Cardiovascular protection and blood pressure reduction: a meta-analysis

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Summary

Background Whether antihypertensive drugs offer cardiovascular protection beyond blood pressure lowering has not been established. We aimed to investigate whether pharmacological properties of antihypertensive drugs or reduction of systolic pressure accounted for cardiovascular outcome in hypertensive or high-risk patients.

Methods In a meta-analysis we extracted summary statistics from published reports, and calculated pooled odds ratios for experimental versus reference treatment. We correlated across-trials odd ratios for differences in systolic pressure between groups.

Findings We analysed nine randomised trials comparing treatments in 62 605 hypertensive patients. Compared with old drugs (diuretics and β-blockers), calcium-channel blockers and angiotensin converting-enzyme inhibitors offered similar overall cardiovascular protection, but calcium-channel blockers provided more reduction in the risk of stroke (13·5%, 95% CI 1·3–24·2, p=0·03) and less reduction in the risk of myocardial infarction (19·2%, 3·5–37·3, p=0·01). Heterogeneity was significant between trials because of high risk of cardiovascular events on doxazosin in one trial, and high risk of stroke on captopril in another; but systolic pressure differed between groups in these two trials by 2–3 mm Hg. Similar systolic differences occurred in a trial of diltiazem versus old drugs, and in three trials of converting-enzyme inhibitor against placebo in high-risk patients. Meta-regression across 27 trials (136 124 patients) showed that odds ratios could be explained by achieved differences in systolic pressure.

Interpretation Our findings emphasise that blood pressure control is important. All antihypertensive drugs have similar long-term efficacy and safety. Calcium-channel blockers might be especially effective in stroke prevention. We did not find that converting-enzyme inhibitors or α-blockers affect cardiovascular prognosis beyond their antihypertensive effects.

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Introduction

Lifetime risk of hypertension is about 20%. Several trials have been done to find the best possible protection against the cardiovascular complications of this widespread condition. Various drugs were tested to see whether their mode of action or ancillary properties could offer benefit beyond their effect of lowering blood pressure.[1–16] In normotensive and hypertensive high-risk patients in the HOPE study,[7] the angiotensin-converting enzyme (ACE) inhibitor ramipril significantly reduced rates of death, stroke, and myocardial infarction compared with placebo. In hypertensive patients enrolled in ALLHAT,[10] fewer cardiovascular events happened during treatment with chlorthalidone than with the α-blocker doxazosin. However, in both studies,[7,10] systolic pressure was 2–3 mm Hg lower in the group with the best outcome, which could have been sufficient to explain the results.[17–19] Two quantitative overviews[20,21] reached opposite conclusions with respect to cardiovascular protection of calcium-channel blockers compared with diuretics or β-blockers. However, neither of these overviews[20,21] specifically assessed blood pressure differences between randomised groups in relation to heterogeneity among trials, or included α-blockers in the group of newer drugs.

We investigated whether pharmacological properties of antihypertensive drugs or blood pressure reduction explained cardiovascular outcome. We focused on systolic pressure because, in middle-aged and older patients, systolic pressure is a better predictor of cardiovascular risk than diastolic pressure,[22] and systolic pressure can be measured more reliably than diastolic pressure.[23] First, we assessed whether differences in achieved systolic pressure between randomised groups led to heterogeneity among outcome trials of old versus new classes of antihypertensive drugs. Second, we used metaregression to measure to what extent blood pressure reduction accounts for results of outcome trials.

Methods

Trials

We searched for outcome trials that tested drugs to lower blood pressure in normotensive or hypertensive patients who did not have overt heart failure at enrolment. Other inclusion criteria were a randomised controlled design, publication in a peer-reviewed journal, inclusion of patients with hypertension, assessment of blood pressure and cardiovascular events, follow-up of 2 years or longer, and sample size of 100 or more. Outcome trials of drugs to lower blood pressure were identified from previous overviews[17,18,20,21,24,25] and from a Medline search for trials with expected publication date before 2001.[25]

For the first part of our review, we selected outcome trials in hypertensive patients that compared old classes of antihypertensive agents, such as diuretics or β-blockers, with new agents such as calcium-channel blockers, ACE inhibitors, or α-blockers. We identified 11 such studies.[1–6,8–10,14,16] We excluded one trial[1] because randomisation was not between old and new drugs but between special intervention and usual care, and a second study[2] because cardiovascular outcome data were

