood pressure from our metaregression models.

For continuous variables (blood pressure, serum creatinine, GFR, and urine albumin excretion) results were expressed as the mean difference in the change in the variable between randomised groups. This difference was calculated by subtraction of the mean change in the variable in the reference group (follow-up value minus baseline value; δ-reference) from the corresponding mean change in the experimental group (follow-up value minus baseline value; δ-experimental) by use of random-effect models.

For binary renal outcomes (the doubling of serum creatinine and occurrence of end-stage renal disease), the pooled relative risk (RR) and 95% CIs were calculated with random-effect models by the method of DerSimonian and Laird.[23] The DerSimonian and Laird Q test was used to assess the degree of heterogeneity between studies, and I^2 was used as a measure to describe the percentage of variability in point estimates that was due to heterogeneity rather than sampling error.[23] To assess the robustness of the findings, sensitivity analyses were done according to study-level characteristics, such as disease status (type 1 or 2 diabetes *vs* no diabetes), and study size ($n<500$ *vs* $n\geq500$). Funnel plots and the Egger regression asymmetry test were used to investigate small-study bias (eg, publication bias). Data were analysed with Stata 8.2. The webappendix provides further details about the statistical analysis.[24–26]

See Lancet Online for webappendix

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No funding source had any role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and all took full responsibility for the decision to submit for publication.

Results

Figure 1 summarises the identification process for eligible clinical trials. We found 127 eligible studies corresponding to 150 group comparisons with a weighted mean follow-up of 4·2 years. 99 group comparisons used trials including only patients with diabetes (weighted mean GFR 84·5 mL/min), 36 included only patients without diabetes (73·4 mL/min), ten included both types of patient (75·0 mL/min), and five did not report information on the presence of diabetes (96 mL/min). The study sample size was 100 or less patients in 98 comparisons (weighted mean follow-up 2·5 years), between 100 and 500 patients

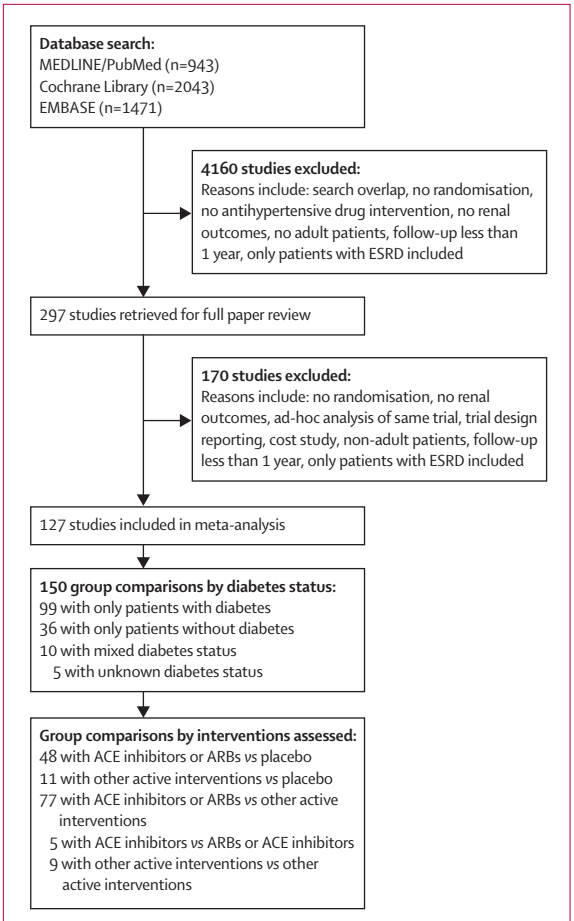

Figure 1: **Identification process for eligible randomised controlled trials**

in 34 comparisons (2·8 years), and 500 or more patients in 18 comparisons (4·5 years). The table shows the main characteristics of studies included in our analysis.

