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Published on: 01 May 2007 - Journal of Hypertension (Lippincott Williams and Wilkins)

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Blood pressure-dependent and independent effects of agents that inhibit the renin–angiotensin system

Blood Pressure Lowering Treatment Trialists' Collaboration*

Objectives **To evaluate the blood pressure-dependent and independent effects of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) on major cardiovascular events.**

Methods **Using data from 26 large-scale trials comparing an ACEI or an ARB with placebo or another drug class, meta-regression analyses were conducted in which treatment-specific relative risks for major cause-specific outcomes [stroke, major coronary heart disease (CHD) events and heart failure] were regressed against follow-up blood pressure differences.**

Results **From a total of 146 838 individuals with high blood pressure or an elevated risk of cardiovascular disease, 22 666 major cardiovascular events were documented during follow-up. The analyses showed comparable blood pressure-dependent reductions in risk with ACEI and ARB ($P \geq 0.3$ for all three outcomes). The analyses also showed that ACEI produced a blood pressure-independent reduction in the relative risk of CHD of approximately 9% (95% confidence interval 3–14%). No similar effect was detected for ARB, and there was some evidence of a difference between ACEI and ARB in this regard ($P = 0.002$). For both stroke and heart failure there was no evidence of any blood pressure-independent effects of either ACEI or ARB.**

Conclusion **There are similar blood pressure-dependent effects of ACEI and ARB for the risks of stroke, CHD and heart failure. For ACEI, but not ARB, there is evidence of blood pressure-independent effects on the risk of major coronary disease events. *J Hypertens* 25:951–958 © 2007 Lippincott Williams & Wilkins.**

Journal of Hypertension 2007, **25**:951–958

Keywords: blood pressure, coronary heart disease, heart failure, meta-analyses, meta-regression analyses, stroke

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Received 27 November 2006 **Revised** 11 January 2007
Accepted 22 January 2007

Introduction

It is well established that the risks of major cardiovascular events are reduced by a broad range of blood pressure-lowering drugs, including angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) [1]. Analyses by the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) have shown that the size of the blood pressure reduction is an important determinant of the size of these treatment effects. It remains uncertain, however, whether mechanisms independent of blood pressure also affect the size of the treatment benefit [2–7]. Agents acting via the renin–angiotensin system have received special attention in this regard, but there have been few formal attempts to investigate any such class-specific effects. Using data from 26 trials of ACEI or ARB that were eligible for inclusion in the BPLTTC overviews, we conducted analyses to determine the relative contribution of blood pressure-dependent and independent mechanisms to the reductions in risk of major cardiovascular events produced by these inhibitors of the renin–angiotensin system.

Methods

Analyses were designed and conducted by the members of the Blood Pressure Lowering Treatment Trialists' Collaboration (the Collaboration). The primary aim of this Collaboration is the conduct of prospectively planned overviews (meta-analyses) of randomized trials of different blood pressure-lowering regimens on major cardiovascular events [8] among patients with high blood pressure, diabetes, a history of coronary heart disease (CHD) or cerebrovascular disease.

Trials included

Trials already participating in the Collaboration that had a treatment group assigned to an ACEI or an ARB, and with results published by the end of 2004, were included in these analyses [6,7,9–32]. These trials fall into three broad groups: trials with a placebo comparator; trials with a 'conventional' therapy (a diuretic or beta-blocker) comparator; and trials with a calcium antagonist comparator. Two potentially eligible ACEI trials were not included because data were unavailable [33,34]. When a trial included more than two treatment arms

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[9,17,20,25] estimates of effect for all possible comparisons were calculated except when early termination of one arm made such estimates infeasible [35,36].

None of the completed BPLTTC trials has involved direct head-to-head comparisons of an ACEI and an ARB. Such comparisons have, however, been undertaken in other completed trials, mainly among patients with heart failure or acute myocardial infarction [3,4,37]. We therefore sought data on the same primary study outcomes from all these trials that otherwise met the inclusion criteria listed in the original Collaboration protocol [8]. Data from these non-BPLTTC trials are reported here in supplementary meta-analyses to assist in the interpretation of findings from the primary analyses.

Outcomes

The primary outcomes for these analyses were: (i) non-fatal stroke or death from cerebrovascular disease; (ii) non-fatal myocardial infarction or death from CHD, including sudden death; (iii) heart failure causing death or requiring hospitalization.