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Characteristic	Trials								
	UKPDS[16,27]*	STOP2[6]	CAPPP[4]	NORDIL[9]	INSIGHT[8]	ALLHAT[10]	MIDAS[3]	NICS[5]	VHAS[63]†
Masking type	Open	Open	Open	Open	Double	Double	Double	Double	Open
Number of patients	1148	6614	10985	10881	6321	24335	883	414	1414
Treatment									
Reference	Atenolol <180/105	HCTZ/A or β-blockers	Diuretic or β-blockers	Thiazide or β-blockers	HCTZ/A	Chlorthalidone	HCTZ	Trichlormethiazide	Chlorthalidone
Experimental	Captopril <150/85	ACEIs DHPs	Captopril	Diltiazem (SR)	Nifedipine (GITS)	Doxazosin	Isradipine	Nicardipine (SR)	Verapamil (SR)
Age (mean [SD], years)	56 (8)	76 (··)	53 (8)	60 (7)	65 (7)	67 (8)	59 (9)	70 (7)	53 (7)
Mean systolic/diastolic blood pressure (mm Hg)									
At entry	160/94	194/98	161/99	173/106	167/96	145/83‡	150/97	172/94	169/102
Difference during follow-up§	–1/–1	–0·3/+0·5	–3/–1	–3·1/+0·2	~0/~0	–2/+1	–3·5/~0	–0·7/–1·2	–1·0/+0·4
Proportion of patients (%)									
Women	45	67	47	51	54	47	22	67	51
Cardiovascular complications	··	~20	4	~8	~20	45	~4	~28	5
Diabetes mellitus	100	11	5	7	21	36	··	··	4‖
Follow-up (years)									
Median	8·4	··	··	··	··	3·3	3·0	4·3	2·0
Mean	··	5·0	6·1	4·5	3·5	··	··	··	··

ACEIs=angiotensin-converting enzyme inhibitors; DHPs=dihydropyridine calcium-channel blockers (felodipine or isradipine); GITS=gastro-intestinal therapeutic system; HCTZ=hydrochlorothiazide; HCTZ/A=hydrochlorothiazide plus amiloride; SR=sustained release. Acronyms of trials are explained in the appendix. *UKPDS compared captopril with atenolol and tested two levels of control of systolic/diastolic blood pressure. †In VHAS, study drug was given in a double-blind fashion during the initial 6 months and thereafter in an open way. ‡90% of ALLHAT patients had blood pressure measured at entry while on antihypertensive treatment. §Negative values indicate tighter blood pressure control on old drug classes. ‖Patients on antidiabetic drug treatment.

Table 1: **Characteristics of trials in hypertension comparing different active treatments**

published only in aggregate form. In our analysis, we combined three small trials[3,5,14] that tested a calcium-channel blocker against a thiazide; in these trials less than 40 cardiovascular events occurred in 414 Japanese patients followed up for 5 years,[5] or less than one event per 1000 patient-years.[3,14]

To study the relation between odds ratios of experimental versus reference treatment, and the corresponding baseline-corrected blood pressure differences, we included the nine trials in hypertensive patients that we selected for the first part of our overview,[3–6,8–10,14,16] two reports comparing tight with relaxed blood pressure control,[26,27] 11 older studies in patients with systolic or diastolic hypertension comparing active treatment with no treatment[28,29] or with placebo,[30–38] three placebo-controlled studies in isolated systolic hypertension,[39–41] and three placebo-controlled trials of ACE inhibitors in normotensive and hypertensive patients at high cardiovascular risk.[7,12,15] Among these 27 studies, two had a single-blind design with alternate allocation of consecutive patients to placebo or active treatment.[34,41] We excluded from our metaregression seven small trials in hypertension,[42–48] which (in keeping with our exclusion criteria) accumulated fewer than 100 patients[46–48] or less than 2 years of follow-up,[43,45] or did not provide information on systolic pressure[44] or cardiovascular events.[42] Because blood pressure, in particular systolic pressure,[49] was not reported, we also excluded the HDFP study[49] and two placebo-controlled trials on progression of atherosclerotic disease under treatment with quinapril[11] or amlodipine.[13] Because of similarity in design and few events we combined four small trials published in 1980 or before,[29,36–38] and two placebo-controlled trials on progression of atherosclerosis with use of ACE inhibitors.[12,15]

We did not include trials that compared old with old drugs (ie, β-blockers with diuretics)[50–52] or new with new compounds (ie, ACE inhibitors with calcium-channel blockers),[53,54] because we could pool only few studies in outcome analysis, and because in metaregression analysis it was clinically difficult to define what was the reference treatment for calculation of odds ratios.