13 trials (n=37 089) were included that compared the effect of ACE inhibitors or ARBs on the occurrence of end-stage renal disease with the effect of other antihypertensives. In these trials, a small reduction was seen in the risk of end-stage renal disease in favour of either ACE inhibitors or ARBs (p=0·04; figure 2, A) with no differences in the degree of change of systolic (–1·32 mm Hg, 95% CI –4·03 to 1·38) or diastolic (–0·58 mm Hg, –2·2 to 1·04) blood pressure between the groups. We did not record any interstudy heterogeneity (p=0·48, I^2=0%). The Egger test suggested no evidence of small-study bias (p=0·23), although this factor is discussed in more detail later. No significant benefit of ACE inhibitors or ARBs over other antihypertensive drugs was seen in patients with diabetes (four trials, n=14 437; figure 2, A).

11 trials (n=3376) were included that compared the effect of ACE inhibitors or ARBs with active comparators on the doubling of creatinine. We saw a non-significant reduction in the risk of doubling of creatinine in favour of either ACE inhibitors or ARBs (p=0·07; figure 2, B). There were no differences in the degree of change of systolic (–0·97 mm Hg, –3·09 to 1·14) or diastolic (0·23 mm Hg, –0·99 to 1·46) blood pressure between randomised groups. As with the comparison on occurrence of end-stage renal disease, we recorded no significant interstudy heterogeneity (p=0·26, I^2=0%) or small-study bias (p=0·66). In patients with diabetes (six trials, n=3044), ACE inhibitors or ARBs showed no benefit compared with other antihypertensive drugs (RR 1·09, 0·55–2·15).

We included 38 trials (n=5711) that compared the effect of ACE inhibitors or ARBs on serum creatinine concentration with that of other antihypertensives. ACE-inhibitor or ARB treatment led to a small reduction in creatinine concentration (p=0·01; figure 3, A) and in the degree of change of systolic blood pressure (–1·49 mm Hg, –2·92 to –0·05), but not diastolic blood pressure (–0·59 mm Hg, –1·55 to 0·37). Some small-study bias (p=0·07) and interstudy heterogeneity (p<0·0001, I^2=66·3%) was indicated. In patients with diabetes, no benefit on creatinine was seen (figure 3, A).

44 trials (n=5266) in our analysis compared the effect of ACE inhibitors or ARBs on urine albumin excretion with other antihypertensive drugs (figure 3, B). ACE-inhibitor or ARB treatment resulted in a small reduction in daily urinary albumin excretion (p=0·001). There were no differences between groups in the degree of change of systolic (–0·95 mm Hg, –2·51 to 0·61) or diastolic (–0·08 mm Hg, –1·03 to 0·87) blood pressure. However, we recorded substantial evidence of small-study bias (p=0·001) and significant study heterogeneity (p<0·0001, I^2=57·8%). In patients with diabetes, a small reduction in daily urine albumin excretion was seen (figure 3, B).

	Number of group comparisons (number of patients)	Mean (range) sample size	Mean proportion of patients with hypertension (range)	Proportion of studies only including patients with diabetes (%)	Mean (range) baseline GFR (mL/min)	Mean (range) baseline creatinine (μmol/L)	Mean (range) baseline albuminuria (mg/day)
Group comparisons							
All	150 (73 514)	490 (11–33 357)	64·9 (0–100)	73%	86·9 (15·8–184·2)	113·1 (68–389)	602·8 (7·2–3100)
ACE inhibitors or ARBs *vs* placebo	48 (16 588)	345 (11–4912)	32·6 (0–100)	89%	97·8 (15·8–184·2)	110·5 (69·8–389)	535·5 (7·3–1900)
ACE inhibitors or ARBs *vs* other active interventions	77 (43 439)	564 (13–33 357)	85·7 (0–100)	62%	77·4 (18·8–150)	127·0 (68–349·2)	519·5 (7·2–3000)
ACE inhibitors *vs* ARBs	5 (594)	118 (24–250)	75 (0–100)	60%	80·3 (38·4–96·7)	157·3 (70·7–265·2)	92·6 (92–102)
Other active interventions *vs* placebo	11 (6390)	581 (12–4406)	40 (0–100)	89%	99·5 (64·1–129)	98·4 (78·6–149·4)	1128·7 (7·3–1900)
Other active interventions *vs* other active interventions	9 (6503)	722 (20–6125)	100 (0–100)	75%	76·1 (55·8–98)	141·4 (120·2–152)	950·5 (55–3100)