Blood pressure reductions and risk reductions

Blood pressure differences during follow-up

For each trial, the mean difference in follow-up systolic blood pressure levels between the randomized groups was sought. Whenever possible, this difference was calculated using all available follow-up blood pressure measurements, weighted by the time since the last measurement. The blood pressure difference was assigned a negative value when the follow-up blood pressure level was lower in the first listed agent compared with the second listed agent (see Table 1 for format).

Risk reductions

The logarithm of the odds ratio and relative risk and their variance were calculated for each trial and for each outcome according to the principle of intention to treat. An odds ratio or relative risk of less than one indicates that the risk of the relevant outcome was lower in the first listed agent compared with the second listed agent. Percentage reductions in risk were estimated as $[(1 - \mathrm{OR}) \times 100]$, where OR is the odds ratio.

Statistical analyses

In the primary analysis of data from the 26 trials comparing an ACEI or ARB against placebo or another drug class, the association between the difference in follow-up systolic blood pressure levels and the log odds ratio for each of the three outcomes was investigated using random effects meta-regression analysis with inverse variance weighting [38]. Analyses were carried out using the metareg routine in STATA (release 8.0; Stata Corporation, College Station, Texas, USA). Standard methods for the comparison of regression models were used [38]. Initially, using a single regression model, separate regression lines were fitted for trials in which ACEI were the investigational treatment and in which ARB were the investigational treatment. For each outcome, the slopes of these lines were compared, so as to test for a differential effect of blood pressure reduction on risk in trials of ACEI compared with ARB. If these slopes were not significantly different ($P > 0.05$), a parallel lines regression model was fitted, which assumes equal effects of blood pressure reduction with ACEI and ARB. Using this model, the null hypothesis of no separation between the two parallel lines was tested to explore whether there was evidence of a differential effect of the two drug classes independent of blood pressure lowering. Assumptions of linear associations between differences in follow-up blood pressure levels and log odds ratios were tested using standard graphical methods [38]. The intercept of each regression line, a, estimates the value of the log odds ratio when the difference in blood pressure reduction is zero. The slope, b, of each regression line estimates the log odds ratio for a unit change in follow-up systolic blood pressure difference. Both were reported with 95% confidence intervals.

Previous reports from the Collaboration [1] provided clear evidence that regimens based on calcium antagonists, compared with those based on ACEI and diuretics/beta-blockers, provide significantly less protection against hospitalized or fatal heart failure. This effect was independent of differences in achieved blood pressure reduction, and, for this reason, trials with calcium antagonist comparator arms were excluded from the primary analyses of heart failure in this study. To check the validity of this assumption, however, and to test whether the main results were dependent upon other comparator treatments, a series of sensitivity analyses were performed. The heart failure analyses were repeated including the trials with calcium antagonist comparator arms; the stroke and CHD analyses were repeated after the exclusion of trials with calcium antagonist comparator arms; and, for all outcomes, analyses were repeated after excluding trials with diuretic/beta-blocker comparator arms.

In the supplementary meta-analyses of data from the three trials [3,4,37] in which there was a direct randomized comparison of an ACEI and an ARB, overall estimates of relative risk and 95% confidence intervals were calculated for stroke, CHD and heart failure using a random effects model [38].

Results

There were 17 ACEI trials involving 101 626 individuals, and nine ARB trials involving 45 212 individuals (Table 1). Overall, a total of 22 666 events (6419 stroke, 9048 CHD and 7199 heart failure) were included. The mean age of individuals in the ACEI trials was 65 years, of whom 61% were men. In the ARB trials, the mean age of

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Table 1 Characteristics of trials included by randomized comparison