	Zelen's p-value*	Pooled estimates of advantage of new versus old drugs expressed in percent†		
		Estimate (SD)	95% CIs	p
Cause of death‡				
Stroke				
CCBs	0·95	–5·3 (17·9)	–31·4 to 30·7	0·79
ACEIs	0·89	–5·6 (18·6)	–32·5 to 31·8	0·79
CCBs and ACEIs	0·99	–5·4 (14·0)	–26·8 to 22·5	0·70
Myocardial infarction				
CCBs	0·13	22·6 (16·6)	–9·2 to 65·8	0·19
ACEIs	0·32	–6·3 (15·1)	–28·9 to 23·4	0·68
CCBs and ACEIs	0·10	7·9 (12·1)	–13·6 to 35·0	0·53
Sudden death				
CCBs	0·46	–8·8 (18·4)	–34·5 to 26·8	0·64
ACEIs	0·07	3·8 (19·3)	–26·5 to 46·7	0·89
CCBs and ACEIs	0·12	–5·3 (15·1)	–28·0 to 25·1	0·74
Myocardial infarction plus sudden death				
CCBs	0·92	7·9 (12·2)	–13·8 to 35·2	0·53
ACEIs	0·07	–2·5 (11·6)	–21·4 to 20·9	0·85
CCBs and ACEIs	0·20	2·5 (9·3)	–13·8 to 22·1	0·81

ACEIs=angiotensin-converting enzyme inhibitors; CCBs=calcium-channel blockers. *The hypothesis of heterogeneity across the reviewed trials was rejected for all fatal outcomes. †Negative values indicate better outcome on the new drugs. ‡The reviewed trials are those listed in table 1 with the exception of ALLHAT, because cardiovascular mortality was unavailable from the published report.[10] Cause-specific cardiovascular mortality was also not reported for MIDAS,[3] NICS,[5] and VHAS.[63]

Table 2: **Pooled estimates of advantage of new versus old antihypertensive drugs with respect to cause-specific mortality**

Outcomes

We based our analysis on the summary statistics published in 37 reports[3–10,12,14–16,26–41,55–63] on the 27 selected trials. Apart from fatal combined with non-fatal events in the EWPHE trial,[30,55] all outcome results were reported on the basis of an intention-to-treat principle. EWPHE was one of the first intervention studies on treatment of hypertension and was planned in 1971. Patients who were randomised and who left the double-blind part of the study were followed up until July 1, 1984, but only date and cause of death were recorded.

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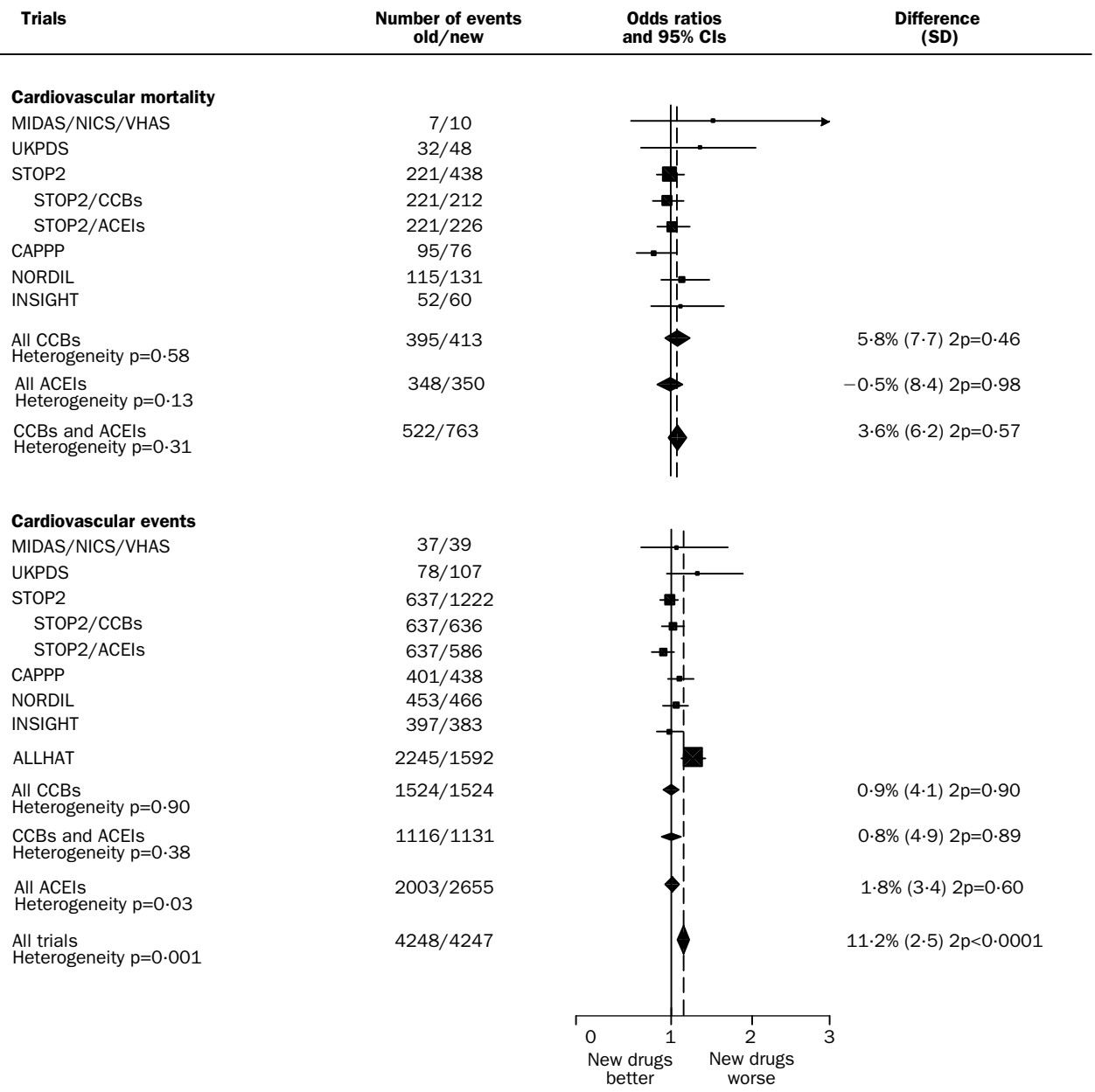

