

Management of hypertension: is it the pressure or the drug?

Blood Pressure Reduction Is Not the Only Determinant of Outcome

Peter S. Sever, FRCP; Neil R. Poulter, FRCP

Whether certain classes of antihypertensive drugs confer benefits beyond those associated with lowering blood pressure remains a highly controversial issue. Data from several meta-analyses have been used to support the notion that most, if not all, of the cardiovascular benefits reported with the use of different classes of antihypertensive drugs are simply a consequence of the extent to which they lower blood pressure. However, we submit evidence in this review that the diverse pharmacological actions of several antihypertensive medications may have benefits beyond their blood pressure-lowering effects and that, in the case of certain classes of drugs, notably β -blockers, adverse metabolic effects of these drugs may actually mitigate the potential benefits of blood pressure lowering.

The Early Placebo-Controlled Hypertension Trials and the Shortfall in Coronary Heart Disease Prevention

The early placebo-controlled trials of the treatment of hypertension, several of which were undertaken in high-risk patient populations, provided convincing evidence for substantial reductions in the risk of stroke but little or no evidence for benefits on coronary heart disease (CHD) events.¹⁻⁶ However, the design, numbers of patients recruited, and event rates in individual trials provided inadequate power to eval-

uate the impact of treatment on CHD events. In only 1 trial, the Hypertension Detection and Follow-up Programme (HDFP),⁷ was a reduction in CHD events observed in those assigned "special care" compared with those assigned "usual care." The conduct of this particular trial, however, differed from the other early trials in that those in the special care group would have been likely to benefit from more comprehensive intervention on other cardiovascular risk factors.

In the first meta-analysis of the placebo-controlled trials of antihypertensive drug therapy,⁸ HDFP was excluded, presumably because the authors of the meta-analysis considered that outcome benefits could have occurred independently of blood pressure reduction. In subsequent meta-analyses, however, for reasons that are unclear, HDFP was included.⁹

From observational studies^{10,11} (Figure 1), it was possible to estimate the potential cardiovascular risk reduction associated with a blood pressure difference of 10- to 12-mm Hg systolic and 5- to 6-mm Hg diastolic pressure, the average reduction in blood pressure observed in the early trials. In the case of stroke, the relative risk reduction of 42% observed in the trials was compatible with the 35% to 40% difference associated in prospective observational studies, with a long-term difference of 5 to 6 mm Hg in diastolic pressures. In the case of CHD, however, the observed risk reduction of 14% to 16% (9% if HDFP is excluded) fell short of the 20% to 25%

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From Imperial College, London, UK (P.S.S., N.R.P.), and the Department of Preventive Medicine, RUSH Medical College of RUSH University at RUSH University Medical Center, Chicago, Ill (W.J.E., M.C.J., H.R.B.).

Correspondence to Professor Peter Sever, International Centre for Circulatory Health, Imperial College London, 59 N. Wharf Rd, London, W2 1PG, UK (e-mail p.sever@imperial.ac.uk), or William J. Elliott, MD, PhD, 1700 W. Van Buren, Suite 470, Chicago, IL 60612 (e-mail welliott@rush.edu). (Circulation. 2006;113:2754-2774.)

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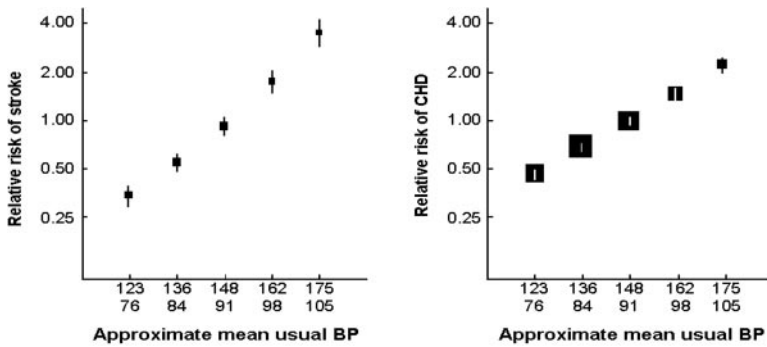


Figure 1. Relative risks of stroke (843 events) and CHD (4856 events) for 5 categories of blood pressure (BP) from the combined results of prospective observational studies. Estimates of usual systolic (SBP) and diastolic (DBP) blood pressures are taken from the average values 4 years after baseline in the Framingham study. Squares represent disease risks in each category relative to the risk in the whole study population; sizes of squares are proportional to number of events in each DBP category; and 95% CIs for estimates of relative risk are denoted by vertical lines.¹⁰

risk difference predicted from observational data for a similar difference in blood pressure. This apparent shortfall could have represented the play of chance because the upper 95% confidence limit for this significant CHD reduction in these trials was 22%. Alternatively, these observations could reflect a genuine shortfall in the protective effects against CHD events of what were exclusively older antihypertensive therapies (diuretics and β -blockers).

Observations from 2 trials conducted by the Medical Research Council in the United Kingdom suggested that treatments based on diuretics or β -blockers might confer different degrees of protection against stroke and CHD.^{3,12} Notably, in the Medical Research Council trial in older subjects with hypertension,¹² protection against CHD events was observed with diuretic-based treatment but not with β -blocker-based treatment. More recently, meta-analyses of β -blocker-based trials in hypertension have suggested that this class of agent confers less reduction in cardiovascular risk than other classes of antihypertensive drugs,¹³ particularly in those without prior evidence of cardiovascular disease. In contrast, when β -blockers have been assessed in long-term trials after myocardial infarction, allocation to active treatment or control resulted in differences of only a few millimeters of mercury (as little as 1 to 2 mm Hg in some individual trials).¹⁴ The average reduction in recurrent CHD events of 26% was too large to be attributed to this minor degree of blood pressure reduction and was perhaps indicative of pharmacological benefit independent of blood pressure lowering. These observations also highlight the potential for drug-induced benefits on cardiovascular events to be dependent on the patient subgroup.

Trials With Calcium Channel Blockers and Drugs That Block the Renin-Angiotensin System in High-Risk Patients

Placebo Controlled

Because of the cardiovascular benefits observed in these early placebo-controlled trials of blood pressure reduction, it became increasingly difficult to repeat placebo-controlled studies in hypertensive patients using newer drugs such as angiotensin-converting enzyme inhibitors (ACEIs) and calcium channel blockers (CCB), and with the exception of the Systolic Hypertension in Europe Trial (SYST-EUR),¹⁵ which compared nitrendipine with placebo in patients with isolated systolic hypertension, other trials comparing ACEI or CCB with placebo were carried out in very different patient populations that were not recruited on the basis of hypertension but included those with established cardiovascular or renal disease.^{16,17} Therefore, unlike many of the early trials with diuretics and β -blockers, these trials did not assess reduction in CHD or stroke risk in primary prevention in hypertensive subjects. The risk reductions of 30% to 40% in stroke and \approx 20% in CHD observed in placebo-controlled trials with ACEIs or CCBs in high-risk patients were associated with 5/2-mm Hg (ACEI) and 8/4-mm Hg (CCB) differences in blood pressure^{16,17} (Figure 2). These observations suggest that considerably greater risk reductions occur for a given difference in blood pressure than would have been predicted from the observational data (albeit in lower-risk populations).

In the Heart Outcomes Prevention Evaluation (HOPE),¹⁸ \approx 9000 patients, who were on average 66 years of age and had evidence of vascular disease or diabetes, were randomly

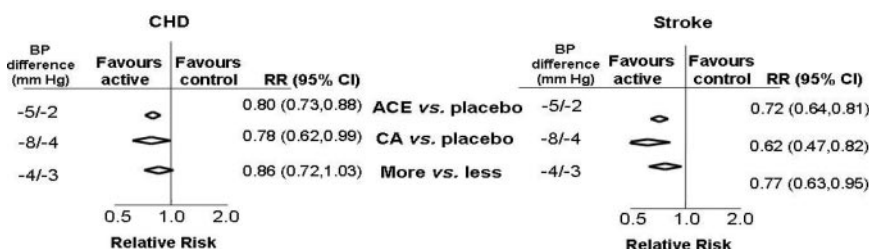


Figure 2. CHD and stroke events in studies comparing ACEIs and calcium antagonists with placebo and more and less intensive blood pressure-lowering regimens. BP indicates blood pressure; RR, relative risk.

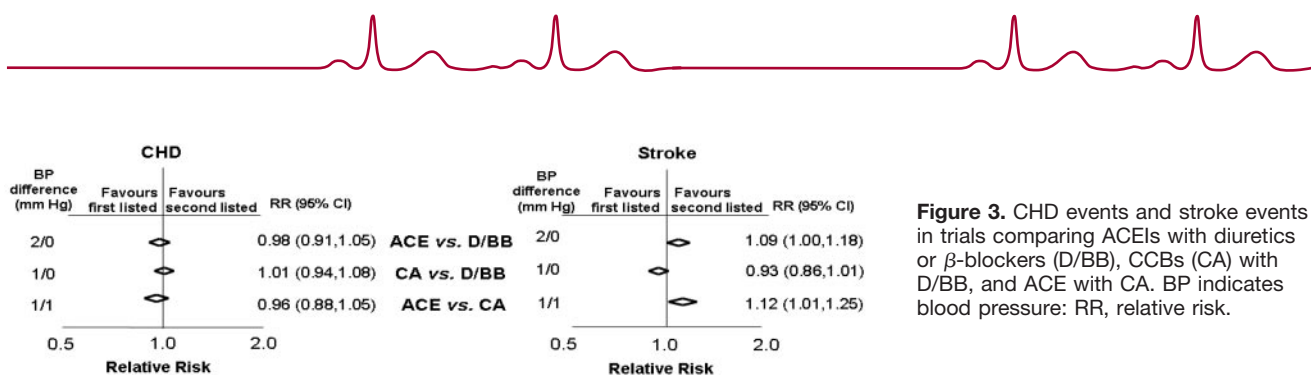


Figure 3. CHD events and stroke events in trials comparing ACEIs with diuretics or β -blockers (D/BB), CCBs (CA) with D/BB, and ACE with CA. BP indicates blood pressure; RR, relative risk.

assigned to ramipril 10 mg daily or placebo for a mean of 5 years. In this study, the primary outcome was a composite of myocardial infarction, stroke, or death from cardiovascular causes. This was reduced by 22% in favor of ramipril, together with a 20% risk reduction in myocardial infarction. The reported blood pressure reduction of 3/2 mm Hg was proposed by the authors to account for no more than one quarter of the reduction in the rates of myocardial infarction. However, in HOPE, owing to administration of the short-acting ACEI ramipril at night and the measurement of blood pressure the following day, the reported differences in blood pressure between the active and placebo treatment arms may have been underestimated.