Comparison	Trial	No. randomly assigned to relevant comparison	SBP difference between randomized groups[b]	Odds ratio (95% CI)		
				Stroke	CHD	Serious heart failure
ACEI trials						
ACEI versus placebo						
	CAMELOT	1332	−5.6	0.65 (0.3–1.6)	0.56 (0.3–1.2)[d]	0.78 (0.2–2.9)
	DIAB–HYCAR	4912	−1.8	1.03 (0.8–1.3)	0.79 (0.6–1.1)	0.84 (0.6–1.1)
	EUROPA	12 218	−4.6	0.96 (0.7–1.3)	0.75 (0.6–0.9)[g]	0.61 (0.4–0.8)
	HOPE	9297	−2.9	0.68 (0.6–0.8)	0.79 (0.7–0.9)	0.85 (0.7–1.1)
	PART2	617	−6.0	1.77 (0.5–6.1)	0.66 (0.4–1.1)	0.70 (0.3–1.9)
	PEACE	8290	−3.0	0.76 (0.6–1.0)	1.00 (0.8–1.2)[d]	0.74 (0.6–1.1)
	PROGRESS[a]	2561	−4.9	0.94 (0.7–1.2)	0.98 (0.7–1.4)	0.92 (0.6–1.5)
	SCAT	460	−3.5	0.22 (0.0–1.0)	0.61 (0.2–1.5)	0.20 (0.0–1.8)
ACEI versus diuretic/beta-blocker						
	AASK	877	−1.0	1.01 (0.6–1.08)	NA	0.92 (0.5–1.7)
	ALLHAT	24 309	2.5	1.15 (1.0–1.3)	0.99 (0.9–1.1)	1.10 (0.9–1.3)
	ANBP2	6083	1.2	1.05 (0.8–1.4)	0.70 (0.5–1.0)	0.94 (0.6–1.4)
	CAPPP	10 985	0.3	1.29 (1.0–1.6)	0.96 (0.8–1.2)	NA
	STOP2	4418	2.1	0.90 (0.7–1.1)	0.98 (0.8–1.3)	1.78 (0.8–3.8)
	UKPDS	758	1.2	1.11 (0.6–2.1)	1.22 (0.8–1.8)	0.89 (0.3–2.6)
ACEI versus calcium antagonist						
	ABCD (H)	470	−2.8	0.70 (0.3–1.6)	0.40 (0.2–0.8)	1.32 (0.5–3.3)
	ABCD (N)	480	−2.4	0.56 (0.2–1.6)	0.84 (0.4–1.6)	1.04 (0.4–2.4)
	ALLHAT	18 102	1.3	1.22 (1.0–1.4)	1.00 (0.9–1.1)	0.80 (0.7–0.9)
	CAMELOT	1340	−0.1	1.32 (0.5–3.8)	0.77 (0.3–1.7)	1.32 (0.3–5.9)
	JMIC–B	1650	3.7	1.07 (0.5–2.1)	0.79 (0.4–1.5)	0.84 (0.4–1.9)
	STOP2	4401	−0.6	1.04 (0.8–1.3)	0.86 (0.7–1.1)	1.44 (0.7–3.0)[i]
ARB trials						
ARB versus placebo						
	CHARM–Added	2548	−2.5	1.15 (0.8–1.8)	0.62 (0.4–0.9)[e]	0.82 (0.7–1.0)
	CHARM–Alternative	2028	−2.1	0.85 (0.5–1.3)	1.61 (1.1–2.3)[e]	0.66 (0.5–0.8)
	CHARM–Preserved	3023	−2.9	0.91 (0.6–1.3)	0.77 (0.5–1.1)[e]	0.85 (0.7–1.0)
	IDNT	1148	−3.0	1.06 (0.5–2.1)	0.94 (0.6–1.6)[g]	0.80 (0.6–1.1)
	RENAAL	1513	−1.3	0.95 (0.6–1.4)	0.73 (0.5–1.1)[g]	0.68 (0.5–0.9)
	SCOPE	4937	−3.2	0.76 (0.6–1.0)	1.11 (0.8–1.6)	NA
	Val–HEFT	5010	−5.2	NA	1.01 (0.8–1.2)[h]	0.72 (0.6–0.8)[i]
ARB versus diuretic/beta-blocker						
	LIFE	9193	−1.1	0.74 (0.6–0.9)	0.99 (0.8–1.2)	0.95 (0.8–1.2)
ARB versus calcium antagonist						
	IDNT	1146	1.0	1.87 (0.9–3.9)	1.64 (0.9–2.9)	0.59 (0.4–0.8)
	VALUE	14 400	2.2	1.14 (1.0–1.3)	1.18 (1.0–1.4)	0.87 (0.8–1.0)
ARB versus ACEI trials						
	ELITE II	3152	NS	1.64 (0.8–3.5)[c]	1.27 (1.0–1.6)[f]	0.86 (0.6–1.3)[i]
	OPTIMAAL	5477	−0.1	1.06 (0.8–1.4)	1.10 (1.0–1.2)	1.16 (0.9–1.4)
	VALIANT	9818	−1.1	0.94 (0.8–1.2)	0.96 (0.9–1.1)	1.01 (0.9–1.1)