Figure 1: **Effects of antihypertensive treatment on cardiovascular mortality and all cardiovascular events in trials comparing old with new drugs**

Solid squares=treatment-to-control odds ratios in trials and have a size proportional to number of events. 95% CI for individual trials are denoted by lines and those for pooled odds ratios by diamonds. Acronyms and references of trials are in the appendix.

For comparison between old and new drugs, we extracted from nine reports[3–6,8–10,14,16] the number of deaths from myocardial infarction, including and excluding sudden death, stroke, and all cardiovascular causes. Additionally, we noted the number of cardiovascular events, fatal and non-fatal strokes excluding transient ischaemic attacks, fatal and non-fatal myocardial infarctions, and fatal and non-fatal cases of congestive heart failure. For metaregression, we used only those events that could be consistently extracted from published reports[3–10,12,14–16,26–41,55–63] on the 27 trials.

We had to accept the definitions of events used by the study investigators. In seven trials,[4,6,7,9,15,26,31] the term all cardiovascular events refers to the primary composite endpoint. In Syst-Eur[40,59,60] and Syst-China[41,61] trials we used individual records of patients and the published definition of all cardiovascular events. For the other studies, we summed major cardiovascular events. Since more than one event might have happened to an individual, this approach is likely to have resulted in slight overestimation of the total number of patients with cardiovascular complications.

Statistical analyses

We assessed the relative benefit of experimental versus reference treatment from odds ratios in stratified 2×2 contingency tables.[17,18] In every trial, the reference group was patients who were left untreated[28,29] or allocated placebo,[7,12,30–41] or patients randomly assigned old classes of drugs[3–6,8–10,14,16] or a treatment strategy leading to poor blood pressure control.[26,27]

We used StatXact for Windows (version 4.0), to check homogeneity of odds ratios by Zelen's test, and to calculate exact 95% CIs. To enable comparisons with other overviews,[17,18,20,21,24] we also derived SDs of pooled odds ratios by analogy with the asymptotic approach by division

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of the exact logarithmically transformed 95% CI by (2×1·96). All pvalues are for two-sided tests.

We used the SAS statistical package (version 6.12), to correlate odds ratios of experimental versus reference treatment with corresponding blood pressure differences. For these calculations, odds ratios were logarithmically transformed. The regression lines were weighted by the inverse of the variance of individual odds ratios. Net treatment effects on blood pressure were calculated by subtraction of the mean change in the experimental group (follow-up minus baseline) from the corresponding mean change in the reference group. If blood pressure at entry differed between groups in the same study, the average pressure was taken as baseline.[4]

Results

Heterogeneity

We assessed heterogeneity in results of trials comparing old with new antihypertensive drugs (table 1). The trials included 33 325 patients randomly assigned old drugs and 29 280 assigned initial antihypertensive treatment with new drugs.