In the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA),¹⁹ >13 000 patients with previous coronary disease, were randomized to perindopril 8 mg daily or placebo. Follow-up was for 4.2 years, with a primary end point of cardiovascular death, nonfatal myocardial infarction, or cardiac arrest. The average age of patients was 60 years, and most were on concomitant β -blockers and lipid-lowering therapy. In those assigned perindopril, there was a highly significant 20% reduction in the primary end point and a 22% reduction in nonfatal myocardial infarction. Although blood pressure was on average 5/2 mm Hg lower in those assigned perindopril, similar proportional risk reduction was seen in those who were not hypertensive at baseline compared with those who were, and in a post hoc analysis, similar risk reductions were observed in those in whom the ACEI had little or no effect on blood pressure, compatible with the hypothesis that in this particular patient group, some of the benefits observed would be independent of blood pressure.

Head-to-Head Comparisons of Active Treatments: Limitations of Trial Design

After the introduction of the ACEI and CCBs, several head-to-head studies were conducted comparing older treatments (diuretic or β -blocker) with either ACEI- or CCB-based treatment.^{16,17} Most of the studies were underpowered to detect potential differences in CHD event rates and indeed failed to do so. Further prospective meta-analyses were conducted in an attempt to determine whether any particular drug class conferred advantages over the older drugs, which were a mixture of diuretic-based, β -blocker-based, or diuretic- and β -blocker-based strategies.^{16,17}

Thus, any potential advantage or disadvantage of either of these drug classes could be masked. Additionally, in the case of diuretic-based treatment, there has been little attempt to assess whether long-term outcome is influenced by the dose of agent used, leading to widespread assumptions that “low-dose” diuretic would be equivalent to the older moderate- and even high-dose diuretics used in the earlier trials.

In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial,²⁰ in which the angiotensin receptor blocker losartan was compared with the β -blocker atenolol, thiazide diuretics were added to each treatment arm in most patients. Pressures throughout the trial were apparently similar, although no detailed analysis of mean blood pressures for the 2 treatment limbs throughout the trial has been published. There were no significant differences in CHD outcome, but significant differences in stroke were seen in favor of losartan, which seem disproportionate to the negligible differences in blood pressure. In light of other studies with β -blockers and subsequently the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) results, it seems likely that this differential outcome on stroke is attributed largely to the inefficacy of the β -blocker-based treatment strategy and potentially explained by lower central aortic pressures²¹ with the losartan-based treatment than with the atenolol-based treatment for equivalent peripheral brachial artery blood pressures.

Recent Meta-Analyses

In an effort to maintain high event rates and thereby to reduce trial costs, most of the more recent hypertension studies were carried out in much-higher-risk patient groups than earlier trials. The conclusion from pooled analyses of these trials comparing older and newer drugs was that there were marginal benefits of diuretics and/or β -blockers versus ACEIs and of CCBs versus ACEIs on stroke outcome¹⁷ (Figure 3). In the case of CHD end points, hazard ratios approximated unity when ACEIs or CCBs were compared with diuretic- and/or β -blocker-based regimens (Figure 3). Similarly, neither the composite end point of total cardiovascular events nor cardiovascular mortality differed significantly between newer and older treatment regimens. In these pooled analyses, overall mean systolic blood pressure differences between treatment groups during follow-up were between 1 and 2 mm Hg.

In the most recent meta-analysis by Verdecchia and colleagues²² (Figures 4 and 5), when outcome was plotted against blood pressure differences, benefits on stroke events

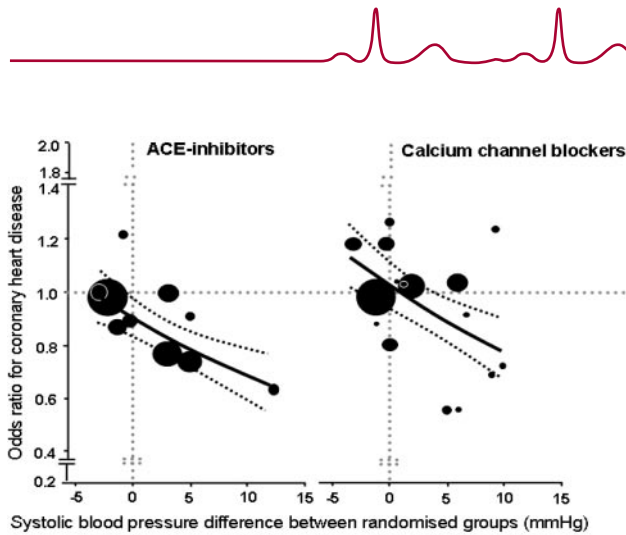


Figure 4. Relationship between odds ratios for CHD and differences in achieved systolic blood pressure between randomized groups in trials with experimental treatment based on ACEIs or CCBs. Circles represent individual trials and have a diameter proportional to the inverse of the variance of the odds ratios in individual trials.²²

were greater than expected in trials with CCBs and benefits on CHD outcome were beyond those expected from the differences in blood pressure in the case of ACEI trials. These observations would, in general, support the favorable evidence on stroke outcome with CCBs reported in earlier meta-analyses and the benefits of ACEIs demonstrated in post-myocardial infarction trials in which the relative risk reduction of $\approx 25\%$ is more than that expected from the observed differences in blood pressure.

Most Recent Data From Head-to-Head Trials: ALLHAT, VALUE, and ASCOT

Data from large individual trials may provide more insight into the benefits or harm of particular drug treatment strategies than information provided by meta-analyses in which the

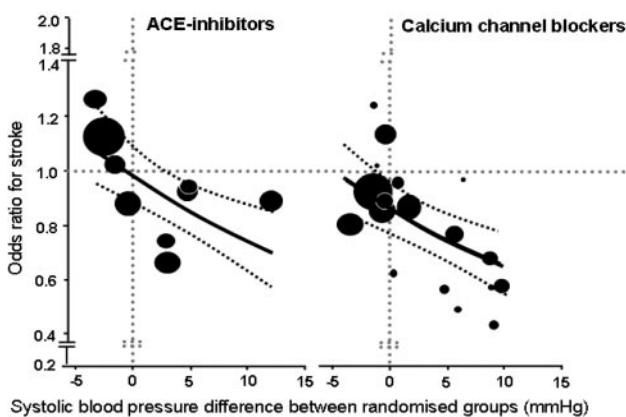


Figure 5. Relationship between odds ratios for stroke and differences in achieved systolic blood pressure between randomized groups in trials with experimental treatment based on ACEIs and CCBs. Circles represent individual trials and have a diameter proportional to the inverse of the variance of the odds ratios in individual trials.²²

inappropriate inclusion of individual trials may distort the overall conclusions, eg, the inclusion of HDFP in the Collins and Peto⁹ meta-analysis and in more recent meta-analyses the inclusion of the CAPtopril Prevention Project (CAPPP),²³ in which randomization was biased and results likely were confounded by 24-hour blood pressure differences.

Three large trials, Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT),²⁴ Valsartan Antihypertensive Long term Use Evaluation trial (VALUE),²⁵ and ASCOT,²⁶ focused on CHD as the primary end point comparing various treatments. In both ALLHAT and VALUE, second-line drugs added to the “newer” first-line treatments and taken by most subjects were invariably “older” drugs such as β -blockers, clonidine and reserpine (ALLHAT), and thiazide diuretics (VALUE). In ASCOT, the newer treatment regimen of a CCB with or without an ACEI was not contaminated by either β -blockers or thiazide diuretics and therefore represents the only true comparison of new versus old combinations of treatment.

ALLHAT²⁴ randomized $>40\,000$ patients in a double-blind study comparing 3 first-line agents: the CCB amlodipine, the ACEI lisinopril, and the α -blocker doxazosin with the diuretic chlorthalidone as the reference drug. The α -blocker limb of the study was terminated early because of an excess of certain cardiovascular end points in the doxazosin arm compared with chlorthalidone. First-line drugs were titrated monthly to achieve a target blood pressure of $<140/90$ mm Hg (amlodipine 2.5 to 10 mg daily, lisinopril 10 to 40 mg daily, chlorthalidone 12.5 to 25 mg daily). If goal blood pressures were not achieved, step 2 medications, including reserpine (0.05 to 0.2 mg daily), clonidine (0.1 to 0.3 mg BID), or atenolol (25 to 100 mg daily), were added. Step 3 medications included hydralazine (25 to 100 mg BID). Hypertensive subjects recruited into ALLHAT were an average of 67 years of age, 47% were female, and 32% were black. Patients were at moderately high risk ($\approx 2\%$ CHD risk per year). The average length of follow-up was 4.9 years. Blood pressure levels at baseline were evenly matched falling from 146/84 mm Hg in all 4 groups to 133.9/75.4 mm Hg (chlorthalidone), 134.7/74.6 mm Hg (amlodipine), 135.9/75.4 mm Hg (lisinopril), and 137.4/76.6 mm Hg (doxazosin). Hence, compared with the chlorthalidone group, the mean follow-up systolic blood pressure was ≈ 2 mm Hg higher in the lisinopril group, 1 mm Hg higher in the amlodipine group, and 3 mm Hg higher in the doxazosin group. Differences in blood pressure between the treatment limbs were greatest during the first 2 years of follow-up, after which dose titration and the addition of second- and third-line therapy reduced these differences.

Despite these mean blood pressure differences, CHD outcomes (the primary end point) were not different among those in the 4 comparator drug groups. There was a 15% excess of stroke in the lisinopril arm compared with chlorthalidone and a 26% excess of stroke when the doxazosin and chlorthalidone groups were compared. Notably, in blacks, there was a 40% excess of stroke in those assigned lisinopril compared with chlorthalidone. The ALLHAT authors con-

cluded that these differences in stroke outcome could not be explained by differences in blood pressure. However, this depends on which reference group is chosen for the derivation of “expected outcome” to compare with that observed. The ALLHAT authors based their expected outcome on the original observational studies referred to previously,^{10,11} not the more recent intervention trials involving high-risk patients in whom smaller differences in blood pressure have been associated with larger differences in outcome. Does ALLHAT provide evidence for benefits beyond blood pressure? Indirectly, it does in that almost identical rates of coronary events occurred among the 4 blood pressure drug classes evaluated despite different degrees of blood pressure reduction, raising the intriguing possibility that had blood pressure levels been equivalent throughout the trial in the ACEI, CCB, and doxazosin and chlorthalidone arms, would the newer treatments have conferred greater protection against CHD events?

The VALUE investigators²⁵ designed a study also focused on CHD end points, but in this case, on a composite end point that included revascularization procedures and hospital-based heart failure, in addition to nonfatal myocardial infarction and fatal CHD. More than 15 000 patients were randomized in a double-blind fashion to either the angiotensin receptor blocker valsartan (80 to 160 mg daily) or the CCB amlodipine (5 to 10 mg daily). Both arms had the diuretic hydrochlorothiazide (12.5 to 25 mg daily) added in an attempt to achieve target blood pressures of <140/90 mm Hg. Further add-on drugs were used as needed to achieve target blood pressure at the discretion of the investigator. VALUE recruited patients of an average age of 67 years, 42% of whom were female. The patient population was at high cardiovascular risk, most with established coronary, cerebral, or other arterial disease. Blood pressure fell from 154.5/87.4 to 139.3/79.2 mm Hg with valsartan-based regimens and from 154.8/87.6 to 137.5/77.7 mm Hg with amlodipine-based regimens. Blood pressure reductions from baseline until the study end were 15.2/8.2 and 17.3/9.9 mm Hg in the valsartan and amlodipine arms, respectively. Differences between the treatment arms were again greatest in the first year of treatment, maximally 4/2 mm Hg in favor of the amlodipine-based regimen, and on average throughout the trial differed by $\approx 3/2$ mm Hg.