Table: **Characteristics of studies in meta-analysis**

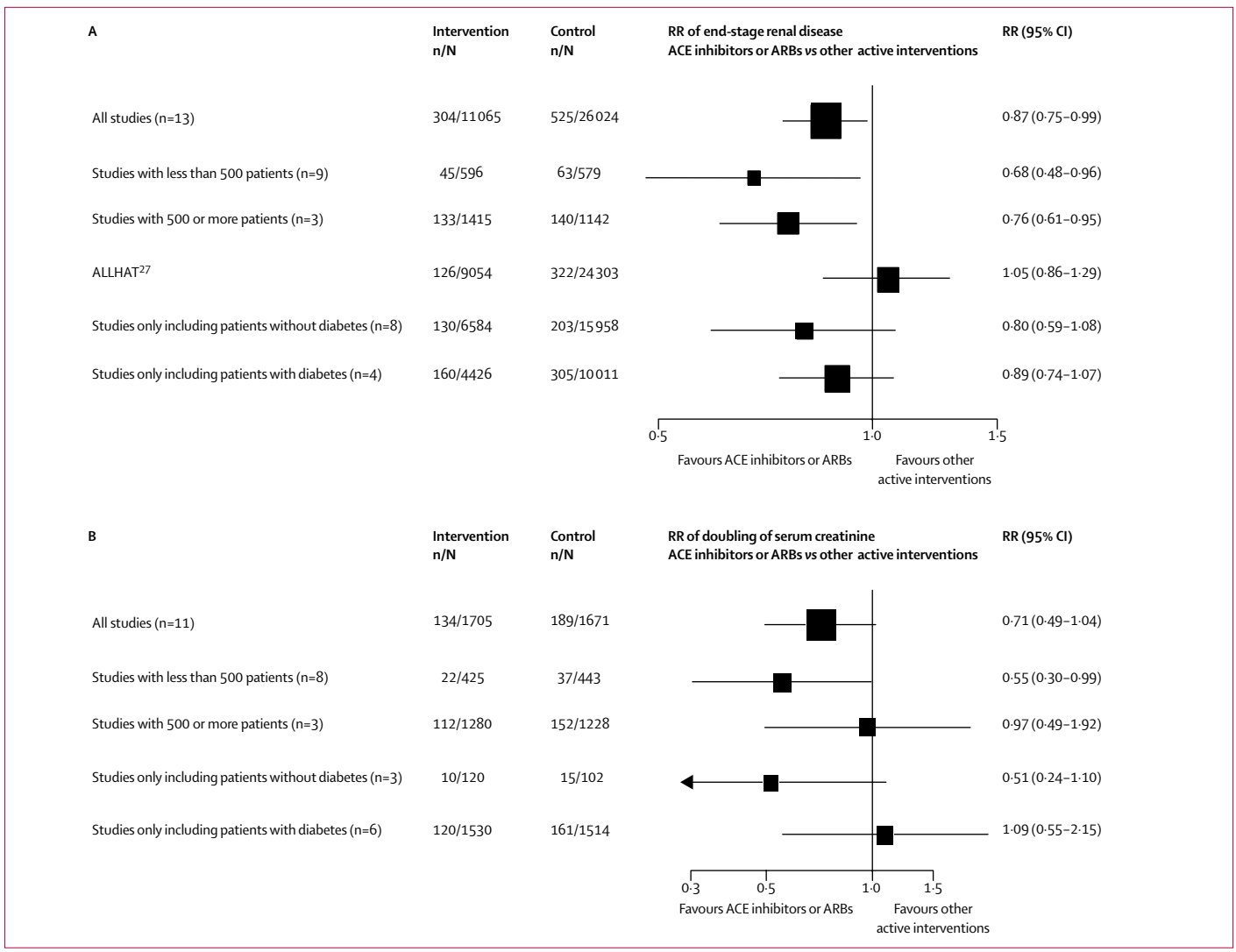

Figure 2: **Effect of ACE inhibitors or ARBs compared with other active interventions on relative risk of (A) end-stage renal disease, and (B) doubling of serum creatinine**
Studies included are: (RR of end-stage renal disease) webreferences 2, 26, 27, 37, 44, 47, 56, 67, 89, 118, 120, 126, and 127; (doubling of serum creatinine) webreferences 6, 8, 26, 27, 56, 67, 89, 90, 95, 115, and 118 (webappendix).

61 trials (n=39 485) were included that compared the effect of ACE inhibitors or ARBs with other antihypertensive drugs on the GFR. Compared with other drugs, ACE-inhibitor or ARB treatment had no effect on the GFR (figure 3, C) or on the degree of change of systolic (–0·16 mm Hg, –1·22 to 0·9) or diastolic (0·11 mm Hg, –0·5 to 0·72) blood pressure. We recorded no significant interstudy heterogeneity ($p=0·94$, $I^2=0\%$) or small-study bias ($p=0·88$). The GFR did not improve in patients with diabetes (figure 3, C).

For the primary outcomes (end-stage renal disease and doubling of creatinine), no significant evidence of small-study bias was seen, but data were based on small numbers of trials (end-stage renal disease, 13 trials, $p=0·23$; doubling of creatinine, 11, $p=0·66$). For the secondary continuous outcomes, more trials had outcome data available, and with significant small-study bias for creatinine (38, $p=0·07$) and urine albumin excretion (44, $p=0·001$). For the occurrence of end-stage renal disease, analysis according to study size (<500, ⩾500 to 1500, and >1500 patients), showed that the apparent beneficial effect of ACE inhibitors or ARBs over other antihypertensive drugs falls as study size increases (figure 2, A), and the p value for a metaregression according to study size was 0·013. However, the trend was greatly affected by ALLHAT,[27] which provided almost half the events of end-stage renal disease and showed no beneficial effect. For doubling of creatinine, analysis by study size also indicated no benefit of ACE inhibitors or ARBs compared with other antihypertensive substances in large studies (figure 2, B).

In trials with the comparator arm as placebo rather than another antihypertensive drug, patients randomly