ACEI, Angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker, CHD, coronary heart disease; CI, confidence interval; NS, not significantly different from zero at 5%; SBP, systolic blood pressure. [a] Only participants assigned to single drug therapy comparison (ACEI versus placebo but not ACEI plus diuretic versus placebo) included. [b] Difference in follow-up blood pressure levels between randomized groups calculated by subtracting level in first listed treatment group from level in second listed treatment group. [c] Non-fatal strokes not included. [d] Fatal myocardial infarction and sudden death not included. [e] Includes fatal cardiovascular events in addition to fatal myocardial infarction and sudden cardiac death. [f] Non-fatal myocardial not included. [g] Sudden cardiac death not included. [h] Fatal and non-fatal myocardial infarction not included. [i] Non-fatal heart failure not included.

participants was 67 years and 58% were men. In both sets of trials, the majority of participants were white Caucasian.

Blood pressure effects

For trials of both ACEI and ARB, the magnitude of the risk reduction achieved for stroke, CHD and heart failure was positively associated with the size of the blood pressure reduction (Table 2). Treatment with ACEI-based regimens achieved a 19% reduction in the risk of stroke, a 16% reduction in the risk of CHD and a 27% reduction in the risk of heart failure for each 5 mmHg reduction in blood pressure. The corresponding reductions in the risk for ARB were 26, 17 and 12% respectively, although the confidence limits around these estimates were wider than for ACEI as a result of the smaller number of patients studied.

Blood pressure-independent effects

For CHD, there was evidence that ACEI provided protection that was greater than that which could be attributed to the blood pressure differences observed. At zero blood pressure reduction, the estimated relative risk reduction for CHD was 9% (3 to 14%, $P = 0.004$; Table 2). There was no such effect apparent for stroke ($P = 0.8$) or heart failure ($P = 0.3$). For no outcome was there evidence that ARB conferred any additional protection beyond that conferred by blood pressure reduction alone, although confidence intervals about these estimates were again wider than for the analyses of ACEI (Table 2).

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Table 2 Estimates of effect attributable to blood pressure and blood pressure-independent effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

	Outcome	ACEI-based regimens vs other regimen	ARB-based regimen vs other regimen	*P* value for no difference in effect between ACEI and ARB-based regimens
Blood pressure effect (OR reduction and 95% CI for 5 mmHg lower blood pressure)	Stroke	19 (2.33)	26 (−12.51)	0.6
	CHD	16 (7.25)	17 (−29.47)	0.7
	Heart failure[a]	27 (13.39)	12 (−41.45)	0.3
Blood pressure-independent effect (OR reduction and 95% CI at zero blood pressure reduction)	Stroke	−2 (−13.8)	1 (−20.18)	0.6
	CHD	9 (3.14)	−8 (−39.17)	0.002
	Heart failure[a]	5 (−5.15)	17 (−12.38)	0.6

ACEI, Angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker, CHD, coronary heart disease; CI, confidence interval; OR, odds ratio. The effect estimates and confidence intervals are odds ratios (and 95% confidence intervals) for each 5 mmHg lower blood pressure and the relative risk (and 95% confidence interval) at zero blood pressure reduction. The null hypothesis of no difference between the two drug classes in either their blood pressure effect or their effect independent of blood pressure is the *P* value. [a] ACEI and ARB trials in which calcium antagonists were a comparator arm were excluded from the primary analyses of the outcome heart failure (see Methods).

Sensitivity analyses

For the outcomes of stroke and CHD, the sensitivity analyses did not provide any evidence to indicate that the observed blood pressure-dependent and independent effects were in any way determined by the composition of the comparator treatment regimen. For the outcome of heart failure, however, the inclusion of trials with a calcium antagonist comparator arm indicated that with zero blood pressure reduction there was a borderline 10% (0 to 19%, $P = 0.06$) reduction in heart failure risk with ACEI treatment and an 18% (9 to 27%, $P = 0.001$) reduction with ARB. These effects were not apparent in the trials that involved other comparator regimens. Given the known limitations of calcium antagonists in preventing heart failure, this finding suggests a blood pressure-independent adverse effect of calcium antagonists rather than a blood pressure-independent protective effect of ACEI or ARB.