Because the ALLHAT report[10] did not include separate information on cardiovascular mortality, this trial could not be included in the review of fatal endpoints (figure 1 and table 2). Cause-specific cardiovascular mortality was not reported for MIDAS,[3] NICS,[5] or VHAS.[63] In trials with information on one or more of the fatal outcomes,[3–6,8,9,16,63] such outcomes did not differ between new and old drugs apart from a 3·22 (95% CI 1·12–11·2,

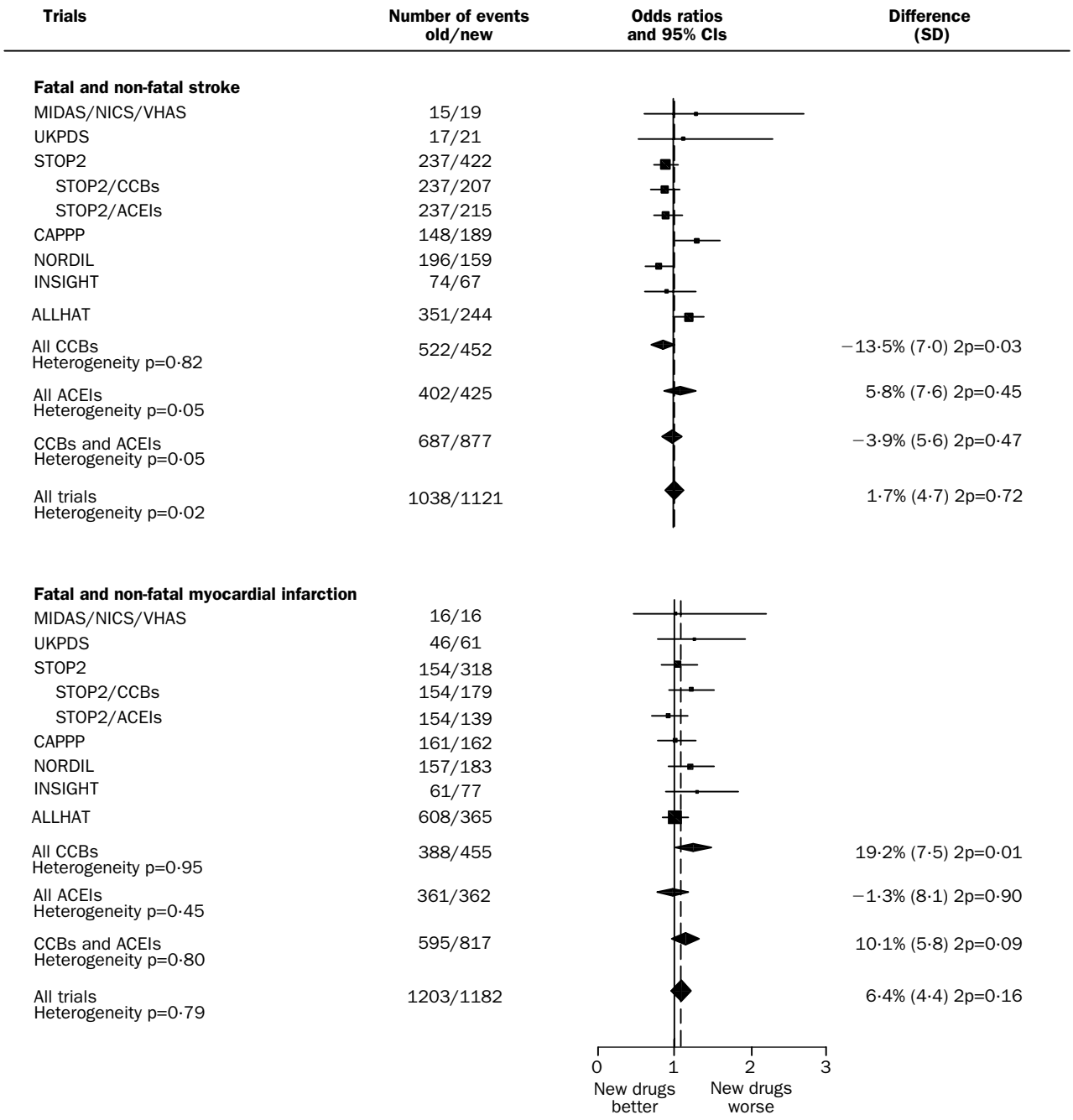

Figure 2: **Effects of antihypertensive treatment on fatal and non-fatal stroke and myocardial infarction in trials comparing old with new drugs**

Fatal and non-fatal myocardial infarction includes sudden death. Acronyms and references of trials are in the appendix.