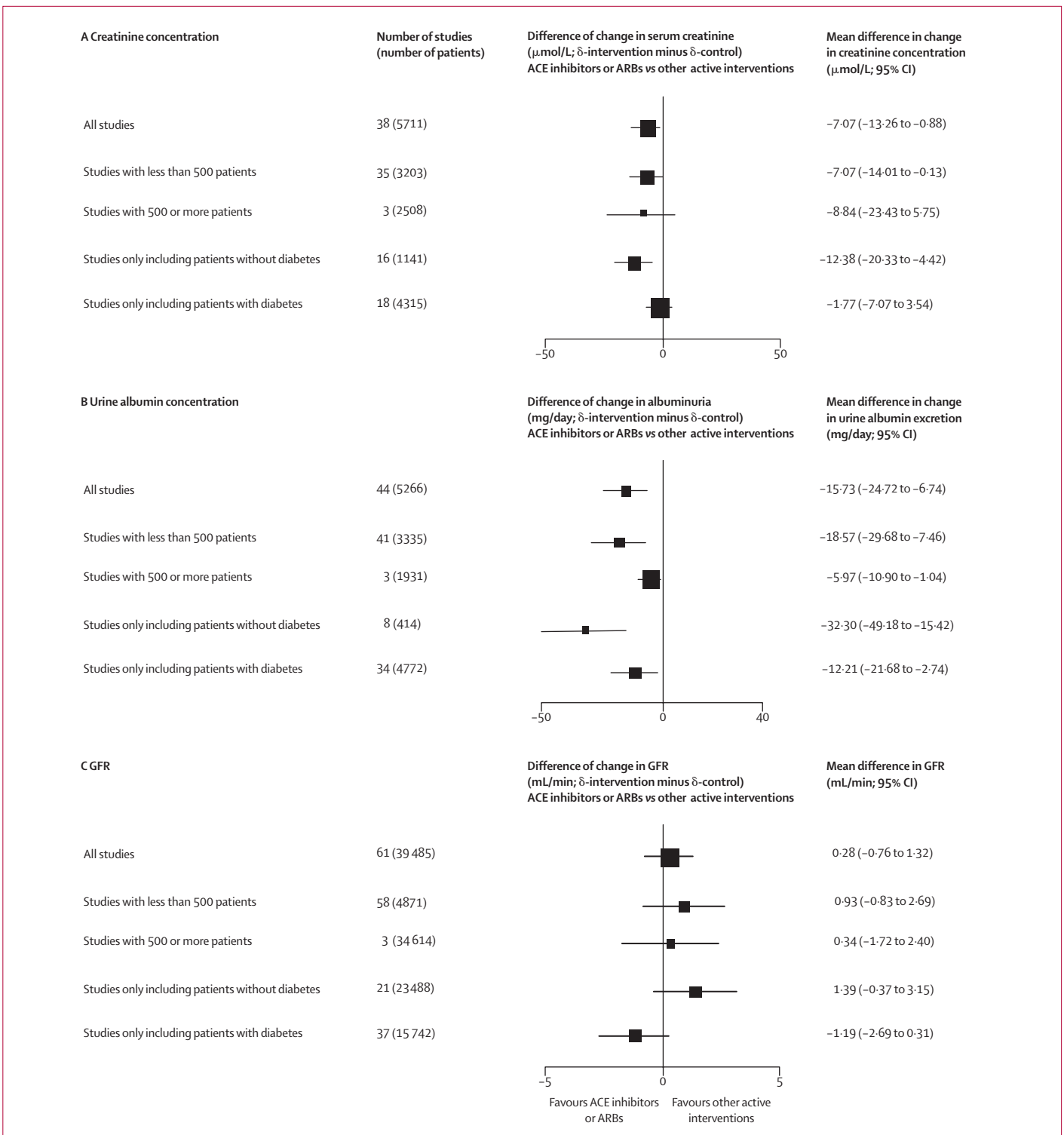

Figure 3: **Effect of ACE inhibitors or ARBs compared with other active interventions on (A) creatinine concentration, (B) urine albumin excretion, and (C) GFR***

Negative values in forest plots indicate a greater reduction in the continuous marker in favour of the ACE-inhibitor or ARB group. Studies included are: (creatinine concentration) webreferences 1, 6, 23, 24, 27, 29, 32, 33, 35, 40, 44, 47, 52, 56, 60, 63, 65, 67, 68, 70, 78, 89, 90, 93, 95, 102, 106–110, 115, 116, 118, 119, 125; (urine albumin excretion) webreferences 1, 6, 11, 15–18, 23, 24, 29, 32, 35, 39, 40, 41, 43, 47, 53, 54, 59, 63, 65, 73, 76, 78, 83, 89, 93, 94, 95, 97, 99, 102, 104, 110, 111, 113, 115, 116, 118, 121, 122; and (GFR) webreferences 1, 2, 5, 6, 7, 8, 11, 12, 15–18, 23, 24, 27, 29, 32, 33, 35–37, 39–41, 43, 46, 47, 49, 52, 55, 56, 59, 63, 65, 68, 76, 78, 83, 88, 90, 93–95, 97, 99, 102, 104, 105, 107, 110, 111, 113, 115, 119–121, 126, 127 (webappendix). *For this group, results from the ALLHAT trial were obtained as a weighted mean by subtracting the results in the diabetes group from the overall study (webreference 127, webappendix).