Comparisons of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

Indirect comparison

The blood pressure-dependent and independent effects of ACEI and ARB on each outcome were compared to examine whether there was evidence of a difference between the two drug classes. The association between the magnitude of reduction in blood pressure and the size of relative risk reduction for stroke, CHD and heart failure were similar for ACEI and ARB (all $P > 0.2$; Table 2). There was also no evidence that ACEI and ARB were different to each other in terms of their likelihood of providing protection independent of blood pressure lowering for stroke or heart failure (both $P = 0.6$). A single combined regression of ACEI and ARB trials was therefore calculated for stroke and heart failure (Fig. 1). There was, however, evidence ($P = 0.002$) of a difference between ACEI and ARB for CHD, suggesting greater protection independent of blood pressure lowering with ACEI than ARB (Table 2, Fig. 1).

Direct comparison

The effects of ACEI and ARB were directly compared in the supplementary meta-analysis of three head-to-head trials [3,4,37], collectively including 18 447 individuals with acute myocardial infarction or heart failure, or both (Table 1). In those studies, the mean age of participants was 67 years and 70% were men. A total of 6181 major cardiovascular events contributed to the analyses. There was an estimated mean 0.7 mmHg lower follow-up systolic blood pressure in the ARB group compared with the ACEI group. The meta-analyses identified no differences between these two drug classes for any of the three outcomes (Fig. 2), but confidence limits were wide and could not exclude true differences of moderate magnitude.

Discussion

The primary analyses, based on the findings from 26 major trials comparing ACEI or ARB with other comparators, show that the size of blood pressure reduction achieved with either drug class is directly associated with the size of the reductions in the risk of stroke, CHD and heart failure. In addition, the analyses also show that for CHD, treatment with an ACEI provides an additional 9% relative risk reduction beyond that explained by the observed blood pressure differences. Although no such effect was observed for ARB, the confidence limits were too wide to exclude a modest effect. There was, however, evidence that this cardioprotective effect of ACEI was significantly greater than any such effect produced by ARB. No similar blood pressure-independent effect was observed for stroke or heart failure for either drug class.

A supplementary meta-analysis involving data from three trials that directly compared an ACEI and an ARB in patients with acute myocardial infarction or heart failure did not detect a difference between these regimens for any outcome. The confidence limits for each estimate of treatment difference were, however, wide and did not exclude the possible existence of a difference in CHD