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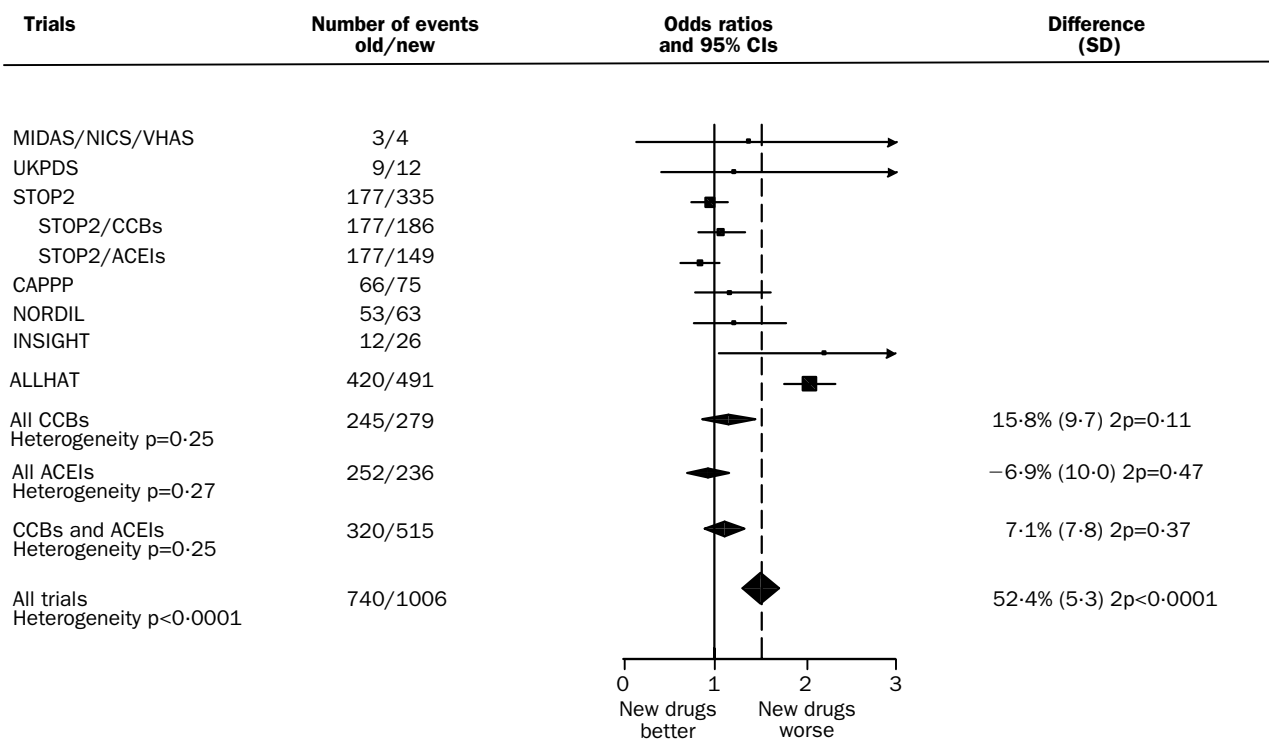

Figure 3: **Effects of antihypertensive treatment on fatal and non-fatal congestive heart failure in trials comparing old with new drugs**
Acronyms and references of trials are in the appendix.