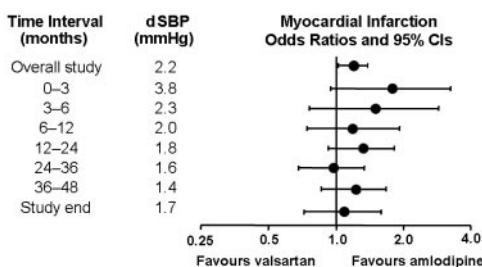


Figure 6. Differences in blood pressure (dSBP) between treatment groups with odds ratios for myocardial infarction and CIs during consecutive time points in the study.²⁵

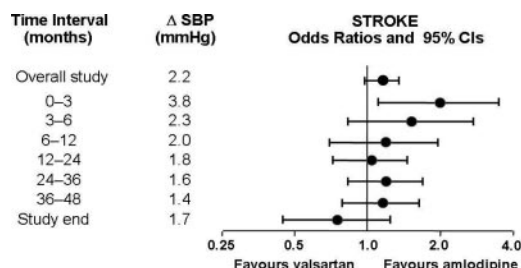


Figure 7. Differences in blood pressure (Δ SBP) between treatment groups with odds ratios for stroke and 95% CIs during consecutive time periods in the study.²⁵

There was a 3% nonsignificant difference between the 2 treatment arms in the primary composite cardiac end point favoring the amlodipine-based limb and a 15% nonsignificant excess of strokes in the valsartan-based regimen and a significant 19% excess of fatal and nonfatal myocardial infarction in those receiving valsartan. The authors of VALUE pursued their belief that blood pressure differences in this trial accounted for the differences in outcome by a time-dependent analysis (Figures 6 and 7) of CHD and stroke events throughout the trial that showed that the excess of stroke and CHD events in the valsartan group was maximal during the first year when blood pressure differences were greatest and that the differences between the arms diminished with time as the blood pressure curves came together. There are problems, however, with this time-dependent analysis because separating out the first year's data and reanalyzing subsequent time intervals lead to a loss of randomization. In this trial, it is difficult to conclude that any benefits were clearly independent of blood pressure reduction with respect to CHD events, although in terms of new-onset diabetes, blood pressure-independent benefits of valsartan were apparent.

ASCOT²⁶ recruited ≈ 20 000 patients 40 to 79 years of age who had either untreated or previously treated hypertension who were then randomized to receive either amlodipine (5 to 10 mg daily) or atenolol (50 to 100 mg daily). After dose titration, the second-line drugs perindopril (4 to 8 mg daily) and bendroflumethiazide-K (1.25 to 2.5 mg daily), respectively, were added as required to achieve goal blood pressures of <140/90 or <130/80 mm Hg in those with diabetes. Thereafter, the third-line drug doxazosin-GITS (4 to 8 mg daily) and other drugs were added to either drug regimen as required to achieve target blood pressures. By way of a factorial design, >10 000 patients with total cholesterol levels of ≤ 250 mg/dL were randomized to atorvastatin 10 mg or placebo.²⁷

The patient population recruited into ASCOT differed substantially from those recruited into several other recently reported hypertension trials in that a history of prior myocardial infarction or current CHD excluded patients from participation. Although 3 additional cardiovascular risk factors were required for entry, the overall risk of the ASCOT patient population was low (<1% per annum CHD event rate) and much less than among those recruited into ALLHAT and

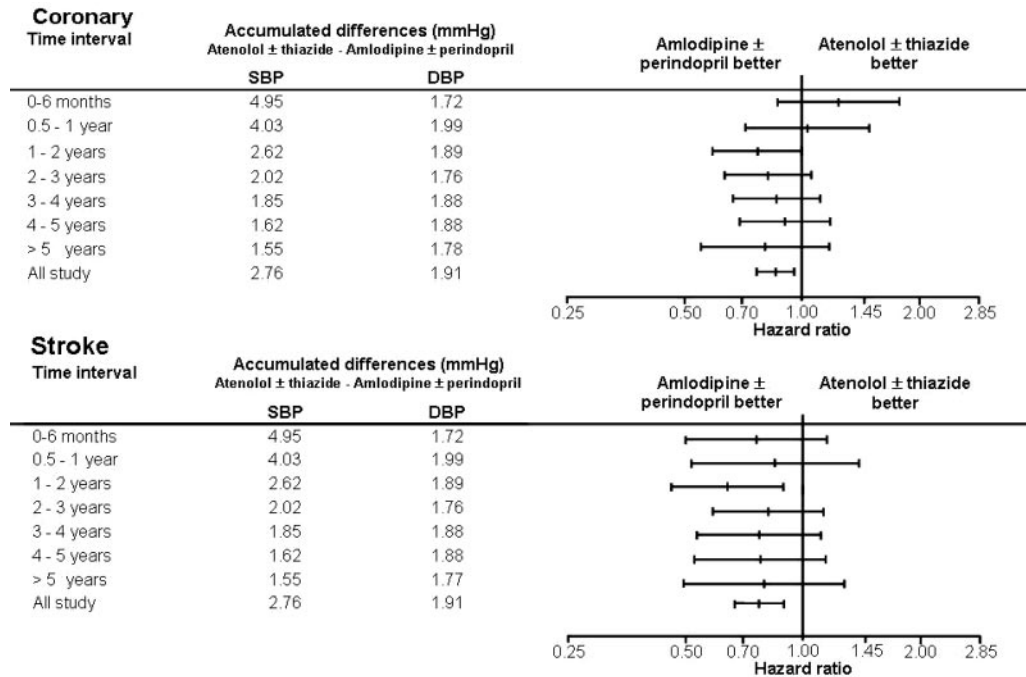


Figure 8. Odds ratios and 95% CIs for coronary and stroke events associated with amlodipine-based vs atenolol-based regimens at various times points and accumulated mean differences in systolic and diastolic blood pressures.

VALUE. The average age of the patients was 63 years, 23% were female, and 95% were white.

Blood pressure levels fell from 163.9/94.5 to 137.7/79.2 mm Hg in the atenolol-based treatment arm and from 164.1/94.8 to 136.1/77.4 mm Hg in the amlodipine-based treatment arm. Again, better blood pressure lowering in favor of the CCB treatment regimen was seen particularly early in the trial. Overall, blood pressure (integrated mean) was 2.7/1.9 mm Hg lower on the amlodipine-based regimen than the atenolol-based regimen, with maximal differences of ≈5 mm Hg systolic in the first year but only 1.6 mm Hg systolic by the end of the trial.

Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA) was stopped prematurely because of significant all-cause mortality differences between the 2 treatment arms and concerns that those patients assigned the β-blocker/thiazide regimen would continue to be disadvantaged if the trial went to its planned completion.

All-cause mortality and cardiovascular mortality were reduced significantly (11% and 24%, respectively) among those allocated to the amlodipine/perindopril regimen. The primary end point (nonfatal myocardial infarction and fatal CHD) was reduced by 10%, but this did not achieve statistical significance. Other prespecified coronary end points, including the primary end point and excluding silent myocardial infarction, and a composite total coronary end point, however, were significantly reduced (13% and 13%, respectively) among those allocated to the amlodipine/perindopril regimen, as were stroke events (23%).

These observations raised the question as to what extent the blood pressure differences, which occurred predominantly early in the trial, explained the differences in cardiovascular events seen in the 2 blood pressure arms of the study.

The observed blood pressure difference of <3/2 mm Hg seen in ASCOT-BPLA might explain an ≈4% to 8% reduction in coronary outcome and an 8% to 14% reduction in strokes based on prospective observational studies^{10,11} and the most recent pooled analysis of clinical trials reported by the Blood Pressure Lowering Treatment Trialists Collaboration.¹⁷

Correcting for blood pressure differences in randomized trials, however, is problematic, and there is no ideal way to do so. Nevertheless, further analyses using in-trial data were undertaken²⁸ in an attempt to ascertain to what extent the beneficial effect of the amlodipine/perindopril regimen could have been explained by the differences in blood pressure and the other variables that occurred after randomization.

First, analyses were performed to evaluate any temporal association between blood pressure differences and coronary and stroke end points using differing censoring points throughout the trial (Figure 8). These analyses were then extended using a technique similar to but more rigorous than the serial median matching carried out in the VALUE trial analyses. It was clear in the ASCOT analyses that for coronary and stroke end points, there was no apparent temporal link between the size of blood pressure differences and the difference in end points between the amlodipine/perindopril regimen and the atenolol/thiazide regimen.

In addition to blood pressure differences, assignment to the atenolol/thiazide regimen was associated with significant metabolic differences compared with the amlodipine/perindopril regimen. Although there were no differences in low-density lipoprotein cholesterol between the 2 limbs (which would not have been expected), serum high-density lipoprotein (HDL) cholesterol, pulse rate, and potassium were lower, and body weight, serum triglycerides, fasting glucose, and creatinine were higher among those on the β -blocker/thiazide regimen. All of these parameters have previously been reported in association with β -blockers and diuretics, and the possibility arose that these adverse metabolic changes could have contributed to differences between the 2 arms of the trial, given that all have been implicated as independent cardiovascular risk factors.

Further analyses were undertaken using updated Cox regression techniques to provide additional information on the role that differences in various measures of blood pressure and serum HDL cholesterol, triglycerides, potassium and creatinine, body weight, pulse rate, and blood glucose could have played in explaining the differential risk reductions observed in ASCOT-BPLA. In these analyses, which should be interpreted cautiously, it appears that blood pressure differences contributed in a minor way to the risk reduction in coronary events but contributed more to stroke differences.²⁸ For stroke, blood pressure appeared to contribute $\approx 30\%$ of the benefits of the amlodipine/perindopril regimen, and for coronary events, HDL cholesterol accounted for $\approx 30\%$ of event rate differences. Overall, in multivariate analyses, differences in blood pressure and the other variables considered accounted for about half the differences in coronary events and $\approx 40\%$ of stroke events (Figures 9 and 10).

The possibility that other factors could have contributed to the outcome differences seen in ASCOT-BPLA has arisen from 2 other sources of information within the trial.