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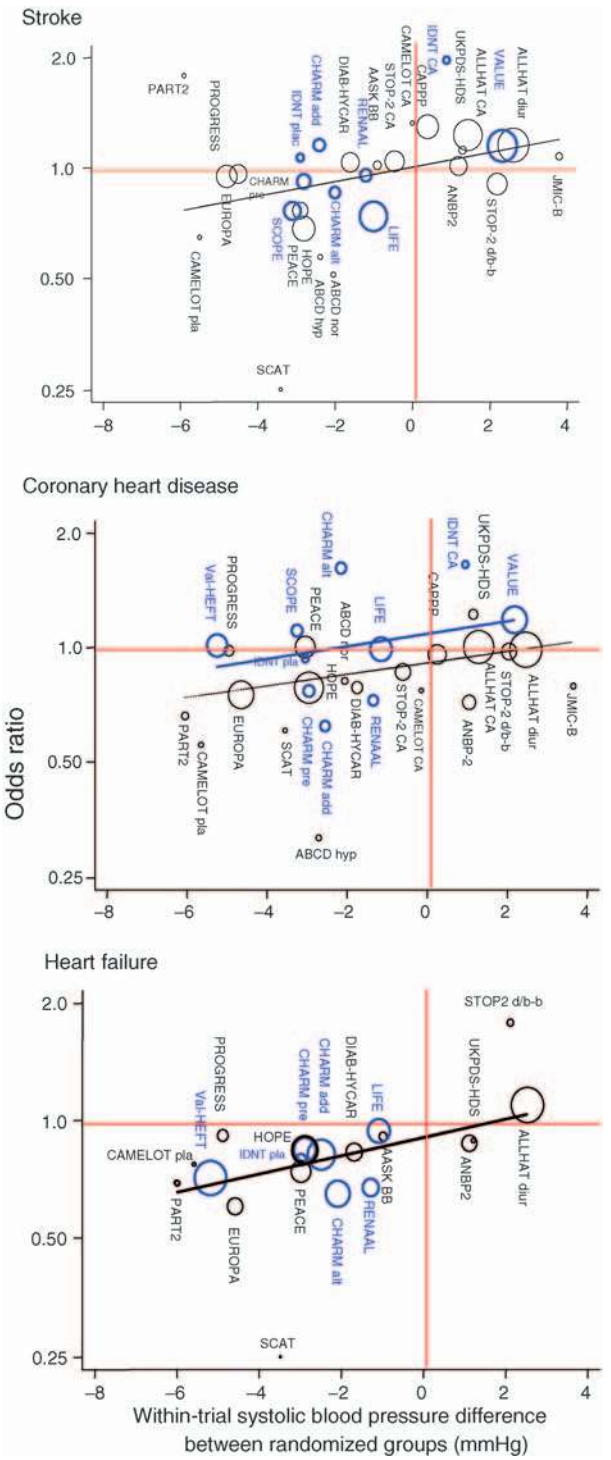
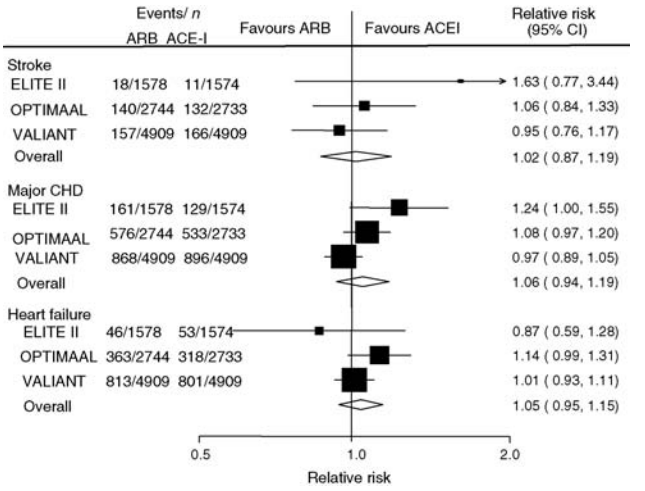
Fig. 1



Associations of blood pressure reduction with risk reduction for stroke, coronary heart disease, and heart failure in trials of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB). Blue circles represent trials of ACEI and black circles represent trials of ARB with the area of each circle inversely proportional to the variance of the log odds ratio. Fitted lines represent the summary meta-regressions for each outcome. ACEI and ARB trials in which calcium antagonists were a comparator arm were excluded from the primary analyses of the outcome heart failure (see Methods).

Fig. 2



Meta-analysis of trials directly comparing angiotensin-converting enzyme inhibitor (ACEI) with angiotensin receptor blocker (ARB)-based regimens for the outcomes of stroke, coronary heart disease (CHD) and heart failure. Boxes and horizontal lines represent relative risk and 95% confidence interval (CI) for each trial. The size of each box is proportional to the inverse of variance of that trial result. Diamonds represent the overall estimate of effect calculated using a random effects inverse variance-weighted method. The width of the diamond represents the 95% CI, and the centre the point estimate of relative risk.

risk of the magnitude suggested by the primary analyses. The confidence limits for coronary disease were consistent with as much as a 19% lower risk, as well as a 6% greater risk, among those assigned the ACEI. Furthermore, patients with heart failure or acute myocardial infarction may respond differently to ACEI and ARB compared with patients selected on the basis of high blood pressure and an elevated cardiovascular risk (who made up the majority of the population in the trials contributing to the meta-regressions).

These findings extend those previously reported by the Collaboration in the second cycle of overviews [1]. Those overviews showed that blood pressure was a major component of the benefit conferred by a range of commonly used blood pressure-lowering regimens. Those analyses were, however, unable to detect or refute any plausibly modest independent effects of ACEI or ARB on any cause-specific cardiovascular outcome. The present analyses provide much more reliable information about the blood pressure-dependent and independent effects of ACEI and ARB for two main reasons: first, the analyses include nine new ACEI and ARB trials with data from an additional 48 745 patients; and second, they involve more sophisticated statistical methods specifically aimed at the identification of blood pressure-dependent and independent components of the treatment effects.