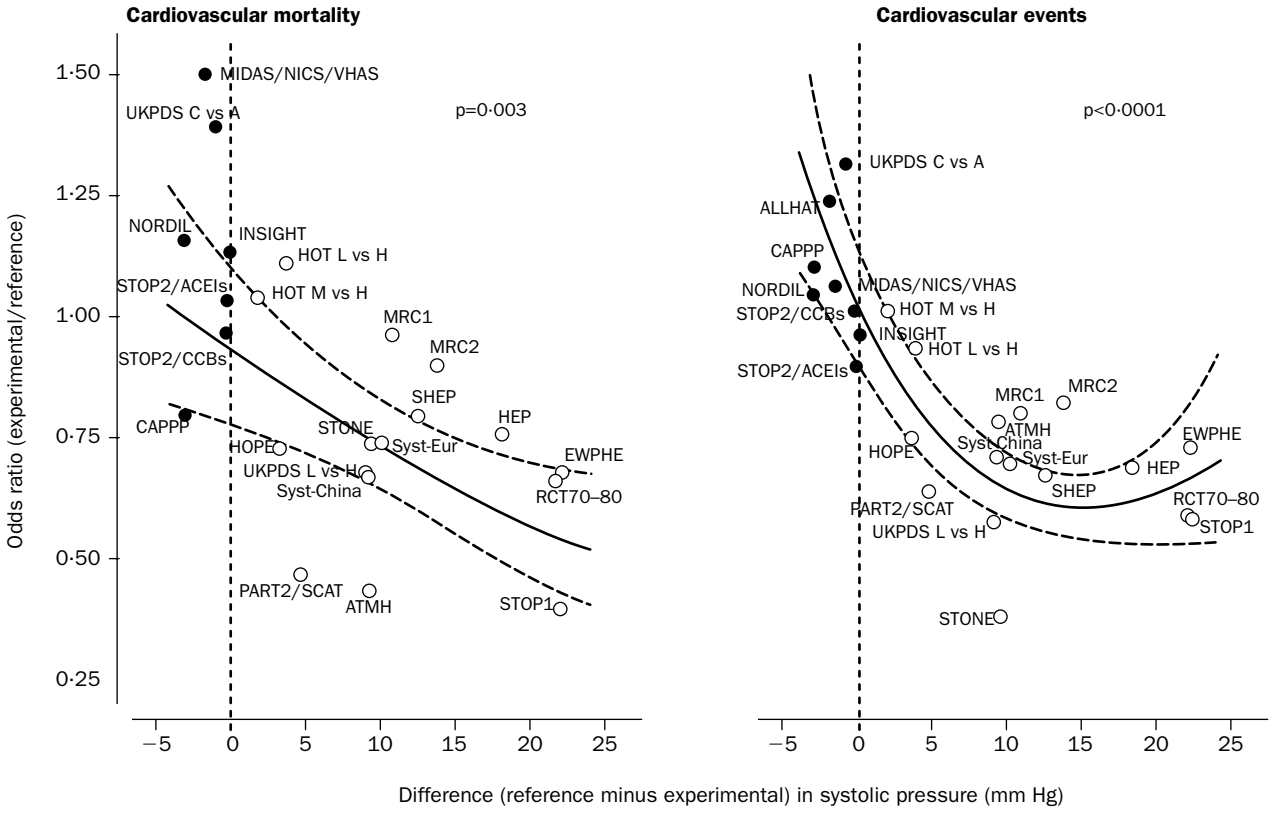

Figure 4: **Relation between odds ratios for cardiovascular mortality and all cardiovascular events, and corresponding differences in systolic blood pressure**
Odds ratios were calculated for experimental versus reference treatment. Blood pressure differences were calculated by subtracting achieved levels in experimental groups from those in reference groups. Negative differences indicate tighter blood pressure control on reference treatment. Regression lines were plotted with 95% CI and were weighted for the inverse of the variance of individual odds ratios. Closed symbols denote trials that compared new with old drugs. Acronyms and references of trials are in the appendix.

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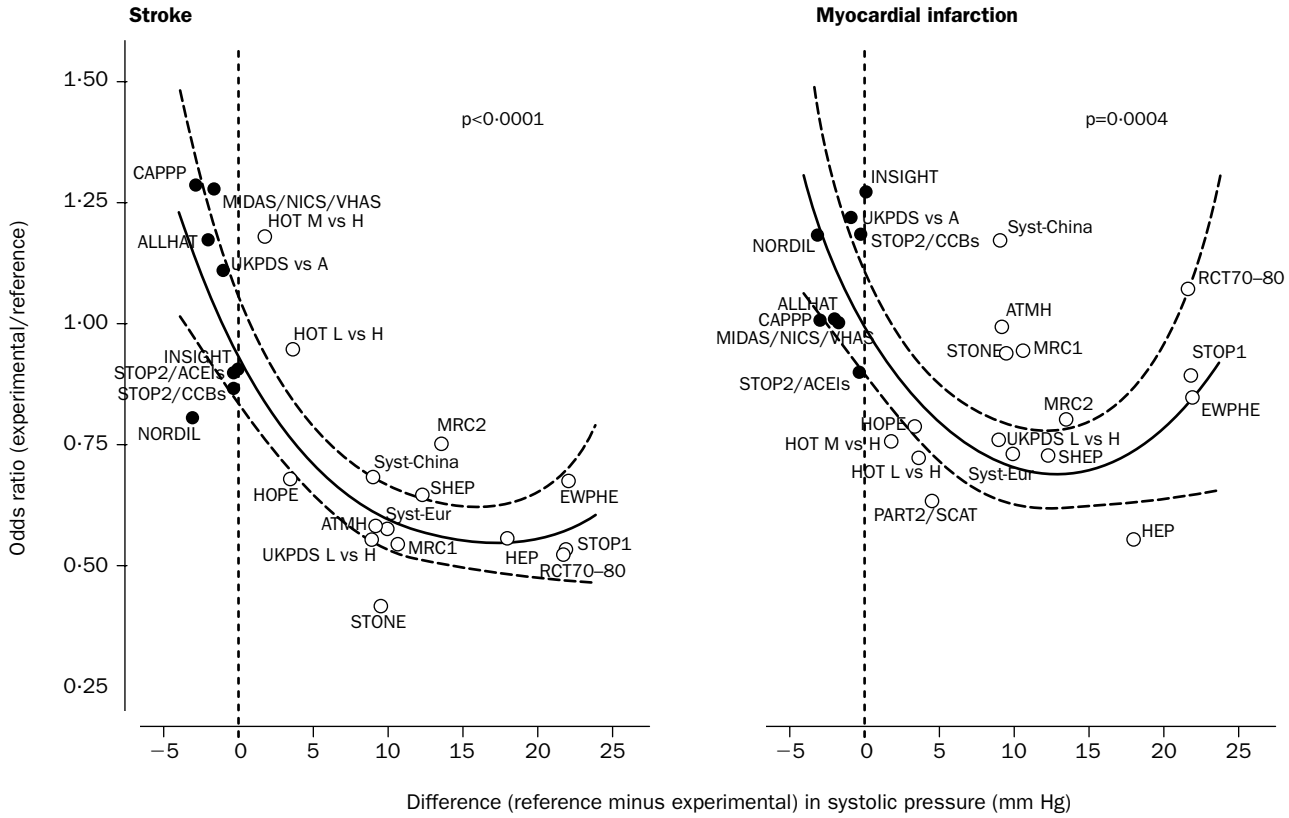