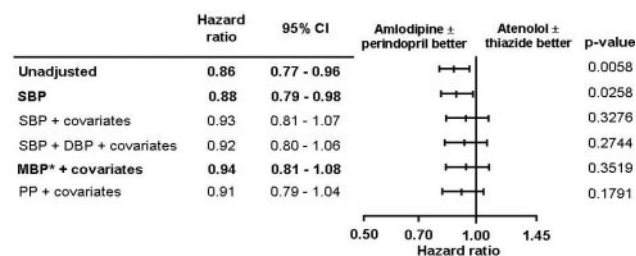
First, an investigation of the differential impact of the amlodipine/perindopril and atenolol/thiazide regimens on central aortic pressure and clinical outcomes (the Conduit

Artery Function Evaluation [CAFE] Study) was a substudy of ASCOT, and the results may shed some light on the mechanisms contributing to the differences in cardiovascular outcomes observed between the 2 treatment limbs in ASCOT-BPLA.²¹

In CAFE, >2000 ASCOT patients had observations on radial artery applanation tonometry and pulse-wave analysis using the Sphygmocor device, and central aortic pressures and hemodynamic indexes were derived on several occasions during the 5 years of the trial. The key results of this substudy were that despite almost identical brachial artery pressures in the 2 blood pressure limbs of the trial, there were substantial reductions in central aortic pressures and other hemodynamic indexes in favor of the amlodipine/perindopril regimen. Central aortic systolic pressure and central aortic pulse pressure were 4 and 3 mm Hg lower, respectively, on the amlodipine/perindopril regimen. In addition, the augmentation index was $\approx 6\%$ lower in the amlodipine/perindopril regimen. This study confirms other reports^{29–31} that β -blockers lower central aortic pressure to a lesser extent than other drugs for an equivalent reduction in peripheral arterial pressure. In this substudy, there was a significant relationship between central pulse pressure and a composite end point of cardiovascular and renal events. The authors of CAFE hypothesized that some of the differences in outcome in ASCOT-BPLA could be explained by differences in central aortic pressures. Another important conclusion from this study was that the reduced beneficial effect of atenolol-based treatment on central arterial hemodynamics was dependent on heart rate slowing; thus, the observations could be extrapolated to other β -blockers and may not be specific to atenolol-based treatment.

Second, a possible further mechanism underlying the observed differences in cardiovascular end points between the 2 treatment arms in ASCOT-BPLA has come about as a result of the prespecified evaluation of any synergy between the use of lipid-lowering therapy and antihypertensive treatments.²² Experimental studies and at least 1 clinical study have indicated the potential for synergy between amlodipine and statins on cardiovascular outcomes.^{32,33} The physicochemical properties of atorvastatin and the dihydropyridine CCB amlodipine, by virtue of their lipophilicity and oppositely charged molecules, lend themselves to tight bonding in the lipid bilayer of cell membranes and hence the potential for prolonged actions on a number of molecular and cellular processes involved in the biology of atherosclerosis in the vessel wall (R.P. Mason and R. Kay, personal communication).

Overall, when both blood pressure treatments in ASCOT-LLA are combined, CHD events (nonfatal myocardial infarction and fatal CHD) were significantly lower in the atorvastatin group than in the placebo group (36%; $P=0.005$). However, in those assigned the amlodipine/perindopril regimen, CHD events were reduced by 53% ($P=0.0001$) in association with allocation to atorvastatin compared with



* MBP = (SBP+DBP)/2

Figure 9. Unadjusted and adjusted hazard ratios for coronary events (nonfatal myocardial infarction and fatal CHD and coronary revascularizations) associated with amlodipine-based vs atenolol-based regimens. Covariates at baseline included age and number of risk factors. Updated covariates were heart rate, glucose, HDL cholesterol, triglycerides, potassium, body weight. *Mean blood pressure (MBP).

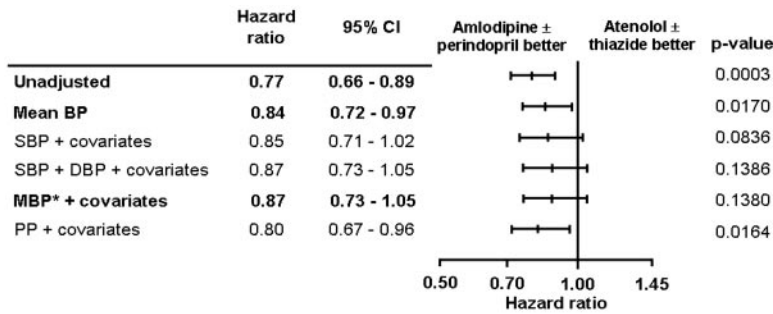


Figure 10. Unadjusted and adjusted hazard ratios for stroke events associated with amlodipine-based vs atenolol-based regimens. Covariates at baseline were age and number of risk factors. Updated covariates included heart rate, glucose, HDL cholesterol, triglycerides, potassium, and body weight. *Mean blood pressure (MBP) equals systolic (SBP) plus diastolic (DBP) blood pressure divided by 2.²⁸

* MBP = (SBP+DBP)/2

placebo, whereas in those assigned the atenolol/thiazide regimen, the risk reduction associated with allocation to atorvastatin compared with placebo was 16% ($P=NS$). Formal testing for interaction between lipid-lowering and blood pressure-lowering therapy was of borderline statistical significance for a tertiary end point ($P=0.025$).³⁴

In our evaluation of the extent to which the observed differences in the 2 blood pressure-lowering strategies in ASCOT-BPLA could be explained by differences in blood pressure and other risk factors that were differentially affected after randomization,²⁸ we concluded that it remained possible that additional mechanisms could have contributed to the event rate differences. The most recent analyses indicate that there may be synergy between the amlodipine/perindopril regimen and lipid lowering with atorvastatin and that this could be one such additional mechanism.

New-Onset Diabetes

In ALLHAT²⁴ and ASCOT,²⁶ important differences were observed in the extent to which different antihypertensive treatment strategies were associated with new-onset diabetes. It seems clear from these 2 studies and earlier observations^{20,35} that β -blocker and thiazide drugs, particularly when used in combination, increase the incidence of new-onset diabetes compared with strategies based on CCBs or drugs that block the renin-angiotensin system. In VALUE,²⁵ in which the thiazide diuretic was added to either a CCB or an angiotensin receptor blocker, new-onset diabetes also occurred less frequently in those originally assigned the angiotensin receptor blocker. Although the duration of new-onset diabetes observed in these trials was short and thus unlikely to be associated with excess cardiovascular risk, it seems probable in the longer term that cardiovascular event rates would be higher in those with new-onset diabetes, a phenomenon clearly independent of drug effects on blood pressure.

Conclusions

Placebo-controlled trials in hypertensive patients of diuretics and β -blockers conferred less-than-expected protection against CHD events than would have been predicted from observational studies. When similar placebo-controlled trials

were carried out with newer agents such as the CCBs in hypertensive patients, benefits on stroke and CHD were compatible with the reductions in blood pressure seen in the trials. However, when placebo-controlled trials have been carried out, notably in patients with ACEIs, in patients recruited on the basis of high cardiovascular risk rather than high blood pressure, the benefits observed appeared greater than would be expected from the differences in blood pressure.

When β -blockers are compared with other classes of drugs, they are less effective in preventing strokes in hypertensive subjects and are probably less effective than diuretics and other classes of drugs, including ACEIs and CCBs, in the primary prevention of CHD for equivalent blood pressure reduction. The disadvantages of β -blocker-based treatment may be partly explained by the hemodynamic effects of β -blockers on central aortic pressure. In addition, adverse metabolic effects of β -blockers, notably on HDL cholesterol, also may contribute to differential effects on CHD outcome as seen in ASCOT. By way of contrast, in the secondary prevention of CHD, β -blockers appear to prevent recurrent CHD to a greater extent than blood pressure reduction would predict.

For ACEIs, their poorer outcome in some trials such as CAPPP and ALLHAT on stroke events is compatible with and hence best explained by blood pressure differences. Recent meta-analyses of trials with ACEIs and CCBs involving high-risk patients seemingly provide evidence of greater cardiovascular risk reductions than expected on the basis of observational studies and the earlier placebo-controlled trials of antihypertensive therapy. These results suggest that at least some of the benefits are independent of blood pressure reduction. Although this article has focused on CHD and stroke outcomes, for other cardiovascular end points such as heart failure and renal end points, benefits of particularly ACEIs are largely independent of their effects on blood pressure.

We therefore believe that there is strong evidence to support the view that some of the cardiovascular benefits of antihypertensive agents arise from properties beyond blood pressure lowering as measured conventionally in the clinic

and may be differential among particular subgroups of patients.

We accept that evidence to the contrary is extensive³⁶ and that this issue will remain controversial. However, standing back from either the meta-analyses of potentially heterogeneous data or specific findings cherry-picked from various trials, we should consider whether it is likely that all antihypertensive agents would have an equal impact on all cardiovascular outcomes for the same degree of lowering clinic blood pressures.

Given the established multifactorial origin of cardiovascular outcomes and that different antihypertensive agents have differential impacts on many of the established cardiovascular risk factors, it would be extraordinary if all these agents were “equal” once brachial artery pressures were standardized. Different antihypertensive agents for the same degree of blood pressure will have significantly and clinically important differential effects on multiple variables, including lipid profiles, glucose, insulin, potassium, creatinine, angiotensin, catecholamines, pulse rate, body weight, and central pressure, not to mention 24-hour blood pressure control. Why would all, or any, of these effects be considered trivial (compared with, say, 2-mm Hg systolic pressure) or together exert a neutral effect such that the only property of all antihypertensive agents that is of value is the lowering of brachial blood pressure?

It is our view that, on the basis of differential mechanisms of action and diverse effects on major cardiovascular risk factors, different classes of antihypertensive agents are likely to provide different cardiovascular protection and that, given sufficiently sensitive tests, these differences could be shown more clearly.

Meanwhile, we believe that the apparent anomalies in the results of several trials in hypertension described above may well reflect not just chance variation but real differences beyond the magnitude of lowering blood pressure between the agents used in the trials.

Disclosures

Dr Sever has received research grants from, served on speaker's bureaus for or received honoraria from, and has served as consultant to Pfizer Inc, Servier Laboratories, AstraZeneca, Takeda Pharmaceuticals and Novartis AG. Dr Poulter has received research grants from Pfizer Inc, Servier Laboratories, Mars Inc, and Menarini. He has served on speaker's bureaus for, received honoraria from, and served as consultant for Pfizer Inc, Servier Laboratories, AstraZeneca, Takeda Pharmaceuticals, Novartis AG, Squibb/BMS, Sanofi-Aventis, and other pharmaceutical companies.