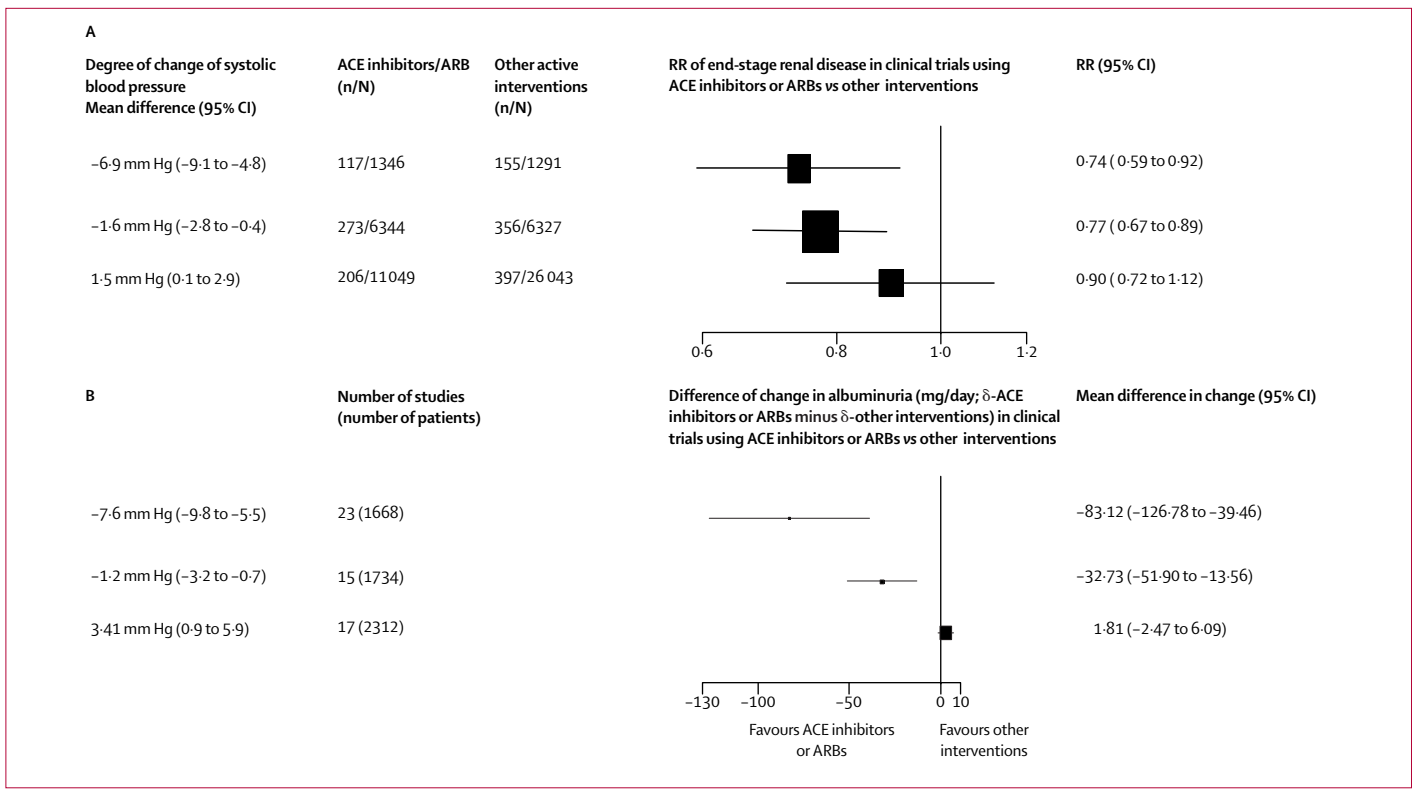

Figure 4: **Stratified effect of ACE inhibitors or ARBs on (A) RR of end-stage renal disease and (B) urine albumin excretion, according to difference achieved in systolic blood pressure between randomised groups**

Data on these figures include information from placebo-controlled trials and trials with active interventions.