The main potential limitation of these analyses is that indirect comparisons between the effects of ACEI and

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ARB could be confounded by the use of different comparator drug regimens. A series of sensitivity analyses did not suggest that the inclusion or exclusion of trials with a particular comparator treatment regimen produced results substantially different from the main findings for stroke and CHD. In addition, exclusion of the HOPE trial, about which there has been some controversy [39] also had no material effect on the conclusions. For heart failure, in which the effect estimates were systematically altered by the inclusion of the trials that included a calcium antagonist comparator, the results of the sensitivity analyses were consistent for both ACEI and ARB, and appeared to reflect the known limitations of calcium antagonists in preventing heart failure [1].

In conclusion, these analyses confirm that the size of the reduction in blood pressure achieved with either ACEI or ARB is a major determinant of the size of the reductions in coronary disease, stroke and heart failure risks. In addition, these analyses have identified a potentially important blood pressure-independent protective effect of ACEI on the risk of CHD. In particular, there was clear evidence of protection against coronary disease with ACEI even in the absence of any reduction in blood pressure. This blood pressure-independent effect was equivalent to the estimated effect of an additional 3 mmHg reduction in systolic blood pressure. These findings, therefore, suggest that the coronary disease prevention afforded by a blood pressure-lowering regimen may be determined by the choice of agent as well as the size of the blood pressure reduction achieved. Maximization of the benefit may therefore be achieved with a regimen that includes an ACEI together with other drugs in an effort to optimize the size of the blood pressure reduction achieved.

These analyses did not detect a blood pressure-independent beneficial effect of ARB on coronary disease risk, although a real effect of modest magnitude could not be excluded. The results confirm and extend those of other systematic reviews [40,41], however, which have questioned the probity of claims that ARB might increase the risk of CHD [42]. Neither these analyses nor earlier analyses conducted by the Collaboration [1,43] have provided any convincing evidence of an adverse effect of ARB on any major cardiovascular outcome. The observation of greater blood pressure-independent effects on coronary disease in the ACEI trials than in ARB trials, although statistically significant, was neither confirmed nor refuted by meta-analyses of the trials of head-to-head comparisons of ACEI and ARB among patients with acute myocardial infarction or heart failure. These trials even in combination were, however, too small to detect a difference reliably of the magnitude suggested by the primary analyses. An ongoing very large-scale trial [44] comparing the effects of an ACEI and an ARB (and their combination) in a broader high-risk patient group will therefore provide important additional information on this question. In the longer term, studies of direct renin inhibitors [45] will add an important further dimension to this field.

Acknowledgements

Members of the Blood Pressure Lowering Treatment Trialists' Collaboration: L. Agodoa, C. Anderson, F. Asseibergs, C. Baigent, H. Black, B. Brenner, M. Brown, C. Bulpitt, R. Byington, J. Chalmers, R. Collins, J. Cutler, B. Dahlof, B. Davis, D. de Zeeuw, J. Dens, R. Estacio, R. Fagard, K. Fox, T. Fukui, L. Hansson (deceased), R. Holman, L. Hunsicker, Y. Imai, M. Ishii, Y. Kanno, J. Kostis, K. Kuramoto, E. Lewis, M. Lièvre, L.H. Lindholm, L. Liu, J. Lubsen, S. Lueders, S. MacMahon, E. Malacco, G. Mancia, M. Matsuzaki, B. Neal, S. Nissen, T. Ohkubo, T. Ogihara, C. Pepine, M. Pfeffer, B. Pitt, P. Poole-Wilson, M. Rahman, W. Remme, G. Remuzzi, A. Rodgers, P. Ruggenenti, T. Saruta, J. Schrader, R. Schrier, P. Sever, P. Sleight, J. Staessen, K. Teo, G. Viberti, J. Wang, P. Whelton, L. Wing, Y. Yui, S. Yusuf, A. Zanchetti.

Representatives of trials of ARB in acute myocardial infarction and heart failure: CHARM, K. Swedberg; ELITE II, P. Poole-Wilson; OPTIMAAL, J. Kjekshus; VALIANT, M. Pfeffer.

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Sponsorship: B. Neal was supported by a Fellowship awarded by the National Heart Foundation of Australia and the Collaboration Coordinating Centre by programme and project grants provided by the National Health and Medical Research Council of Australia.

There are no conflicts of interest.

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