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It Is Not Beyond the Blood Pressure; It Is the Blood Pressure

William J. Elliott, MD, PhD; M. Charlotte Jonsson; Henry R. Black, MD

Epidemiological studies have clearly shown that the risk of adverse cardiovascular (CV) events (including CV death) increases as blood pressure (BP) increases. A recent compilation of data from 61 long-term studies showed that for every 20/10-mm Hg increase in BP, beginning at 115/75 mm Hg, the risk of CV death doubles.¹ A more contentious issue in the recent medical literature involves a claim of a “BP-independent effect” of specific antihypertensive medications on CV events^{2–5} or subtypes of such

events.⁶ Many preclinical data and small studies with surrogate end points have suggested that there should be “benefits beyond BP control” with angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), and/or calcium channel blockers (CCBs). This point of view, however, has little supportive evidence from randomized clinical trials, the “highest form of medical evidence” according to the Cochrane Collaboration. Indeed, there are much better data from clinical trials to support the beneficial effects of statins, “inde-

Blood Pressure Differences and Major CV Outcomes in Large Actively Controlled Clinical Trials of Antihypertensive Agents

Trial	Concordance Between		Trial	Discordance Between	
	Δ SBP,* mm/Hg	Patients With Major CV Events,† n (OR, <i>P</i>)		Δ SBP,* mm Hg	Patients With Major CV Events,† n (Odds Ratio, <i>P</i>)
ALLHAT (D vs α)	2.4	2829 vs 1947 (0.83, <0.001)	ANBP-2 (D vs ACE-I)	1.4	394 vs 429 (0.88, 0.07)
ALLHAT (D vs ACE-I)	2.3	3941 vs 2514 (0.91, <0.001)	INSIGHT (D vs CCB)	0.1	397 vs 383 (0.96, 0.57)
ALLHAT (D vs CCB)	1.1	3941 vs 2432 (0.96, 0.12)	MOSES (CCB vs ARB)	1.5	171 vs 149 (0.82, 0.12)
ASCOT (β vs CCB)	-2.7	1602 vs 1362 (1.20, <0.0001)	SHELL (D vs CCB)	1.1	66 vs 65 (0.98, \approx 0.92)
INVEST (β vs CCB)	-0.3	1119 vs 1150 (0.97, 0.56)			
VALUE (CCB vs ARB)	2.2	1021 vs 1074 (est, 1.05, \approx 0.28)			
STOP-2 (D/ β vs CCB)	-0.3	637 vs 636 (0.99, 0.90)			
STOP-2 (D/ β vs ACE-I)	-0.3	637 vs 586 (0.90, 0.10)			
LIFE (β vs ARB)	-1.4	588 vs 508 (0.85, 0.0009)			
NORDIL (D/ β vs CCB)	3.1	453 vs 466 (1.04, 0.53)			
CAPPP (β vs ACE-I)	3.0	438 vs 401 (1.10, 0.18)			
CONVINCE (D/ β vs CCB)	-0.1	365 vs 364 (0.99, 0.88)			

D indicates diuretic; α , α -blocker; est, estimated; and β , β -blocker. "Large" indicates that there were >50 major CV events in each randomized arm.

*Change in systolic blood pressure for first mentioned agent minus that of second mentioned agent.

†As defined by each trial.


pendent of cholesterol lowering," than for antihypertensive drugs.⁷ This review presents the position that nearly all the positive effects of antihypertensive drugs to reduce clinical events can be attributed to their success in reducing BP.

CV Events in Actively Controlled Clinical Trials

The most reliable and unbiased way to relate BP-lowering efficacy to outcomes is to examine the existing database of large clinical trials to ascertain how many actively controlled trials (in which antihypertensive drug therapy was provided to both randomized groups) observed concordance between better BP lowering and prevention of CV events (the Table). Sixteen comparisons in clinical trials provided this information. In only 4 trials—those we consider discordant for BP reduction and CV outcomes (the Australian National Blood Pressure Trial 2 [ANBP-2],⁸ the International Nifedipine GITS [Gastrointestinal Therapeutic System] Study: Intervention as a Goal in Hypertension Treatment [INSIGHT],⁹ the Morbidity and Mortality After Stroke: Eprosartan Compared With Nitrendipine in Secondary Prevention [MOSES],⁴ and the Systolic Hypertension in the Elderly Long-Term Lacidipine trial [SHELL]¹⁰)—was better BP control not correlated with improved CV outcomes. In the other 12 arms of 9 trials in which comparisons between drug classes were performed (the Antihypertensive and Lipid-Lowering to Prevent Heart Attack Trial [ALLHAT],^{11,12} the Anglo-Scandinavian Cardiac Outcomes Trial [ASCOT],¹³ the International Verapamil SR/Trandolapril Trial [INVEST],¹⁴ the Valsartan Antihypertensive Long-term Use Evaluation [VALUE],¹⁵ the Second Swedish Trial in Old Patients With Hypertension [STOP-2],¹⁶ the Losartan Intervention for Endpoint Reduction [LIFE] trial,³ the Nordic Diltiazem trial [NORDIL],¹⁷ the Captopril

Primary Prevention Project [CAPPP],¹⁸ and the Controlled Onset Verapamil Investigation for Cardiovascular Endpoints [CONVINCE] trial¹⁹), those individuals who had better BP control had fewer major CV events. Significant differences in CV outcomes were observed in none of the discordant trials, whereas 4 of the concordant trials (LIFE, 2 comparisons in ALLHAT, and ASCOT) observed a significant reduction in CV events in the group achieving the lower BP. These included 4 of the 5 trials with the greatest observed differences in systolic BP. The concordant trials had many more patients with events (31 011 versus 2054, a 15-fold difference) and numbers of patients enrolled (186 368 versus 15 638, a nearly 12-fold difference) compared with the discordant trials. Because the statistical power in most studies is directly proportional to the number of observed end points, the discordant studies would be much more likely to estimate benefits imprecisely, whereas the point estimates from concordant studies should be more accurate and reliable.

The Table does not include placebo-controlled clinical trials of antihypertensive drugs for several reasons. The most troubling aspect of understanding the outcomes of recent placebo-controlled studies in hypertension is that, for ethical reasons, the intention-to-treat analyses are likely to be biased toward a null result because individuals who were assigned placebo but whose BPs remain uncontrolled often were switched to or have active drug therapy added during follow-up. The Shanghai Trial of Nifedipine in the Elderly (STONE) is probably the best recent example of this phenomenon.²⁰ Therefore, BP differences between active and placebo therapy would be greatly underestimated, and the true relative benefit of therapy also would be reduced. This is likely to have occurred in the Heart Outcomes Prevention Evaluation (HOPE), in which additional (nonstudy) antihypertensive



drugs may well have been given to those initially randomized to placebo and whose BPs were uncontrolled. The addition of active antihypertensive therapy undoubtedly reduced the BP difference between the 2 randomized arms, as well as the potential impact of BP lowering on outcomes.² In addition, a 39-patient substudy using ambulatory BP monitoring noted a much larger difference in BPs between the randomized groups, suggesting that the observed 3/2 mm Hg was a significant underestimate of the real BP difference between the 2 groups.²¹

The second potential problem with most placebo-controlled trials of antihypertensive drugs is that most of these trials included individuals who were not hypertensive, and the tallies of CV events during the studies often are presented only in aggregate, making it impossible to determine exactly how many hypertensive patients suffered each type of event during the trials. This is more commonly a problem for the placebo-controlled trials of ACE-Is (eg, HOPE, the Perindopril Protection Against Recurrent Stroke Study [PROGRESS],²² the European Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease Study [EUROPA],²³ and the Prevention of Events With Angiotensin Converting-Enzyme Inhibition [PEACE²⁴] trial) than CCBs (eg, A Coronary Disease Trial Investigating Outcome With Nifedipine [ACTION]).^{25,26} But these trials, as well as studies like the Comparison of Amlodipine Versus Enalapril to Limit Occurrences of Thrombosis (CAMELOT), suggest that lower BPs may be associated with improved outcomes, even in those subjects not currently considered hypertensive.

Antihypertensive Agents With Beneficial Effects on Individual CV Events

A rational method of approaching the question of whether specific types of antihypertensive agents have benefits beyond BP control is to identify specific types of agents that appear to have a beneficial effect on a specific type of CV event and then examine the clinical trials that used these agents for evidence of BP-independent benefits. This method involves performing meta-analyses of clinical trials comparing various drug classes and then using meta-regression to assess the dependence of the beneficial effects on the achieved BPs. Other, less direct ways to approach this question include animal studies and small studies with surrogate end points, but we prefer to examine data from clinical trials, which (when well conducted and analyzed) are the least biased type of experiments involving humans.

Because many clinical trials in hypertension have used a diuretic and/or a β -blocker as standard therapy to which other drugs were compared, it is simplest (and now customary^{27–31}) to summarize the outcomes observed in these trials in meta-analyses comparing an initial ACE-I or CCB with an initial diuretic/ β -blocker. This strategy is not as useful for ARBs, however, because most recent trials used a diuretic as

second-line therapy in those patients originally assigned to the ARB.^{29–31}

ACE-I Versus Diuretic/ β -Blocker

The results of a traditional meta-analysis (using the method of Mantel-Haenszel and the Riley-Day test for inhomogeneity) comparing an initial ACE-I with an initial diuretic/ β -blocker are shown in Figure 1. The trials include CAPPP,¹⁸ STOP-2,¹⁶ the United Kingdom Prospective Diabetes Study #39 (UKPDS³²), the African American Study of Kidney Disease and Hypertension (AASK^{33,34}), ALLHAT,¹² the pilot study for the Hypertension in Very Elderly Trial (HYVET-Pilot³⁵), and ANBP-2.⁸ Unfortunately, only mortality and major CV events have been published for the AASK trial, but the numbers of affected patients were very small, and omitting the results of this trial from these analyses does not substantively change the summary odds ratios.

These meta-analyses reveal significant differences only for stroke and heart failure (HF) end points; for each of these, the initial ACE-I was slightly but significantly ($P \approx 0.03$) worse than an initial diuretic/ β -blocker. Importantly, coronary heart disease (CHD) end points were not significantly reduced with the initial ACE-I versus an initial diuretic/ β -blocker ($P = 0.42$), as might have been expected from other data, despite >3000 affected patients. Even when data from 3 other studies (hypertensive subgroup of the Appropriate Blood Pressure Control in Diabetics study [ABCD³⁶], the Fosinopril Amlodipine Cardiac Events Trial [FACET³⁷], the Japanese Multicenter Investigation of Cardiovascular Disease-B [JMIC-B³⁸]) that compared an initial ACE-I with an initial CCB, and 2 studies comparing an initial ACE-I to an initial ARB (COOPERATE³⁹ and the Diabetics Exposed to Telmisartan and Enalapril [DETAIL] study⁴⁰) are added to the meta-analysis (along with those of the other arms of both ALLHAT and STOP-2), there is not a significant difference in CHD events between those who received an initial ACE-I (1331 of 21 903) compared with those who received a different initial antihypertensive drug (2963 of 39 299). The summary odds ratio for this comparison is 0.95 (95% CI, 0.89 to 1.02; $P = 0.15$). The fact that no significant difference in CHD events is found in meta-analyses of an initial ACE-I versus either an initial diuretic/ β -blocker or any other antihypertensive agent makes it difficult to argue that this class of drug has a beneficial effect on CHD events that is independent of BP control. This point is especially well made by PROGRESS.²² Monotherapy with an ACE-I reduced BP by only 5/3 mm Hg compared with placebo and did not significantly prevent either recurrent strokes or CV events. When the diuretic was used in combination with the ACE-I, BP was reduced by 12/5 mm Hg compared here with 2 placebos, which was then associated with highly significant prevention of both strokes and CV events.²² Similarly, when data from these other 5 studies (along with results from the non-ACE-I arms of STOP-2 and ALLHAT) are added to those of Figure 1, the significant difference in stroke persists. In all hyper-