assigned to receive ACE inhibitors or ARBs were at lower risk of end-stage renal disease and doubling of creatinine, than was placebo (webtable 1), and also showed reductions in serum creatinine and urine albumin excretion (webtable 2). However, GFR was not affected (1·22 mL/min, –0·95 to 3·39). These effects were associated with the expected reduction in blood pressure in the ACE-inhibitor or ARB groups (reductions ranging from –2·27 to –5·96 mm Hg; webtables 1 and 2). Similar benefits were seen in patients with diabetes. We also recorded substantial evidence of small-study bias in trials investigating the effect of ACE inhibitors or ARBs on serum creatinine (p=0·07) and urine albumin excretion (p=0·006; webtable 2). In general, the benefits of ACE inhibitors or ARBs over placebo were greater in the small trials (webtables 1 and 2).

To assess the effect of the blood-pressure reduction on renal outcomes, the difference in change in blood pressure between randomised groups was calculated as a categorical variable by generation of tertiles of the difference in change of systolic blood pressure. 20 placebo and head-to-head trials of ACE inhibitors or ARBs in which end-stage renal disease was a trial outcome were included in the metaregression. The log odds ratio for end-stage renal disease increased by 0·13 (p=0·06) for a per-tertile increase of achieved blood pressure. Trials with large blood pressure differences were associated with a greater reduction in the incidence of end-stage renal disease than trials with small differences (figure 4, A). The association of blood-pressure reduction with difference in change in albuminuria in 55 trials was more substantial (for a per-tertile increase in achieved blood pressure, the difference in change in albuminuria increased by 30·52 mg/day, p=0·02; figure 4, B).

See Lancet Online for webtables 1 and 2

Discussion

This analysis confirms the importance of blood-pressure control per se in the prevention of renal disease, in view of the larger renoprotective effect of ACE inhibitors or ARBs in placebo-controlled trials than in active comparator studies. Indeed, when blood-pressure differences were reduced substantially by anti-hypertensive treatment in control groups, there was no evidence of a significant salutary effect of ACE inhibitors or ARBs on renal outcomes in patients with diabetes. By contrast, small benefits of the drugs were seen in non-diabetic renal disease, although uncertainty remains because of evidence of small-study bias. These findings have implications for the use of ACE inhibitors or ARBs in patients with hypertension, diabetes, and renal disease, and for the design of future studies to investigate renoprotection strategies.

Trials with a placebo comparator indicated a renoprotective effect of ACE inhibitors or ARBs, but this effect is most readily explained by their action to reduce blood pressure compared with placebo (with a difference of between 2·3 to 6·0 mm Hg seen in these trials, webtables 1 and 2). Systemic blood pressure is a major determinant of the progression of renal disease,[17–19] and blood-pressure differences that are inevitable in placebo-controlled trials of ACE inhibitors or ARBs confound interpretation of effects on renal endpoints. This interpretation was supported by the results of our exploratory metaregression analysis, showing the importance of lower blood pressure on end-stage renal disease and urine albumin excretion (figure 4), and is consistent with previous findings from overviews of clinical trials examining effects of antihypertensive drugs on cardiovascular outcomes.[15,16] These conclusions would be strengthened if metaregression could be used to investigate the renoprotective effects of antihypertensive drugs other than ACE inhibitors and ARBs compared with placebo. Although such a benefit has been suggested for calcium-channel blockers,[28] there were insufficient trials of this type for us to undertake such an analysis reliably.