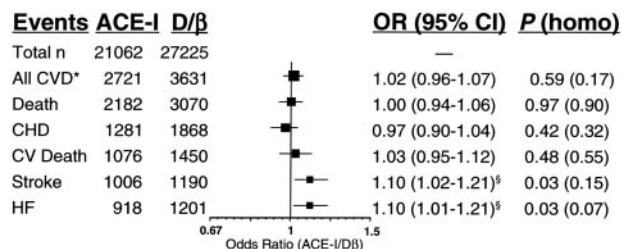


Figure 1. Meta-analysis of CV outcomes in hypertension clinical trials comparing an initial ACE-I with an initial diuretic or β -blocker (D/ β). The probability values for each end point are shown in the right column. The first pertains to the summary odds ratio (OR); the second indicates the result for the test for homogeneity across trials. *All CVD indicates all major CV disease events (the first occurrence of CV death, MI, or stroke, which was estimated for some trials). $\S P < 0.03$.

tension studies that included an ACE-I, 1013 events were reported among 20 842 patients receiving an initial ACE-I as opposed to 1780 events among 38 237 patients given a different antihypertensive drug (summary odds ratio, 1.13; 95% CI, 1.04 to 1.22; $P < 0.004$; P for homogeneity = 0.42). For HF, adding the amlodipine arm of ALLHAT causes the significant difference seen previously to disappear. For all hypertension studies that included an ACE-I, 929 HF events were reported among 20 847 patients receiving an initial ACE-I compared with 2112 of 38 252 given a different antihypertensive drug (summary odds ratio, 0.99; 95% CI, 0.91 to 1.07; $P = 0.77$; P for homogeneity = 0.22).

It therefore appears that an initial ACE-I is associated with an increased risk for stroke compared with either an initial diuretic/ β -blocker or any other drug, but no other end point is significantly different compared with both an initial diuretic/ β -blocker and any other active antihypertensive drug.

CCB Versus Diuretic/ β -Blocker

The results of a traditional meta-analysis (using the same methods as above) comparing an initial CCB with an initial diuretic/ β -blocker are shown in Figure 2. The 13 trials

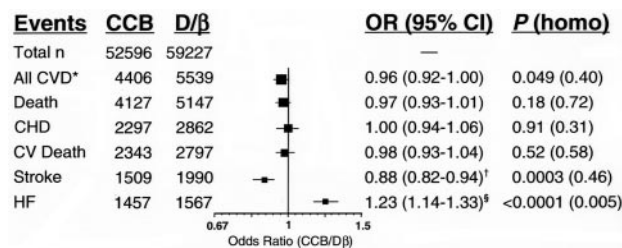


Figure 2. Meta-analysis of CV outcomes in hypertension clinical trials comparing an initial CCB with an initial diuretic or β -blocker (D/ β). Data for HF from the ELSA are not available. The probability values for each end point are shown in the right column. The first pertains to the summary odds ratio (OR); the second indicates the result for the test for homogeneity across trials. *All CVD indicates all major CV disease events (the first occurrence of CV death, MI, or stroke, which was estimated for some trials). $\S P < 0.0001$; $\dagger P = 0.0003$.

include the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS⁴¹), the Verapamil Hypertension Atherosclerosis Study (VHAS⁴²), STOP-2,¹⁶ National Intervention Cooperative Study in Elderly Hypertensives (NICS-EH⁴³), INSIGHT,⁹ NORDIL,¹⁷ AASK,³³ the European Lacidipine Study of Atherosclerosis (ELSA⁴⁴), ALLHAT,¹² CONVINCE,¹⁹ the Systolic Hypertension in the Elderly Long-term Lacidipine trial (SHELL¹⁰), INVEST,¹⁴ and ASCOT.¹³ Again, only mortality and major CV events have been published for the AASK trial.

These meta-analyses reveal significant differences only for stroke and HF end points. For stroke, the initial therapy with a CCB was significantly ($P < 0.0003$) better than an initial diuretic/ β -blocker (by $\approx 12\%$), but for HF, the CCB was worse (by $\approx 23\%$; $P < 0.0001$). The significant benefit of CCBs in preventing stroke also was seen when all studies that included an initial CCB were compared with any other active antihypertensive agent. The additional trials for this comparison include ABCD,³⁶ the Irbesartan Diabetic Nephropathy Trial (IDNT^{45,46}), VALUE,¹⁵ and MOSES.⁴ In this meta-analysis, there were 1917 patients with strokes among the 61 448 individuals who received a CCB first compared with 3379 patients with strokes among the 88 825 people who received a different initial antihypertensive drug (2934 of 38 856). The summary odds ratio for this comparison is 0.91 (95% CI, 0.86 to 0.97; $P = 0.003$; with P for homogeneity = 0.12).

ARB Versus Any Other Antihypertensive Drug

Because only the LIFE trial compared an ARB with a diuretic/ β -blocker and nearly all other ARB trials used a diuretic in the treatment regimen that included the ARB, it is not useful to restrict the analyses (as above) to the ARB versus a diuretic/ β -blocker. Furthermore, many trials have compared an ARB with a placebo, but these typically allowed other drugs to be added as necessary to control BP. These approaches can be subjected to separate meta-analyses.

The results of a traditional meta-analysis (using the same methods as above) comparing an initial ARB with any other initial active antihypertensive drug are shown in Figure 3. The 6 comparisons that did not involve a placebo as a randomized treatment option included IDNT,^{45,46} LIFE,³ COOPERATE,³⁹ VALUE,¹⁵ and MOSES.⁴ Estimates were used for the numbers of patients with CV deaths or major CV events in VALUE because they have not yet been reported. Similarly, the number of patients with myocardial infarctions (MIs) in MOSES also has not yet been revealed, so MOSES was not included in the meta-analysis of this end point.

Interpreting these meta-analyses is challenging. There is significant inhomogeneity for both stroke and all CV events, although neither has a significant summary odds ratio. Inhomogeneity in the traditional Mantel-Haenszel method of combining 2×2 tables violates the assumption that the studies involve the same population; theoretically, the calculation of a summary odds ratio is invalid thereafter. The stroke

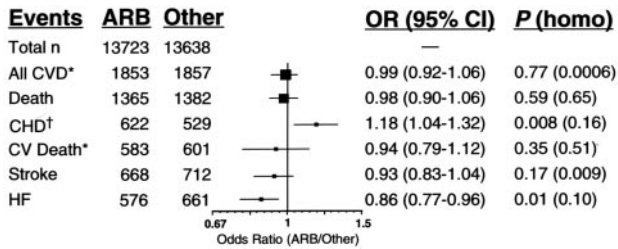


Figure 3. Meta-analyses of CV outcomes in hypertension clinical trials comparing an initial ARB with any other active drug treatment (Other). *All CVD indicates all major CV disease events (the first occurrence of CV death, MI, or stroke, which was estimated for some trials). CV death has not been reported for VALUE, so estimates were used. †Data for CHD in the MOSES trial have not yet been reported. Data for HF also have not yet been reported for MOSES. The probability values for each end point are shown in the right column. The first pertains to the summary odds ratio (OR); the second indicates the result for the test for homogeneity across trials.

inhomogeneity derives primarily from the fact that stroke was significantly decreased in the group receiving the ARB in LIFE but almost significantly increased in the group receiving the ARB in VALUE. The inhomogeneity in major CV events derives mostly from IDNT (in which the ARB was associated with more CV death, MI, or stroke) and LIFE (in which the ARB was associated with a significant 15% decrease in the composite end point). These meta-analyses reveal significant differences between the ARB and other drug therapy only for CHD and HF end points. For the 5 studies that have reported CHD end points, the initial ARB was significantly ($P<0.008$) worse than other drug therapy (by 18%), but for the 4 studies that reported HF end points, the ARB was superior (by $\approx 14\%$; $P<0.01$).

The benefit of an ARB in preventing HF also was seen when all studies that included an initial ARB were compared with any other drug (including placebo). Although SCOPE and MOSES have not yet reported the numbers of their patients who developed HF, the remaining 5 trials (IDNT, RENAAL, LIFE, VALUE, DETAIL) show a highly significant ($P<0.0002$) 18% prevention of HF with the ARB, with a not-quite-significant inhomogeneity among trials ($P=0.055$). The risk of an MI with an ARB has become a controversial topic.^{47,48}

If one adds the results from the placebo-treated group in IDNT, RENAAL, COOPERATE, and ACCESS to the data in Figure 3, MIs were reported in 744 of 16 443 patients given an ARB compared with 721 of 16 924 patients given other agents (summary odds ratio, 1.09; 95% CI, 0.98 to 1.21; $P=0.12$), with no significant inhomogeneity ($P=0.08$). Furthermore, when all 19 trials involving an ARB are included in a single meta-analysis (extending the work of McDonald et al,⁴⁸ who separated the studies according to whether the comparator was placebo or an ACE-I and ignored studies that used a CCB or β -blocker as control), there is no significant increase in MI with an initial ARB (summary odds ratio, 1.05; 95% CI, 0.98 to 1.12; $P=0.17$, with no significant

inhomogeneity [$P=0.56$]). Thus, the preponderance of all the evidence suggests that across all trials, an ARB is not associated with an increased risk of MI but shows a significant decrease in risk of HF.

Unfortunately, after the data from other hypertension trials that involved an ARB are added, the significant inhomogeneity seen in Figure 3 for the end points of all CV disease events and stroke remains. It is therefore difficult to make firm conclusions about these end points, although it is somewhat reassuring that the observed differences remain nonsignificant ($P=0.29$ and 0.06 , respectively).

Summary of Meta-Analyses of Hypertension Trials by Drug Classes

These meta-analyses show only few significant differences across initial antihypertensive drug classes. Compared with an initial diuretic/ β -blocker, stroke is less well prevented with an initial ACE-I but better prevented with an initial CCB. Heart failure is less well prevented with an initial CCB or an ACE-I than a diuretic/ β -blocker but may be better prevented with an initial ARB. Other CV end points show no significant differences across initial drug classes, although an initial ACE-I was associated with a significantly higher risk of HF than an initial diuretic/ β -blocker.

Meta-Regression Analyses of Clinical Trials Involving Drug Classes With Beneficial Effects on Specific CV End Points

Heart Failure

The incidence of HF in hypertension trials has been difficult to relate to BP differences across treatment arms,^{27–29} despite a strong pathophysiological and epidemiological basis for the relationship.⁴⁹ Unlike all other types of CV events, there was no significant correlation between prevention of HF and differences in systolic BP in several meta-regression analyses.^{27–29} Thus, it is difficult to explain the differences observed in the above meta-analyses by differential lowering of BP in the various trials, so we will not consider this end point further.

Stroke

In an attempt to discern a benefit beyond BP control associated with an initial CCB, a meta-regression analysis plotting the odds ratio for stroke in each study against the observed difference in systolic BP during the trial was performed (Figure 4). The curved dotted lines are the 95% confidence limits of a similar analysis published in 2001 by Staessen et al²⁷ that is based on outcomes involving 136 124 patients enrolled in 27 studies, most of which were placebo-controlled trials. It is remarkable that 7 of the 19 trials from which this regression line is derived had points that fell outside the area between the curved dotted lines representing these 95% CIs.²⁷ The area between these curved dotted lines therefore represents the expected range for the results of more recent trials, presuming that the observed results were dependent only on the extent or degree of BP lowering. As shown in Figure 4,

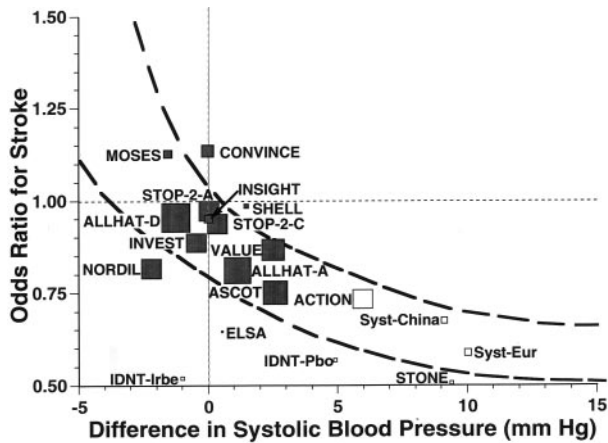


Figure 4. Meta-regression analysis correlating the odds ratio for stroke in clinical trials involving an initial CCB with the observed difference in systolic BP in each trial. The curved dotted lines are the 95% CIs for a similar meta-regression line based on stroke outcomes involving 136 124 patients enrolled in 27 studies.²⁷ The placebo-controlled studies are shown as open squares; the actively controlled trials are shaded. Each trial is represented by a square in proportion to the number of strokes observed in the study. ALLHAT-D corresponds to the diuretic arm of ALLHAT; ALLHAT-A corresponds to the ACE-I arm of the same trial. STOP-2-D corresponds to the diuretic/ β -blocker therapy arm of STOP-2; STOP-2-A corresponds to the ACE-I arm of the same trial.

the data for 7 of 19 trial arms lie outside the 95% CIs: 5 below and 2 above the line. Aside from NORDIL (which was a part of the original data set from which the regression line was derived²⁷ and fell outside the 95% confidence limits in the original publication), the 4 trials that lie below the line observed only very small numbers of strokes (2.34% of the total). If the (vertical) 95% confidence limits for the odds ratio for stroke for each of the studies are added to the figure, all overlap the 95% CIs for the regression line. This suggests that most, if not all, of the benefit of stroke prevention seen with CCBs can be attributed to the observed lowering of systolic BP in those trials.

In an attempt to discern whether some of the decreased ability of an initial ACE-I to prevent stroke can be attributed to the generally poorer control of BP in actively controlled trials that involved an ACE-I, a similar meta-regression analysis was carried out (Figure 5). No squares that are associated with actively controlled studies lie outside the curved dotted lines representing the 95% CIs for the regression line corresponding to data derived from the same 136 124 patients enrolled in 24 clinical trials.²⁷ It could be argued that the results in the 3 placebo-controlled studies in Figure 5 that lie above the 95% confidence limit are confounded by drug treatment given to persons without hypertension. In any case, there is little evidence from these data that stroke outcomes can be attributed to any harmful BP-independent effects of ACE-Is.

Coronary Heart Disease

Figure 6 shows the results of recent trials involving the effects of CCBs on CHD end points superimposed on the meta-regression curve for CHD derived from 136 124 patients enrolled in the same 27 studies as previously.²⁷ Only 5 studies have squares that fall outside the 95% confidence limits: ACTION and INSIGHT (8.44% of the events) fall above the expected range, whereas CONVINCe, IDNT-Placebo, and IDNT-Irbesartan (constituting 5.03% of the events) fall below it. Thus, there is little evidence that CCBs have, in general, benefits or risks beyond BP control for the prevention of CHD events.^{6,50}

Some authors have claimed that ACE-Is significantly prevent CHD events beyond their expected BP-lowering effects (see below).^{6,50} The primary evidence for this allegation is based on data similar to those shown in Figure 7. Although the meta-regression line fit to all the squares shown in Figure 7 does not include the origin, the analysis depends heavily on the inclusion of placebo-controlled trials (open squares in Figure 7). The regression line that includes only the actively controlled (filled) squares of Figure 7 is barely statistically significant ($P=0.042$), whereas it is highly significant ($P<0.0001$) when the placebo-controlled trials are included. Even when placebo-controlled trials are added, however, 7 trial results (comprising 22.4% of the CHD events) fall below the 95% CIs for the previously described regression line (identical in Figures 6 and 7), and 2 (compris-

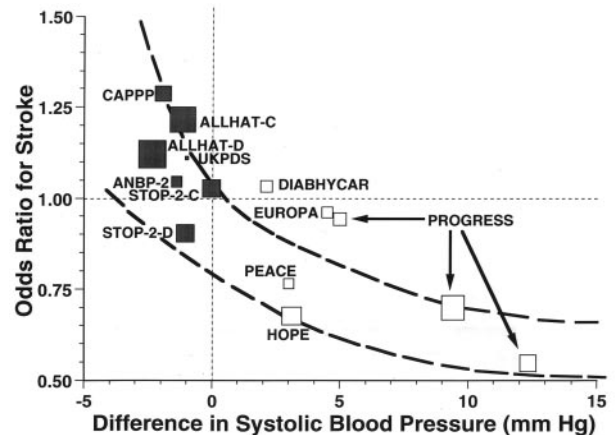


Figure 5. Meta-regression analysis correlating the odds ratio for stroke in clinical trials involving an initial ACE-I with the observed difference in systolic BP in each trial. The curved dotted lines are the 95% CIs for a similar meta-regression line based on stroke outcomes involving 136 124 patients enrolled in 27 studies.²⁷ The placebo-controlled studies are shown as open squares; the actively controlled trials are shaded. Each trial is represented by a square in proportion to the number of strokes observed in the designated arms of the study. There were so few strokes in the HYVET-Pilot, DETAIL, and COOPERATE trials that their squares cannot be seen at the resolution of this figure. ALLHAT-D corresponds to the diuretic arm of the ALLHAT; ALLHAT-C corresponds to the CCB arm of the same trial. STOP-2-D corresponds to the diuretic/ β -blocker therapy arm of STOP-2; STOP-2-C corresponds to the CCB arm of the same trial.

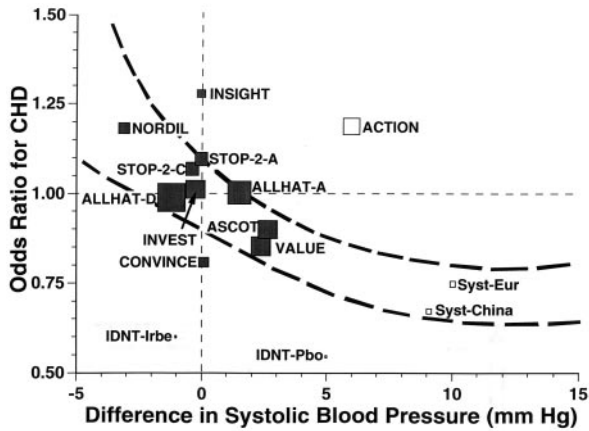


Figure 6. Meta-regression analysis correlating the odds ratio for CHD in clinical trials involving an initial CCB with the observed difference in systolic BP in each trial. The curved dotted lines are the 95% CIs for a similar meta-regression line based on CHD outcomes involving 136 124 patients enrolled in 27 studies.²⁷ The placebo-controlled studies are shown as open squares; the actively controlled trials are shaded. Each trial is represented by a square in proportion to the number of CHD events observed in the designated arms of the study. There were so few CHD events in the ABCD (hypertensive subgroup), CAMELOT, MIDAS, NICOLE, NICS-EH, PREVENT, SHELL, STONE, and VHAS trials that their squares cannot be seen at the resolution of this figure. Abbreviations as in Figure 4.

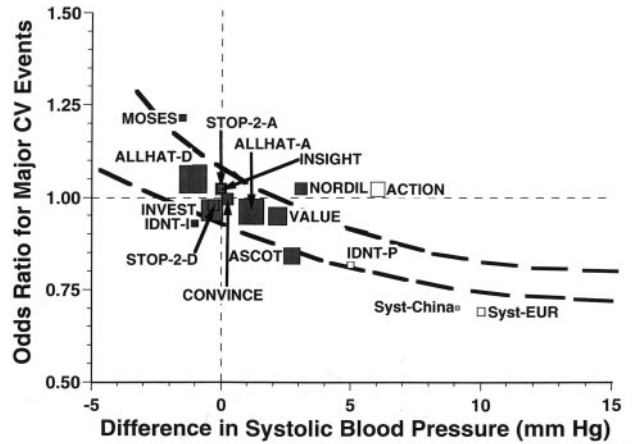


Figure 8. Meta-regression analysis correlating the odds ratio for major CV events (as defined in each trial) in clinical trials involving an initial CCB with the observed difference in systolic BP in each trial. The curved dotted lines are the 95% CIs for the meta-regression line based on outcomes involving 136 124 patients enrolled in 27 studies completed before 2001.²⁷ The placebo-controlled studies are shown as open squares; the actively controlled trials are shaded. Each trial is represented by a square in proportion to the number of events observed in the designated arms of the study. There were so few events in the HYVET-Pilot, DETAIL, and COOPERATE trials that their squares cannot be seen at the resolution of this figure. Abbreviations as in Figure 5.

ing 2.4% of the CHD events) fall above it. Various other analyses have been performed with these data, but this disparity forms the basis for most of the recent conclusions that ACE-Is offer prevention of CHD events beyond BP

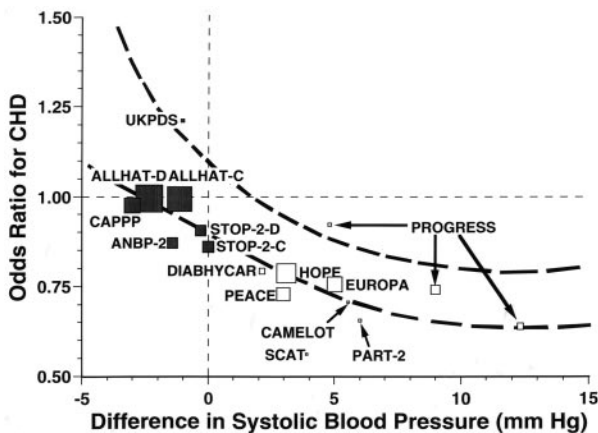


Figure 7. Meta-regression analysis correlating the odds ratio for CHD in clinical trials involving an initial ACE-I with the observed difference in systolic BP in each trial. The curved dotted lines are the 95% CIs for the meta-regression line based on outcomes involving 136 124 patients enrolled in 27 studies completed before 2001.²⁷ The placebo-controlled studies are shown as open squares; the actively controlled trials are shaded. Each trial is represented by a square in proportion to the number of CHD events observed in the designated arms of the study. There were so few CHD events in the HYVET-Pilot, DETAIL, and COOPERATE trials that their squares cannot be seen at the resolution of this figure. Abbreviations as in Figure 5.

control. The most recent published argument is based on a consideration of only CCBs versus ACE-Is for stroke or CHD prevention and regressed the change in BP against the odds ratio after statistically “adjusting” the 32 data points for 6 covariates: drug treatment, an interaction term for drug treatment and change in BP, gender and age of the patients at randomization, the year of publication, and duration of treatment in each trial.⁶ Imprecise estimates are likely whenever the number of observations is <10 to 20 times the number of covariates, which was the case here.