Comparator trials involving other antihypertensive drugs provide the most specific data for the renoprotective effects of ACE inhibitors or ARBs. These findings indicated that there was a small reduction in the incidence of end-stage renal disease (figure 2, A). However, two uncertainties exist in the interpretation of these data. First, neither ACE inhibitors nor ARBs affected GFR compared with other antihypertensive drugs. Second, analysis of the treatment effect of ACE inhibitors or ARBs on end-stage renal disease and doubling of creatinine according to study size showed a reduced benefit in large studies (figure 2). Although statistical tests for the primary outcomes for small-study bias were not significant, such tests have low power, especially when the number of trials is less than 20.[29]

The greater beneficial effect seen in the small studies could indicate valid differences between the small and large studies. Renal function at entry in the very large ALLHAT trial was good compared with some of the small studies that recruited a greater proportion of patients with poor renal function. However, when the ALLHAT investigators stratified the data by degree of renal impairment, there was no evidence for a greater beneficial effect of ACE inhibitors in people with poor renal function.[27] In the ALLHAT trial, participants assigned thiazide diuretics had a roughly 2 mm Hg lower systolic blood pressure than those assigned ACE inhibitors, and this difference in blood pressure might have contributed to the absence of any beneficial effect of ACE inhibitors over thiazides on renal outcomes. However, another possible explanation for the gradient of effect seen in figure 2, A is small-study bias, for two reasons: first, small negative studies are likely to have remained unpublished, and second, those small studies that have been published are likely to be of lower quality than large trials, and more prone to bias.

The discordance we show between the results of small and large studies parallels that seen for intravenous magnesium as a treatment for myocardial infarction. A meta-analysis of small trials had suggested that magnesium treatment reduced mortality,[30] yet the very large ISIS-4 trial showed no benefit of magnesium.[31] The ISIS-4 finding was widely accepted as more valid than the previous meta-analysis,[32] and it was subsequently shown that the misleading result from the meta-analysis of small studies of magnesium could be explained by publication bias.[33] It is possible, but by no means certain, that the small beneficial effect of ACE inhibitors or ARBs on renal outcomes is similarly affected by publication or other sources of small-study bias. It is notable that for the secondary renal outcomes (serum creatinine and urine albumin excretion) with sufficient numbers of trials, tests for small-study bias were highly significant.

In patients with diabetes, the results from the current study emphasise the lack of a proven advantage of ACE inhibitors or ARBs over other antihypertensive drugs in preventing renal disease. Trials with an active comparator did not identify any consistent benefit on the occurrence of end-stage renal disease, doubling of creatinine, or other indices of renal function (figure 2). Although a small benefit was recorded on urine albumin excretion in favour of ACE inhibitors or ARBs compared with antihypertensive drugs, significant small-study bias was also seen. This lack of specific benefit of ACE inhibitors or ARBs in diabetic renal disease accords with findings seen in cardiovascular outcomes.[34]

In conclusion, claims that ACE inhibitors and ARBs are renoprotective in diabetes seem to derive from small placebo-controlled trials that provide uncertain evidence of the existence of any true advantage over and above blood-pressure control. For renal outcomes, blood-pressure lowering remains more important than the drug class prescribed. More persuasive evidence exists that shows a specific renoprotective effect in non-diabetic renal disease than in diabetic renal disease, but uncertainty remains. Further trials of the effect of ACE inhibitors and ARBs on the progression of renal disease will be most informative if their design includes antihypertensive comparators, and if they are adequately powered to detect differences in clinically important renal endpoints. Such studies will have to be very much larger than has hitherto been customary. There seems to be little justification for ACE inhibitors or ARBs to be first-line choices for renoprotection in diabetes on the basis of efficacy, and residual uncertainty still exists about the inherent value of these drugs in other renal disorders. In view of the present analysis, treatment decisions for hypertension in renal disease should be based on the blood-pressure-lowering effect, comparative tolerability, and cost of antihypertensive treatment.

Contributors

J P Casas contributed to the protocol design, data extraction, and statistical analysis. W Chua and S Loukogeorgakis helped with the protocol design and data extraction. P Vallance helped with the data interpretation. L Smeeth helped with the protocol design and statistical analysis. A D Hingorani contributed to the protocol design and data interpretation. R J MacAllister contributed to the protocol design, data extraction, and analysis and interpretation of data. All authors contributed to the writing and revision of the report.

Conflict of interest statement

P Vallance receives payment as a member of the Research Advisory Board for Glaxo-Smith-Kline. The remaining authors declare that they have no conflict of interest.

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