Major Adverse CV Events (Stroke, MI, or CV Death)

As might be expected from the results of the meta-analyses discussed above, meta-regression plots of the odds ratios for major CV events with trials involving an ACE-I (Figure 8) or a CCB (Figure 9) disclose a relatively straight line, with nearly all of the symbols falling within the 95% confidence limits established for this relationship in prior studies.²⁷ A similar conclusion was reached by Staessen et al²⁸ when they considered all trials completed through March 1, 2003.

Brief Consideration of the Opposite Point of View

The most compelling data suggesting a benefit beyond BP control for any drug belong to eprosartan in the MOSES trial.⁴ In this study, eprosartan led to ≈1.5-mm Hg less BP lowering but nonetheless was associated with significant prevention of all CV events (including recurrent events).⁴ Unfortunately for the argument in favor of eprosartan, the

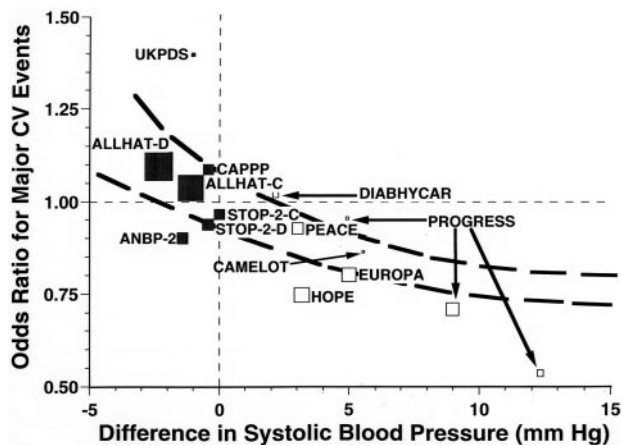


Figure 9. Meta-regression analysis correlating the odds ratio for major CV events (as defined in each trial) in clinical trials involving an initial ACE-I with the observed difference in systolic BP in each trial. The curved dotted lines are the 95% CIs for the meta-regression line based on outcomes involving 136 124 patients enrolled in 27 studies completed before 2001.²⁷ The placebo-controlled studies are shown as open squares; the actively controlled trials are shaded. Each trial is represented by a square in proportion to the number of events observed in the designated arms of the study. There were so few events in the HYVET-Pilot, DETAIL, and COOPERATE trials that their squares cannot be seen at the resolution of this figure. Abbreviations as in Figure 5.

prevention of the primary event did not achieve statistical significance in traditional time-to-first-event analyses ($P=0.15$).⁴ In the 3 other studies that usually are cited as showing a benefit beyond BP control, ramipril (in HOPE),² irbesartan (in IDNT),⁴⁵ and losartan (in LIFE)³ all had better BP control than the comparator (placebo, amlodipine, or atenolol, respectively), as well as fewer primary end points. Of course, IDNT did not have CV events as its primary end point; in fact, CV events were not significantly different across treatment arms.⁴⁶ The measurements of BP in HOPE can be criticized, especially because a subgroup analysis showed far greater BP reduction on ambulatory BP monitoring than was seen in the entire study group.²¹ In addition, LIFE used atenolol as a comparator drug; this strategy has recently been questioned by a meta-analysis of 5 studies that used atenolol as an initial treatment strategy that resulted in a significantly higher risk of death, CV mortality, and stroke.⁵¹ PROGRESS is still the most persuasive single study contradicting the hypothesis that ACE-Is have magical properties; when used alone, perindopril did not reduce CV events significantly better than placebo.

Serial median matching has been used post hoc to reanalyze several clinical trials when the BPs were different across randomized groups after randomization.^{5,52,53} In addition to loss of statistical power as a result of nonpaired subjects, this method turns a randomized clinical trial into a matched case-control study and subjects the prespecified analysis of randomized participants to selection bias. Although it may generate useful hypotheses, the technique is intrinsically

flawed and a weak argument compared with conclusions drawn from clinical trial data that were analyzed according to a prospectively determined protocol.

Conclusions

The evidence favoring BP lowering as a major mechanism of the beneficial effects of all antihypertensive drugs on CV events is clear, pervasive, and convincing. Epidemiological studies show the primacy of BP as the most easily changed parameter that increases the risk of CV events. The preponderance of the evidence from clinical trials also is supportive of this point of view because it is seen for all classes of antihypertensive drugs and for all CV events (except HF). These data are clearest when placebo-controlled trials gave BP-lowering drugs to only a very small minority of participants randomized to placebo. Although more recent studies gave effective antihypertensive therapy (typically excluding a particular class of drugs) to all patients, based on ethical principles, the argument is still strong in favor of BP lowering as the major action of antihypertensive drugs that explains their CV benefits. It is unlikely that a major mistake is being made for most patients by starting with either an ACE-I to prevent stroke or a CCB to prevent CHD or HF, particularly in view of the fact that either is clearly better to control BP and to prevent CV events than placebo. Over time, as ACE-Is and CCBs become less expensive, many more patients will be treated with >1 or both classes of drugs in an effort to control BP better and to prevent more CV events.^{22,37}

In fact, considering that multidrug therapy is now required in almost all hypertensive patients, the argument as to which initial therapy is associated with the best results is virtually moot. Whether a combination of particular drug classes is really superior to any other remains to be proven, despite all the clinical trials that have been done. In our view, the burden of proof that 1 particular class of agent or whether blocking 1 particular mechanism is especially beneficial beyond BP should now be shouldered by those who subscribe to that hypothesis. The overwhelming evidence to date in humans is that lowering BP is the key to reducing CV events.


Disclosures

Dr Elliott has received research grants from Novartis Pharmaceuticals Corp/Omron Healthcare, Pfizer Inc, Mylan Pharmaceuticals, Boehringer Ingelheim, Takeda Pharmaceuticals North America, and AstraZeneca, LP; has served on speakers' bureaus or received honoraria from Pfizer Inc, sanofi-aventis and sanofi-synthelabo, Novartis Pharmaceuticals Corp, Bristol-Myers Squibb Co, AstraZeneca LP, Biovail Pharmaceuticals, Inc, Abbott Laboratories, Solvay Pharmaceuticals, and Kos Pharmaceuticals, Inc; and has served as a consultant to or on advisory boards of Novartis Pharmaceuticals Corp, Pfizer Inc, Bristol-Myers Squibb/sanofi-aventis and Bristol-Myers Squibb/sanofi-synthelabo partnerships, Biovail Pharmaceuticals Inc, and Kos Pharmaceuticals, Inc. Dr Black has received research grants from Pfizer Inc. and the National Institutes of Health; has served on speakers' bureaus or received honoraria from sanofi-aventis and sanofi-synthelabo, Novartis Pharmaceuticals Corp, Bristol-Myers Squibb Co, Boehringer Ingelheim, and Pfizer Inc; and has served as a consultant to or on advisory boards of Myogen,

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Response to Elliott et al

Peter S. Sever, FRCP; Neil R. Poulter, FRCP



We agree with Dr Elliott and colleagues that blood pressure (BP) lowering is a major mechanism by which antihypertensive drugs reduce the incidence of cardiovascular (CV) events. However, we disagree that this is the only mechanism.

Given the authors' belief that randomized controlled trials constitute the "highest form of medical evidence," it is curious that they dismiss placebo-controlled trials, the purest form of randomized trials. The argument that "drop in" during such trials confounds the BP/CV event association is spurious, assuming both exposures are measured reliably, although we accept that this was probably not the case for BP in the Heart Outcomes Prevention Evaluation (HOPE), nor for some of the CV events in the Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT). Similarly, excluding studies on "normotensive patients" seems unreasonable, as evidence dictates that the benefits of BP reduction in trials occur across the whole range of BPs.

That trials generally show concordance between the direction of BP change and CV events is not surprising, but inconsistencies between the size of BP differences and the associated CV event rate differences are clear. Dr Elliott and colleagues describe and yet ignore these disparities (see their Figure 4): heterogeneity in results for angiotensin receptor

blockers compared with β -blockers or with calcium channel blockers, the inefficiency of β -blockers for stroke protection, and discordant effects on stroke and coronary heart disease events in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial. Why were Figures 4 through 8 taken from an old publication (see their reference 27) when the latest analyses (see reference 6) show that angiotensin-converting enzyme inhibitors and calcium channel blockers have significant benefits "beyond BP" on coronary heart disease and stroke events, respectively?

We believe that some of the proposed benefits beyond BP reduction are explained by the inclusion into trials of patients with established CV disease in whom pharmacological properties of the drugs other than those exclusively related to BP reduction may be important. For example, Dr Elliott and colleagues concede that in heart failure, benefits seem largely unrelated to BP lowering.

Superior brachial artery BP reduction is clearly important, but why should significant differences in high-density lipoprotein cholesterol, triglycerides, glucose, potassium, body weight, and central BP be irrelevant? These results are supported by meta-analysis (see reference 6) suggesting benefits due to BP lowering and beyond!



Response to Sever and Poulter

William J. Elliott, MD, PhD; M. Charlotte Jonsson; Henry R. Black, MD

We were pleased to read that Professors Sever and Poulter agreed with us that there is "extensive evidence" in favor of blood pressure reduction being responsible for most (if not all) of the cardiovascular risk reduction seen in clinical trials of antihypertensive drugs. We particularly enjoyed their discussion of the Valsartan

Antihypertensive Long-Term Use Evaluation (VALUE) trial, which many (including some of the investigators¹) feel shows the overriding importance of lowering blood pressure rather than a benefit of the specific drug chosen to initiate the process. Similarly, in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), blood pressure control was much



better among those given initial amlodipine during the first few months of follow-up, when the primary outcome was actually better in the atenolol group.² It will always be difficult to ascribe all the benefits to the initial drug when it is used with many others in clinical trials today.

Whereas many formerly believed in specific benefits of certain antihypertensive drugs on renal end points, as demonstrated for angiotensin-converting enzyme inhibitors (versus placebo) in the patient-level meta-analysis of Jafar et al³ and for an angiotensin receptor blocker (versus a calcium antagonist) by the Irbesartan Diabetic Nephropathy Trial,⁴ a recent systematic review and meta-analysis suggests that these effects may not be independent of blood pressure lowering.⁵ These are the most recent data to support the concept that most, if not all, antihypertensive agents exert most of their beneficial effects by lowering blood pressure, especially systolic blood pressure in older individuals.⁶

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