Figure 5: **Relation between odds ratios for fatal and non-fatal stroke and fatal and non-fatal myocardial infarction, and corresponding differences in systolic blood pressure**

Fatal and non-fatal myocardial infarction includes sudden death. Odds ratios were calculated for experimental versus reference treatment. Blood pressure differences were calculated by subtracting achieved levels in experimental groups from those in reference groups. Negative differences indicate tighter blood pressure control on reference treatment. Regression lines were plotted with 95% CI and were weighted for the inverse of the variance of individual odds ratios. Closed symbols denote trials that compared new with old drugs. Acronyms and references of trials are in the appendix.

p=0·03) increase in fatal myocardial infarction on treatment with nifedipine GITS (gastrointestinal transfer system).[8] Heterogeneity was not significant by Zelen's test in any of the pooled mortality results (table 2). The new drugs were as effective as the old ones in prevention of cardiovascular mortality or deaths from stroke and myocardial infarction with or without sudden death.

With respect to fatal combined with non-fatal outcomes, trials had significant heterogeneity, which was largely attributable to higher risk of cardiovascular complications (figure 1), stroke (figure 2), and congestive heart failure (figure 3) with doxazosin than with chlorthalidone in ALLHAT.[10] For these events, odds ratios were 1·25 (1·17–1·33, p<0·0001), 1·19 (1·01–1·40, p=0·04), and 2·04 (1·79–2·32, p<0·0001), respectively.[10] After exclusion of ALLHAT, slight heterogeneity persisted in overall risk of cardiovascular complications with ACE inhibitors compared with old drugs (figure 1, p=0·03). This result was attributable to higher risk of stroke[4] in patients randomly assigned captopril (figure 2): odds ratio 1·25 (1·01–1·55, p=0·04). In individual trials, patients allocated diltiazem[9] had a lower risk of stroke

	Variance explained and corresponding probability					
	Overall model		Initial blood pressure		Blood pressure difference	
	R^2	p	R^2	p	R^2	p
Outcome						
Cardiovascular mortality						
Systolic	0·47	0·002	0·11	0·05	0·36	0·0004
Diastolic	0·42	0·005	0·10	0·08	0·32	0·001
Cardiovascular events						
Systolic	0·66	<0·0001	0·006	0·56	0·65	<0·0001
Diastolic	0·51	0·002	~0	0·99	0·51	0·001
Stroke						
Systolic	0·71	<0·0001	0·004	0·48	0·71	<0·0001
Diastolic	0·66	0·0001	0·007	0·55	0·65	<0·0001
Myocardial infarction						
Systolic	0·55	0·001	0·02	0·37	0·53	0·0005
Diastolic	0·54	0·001	0·09	0·06	0·45	0·002

Every metaregression model included blood pressure at entry and blood pressure difference between study groups as independent variables and was weighted by the inverse of the variance of individual odds ratios.

Table 3: **Variance explained by initial blood pressure and blood pressure difference**

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	Observed odds ratio (95% CIs)*	Predicted mean odds ratio (95% CIs)†	Difference (% [95% CIs])‡	p§
ALLHAT[10]				
Cardiovascular events	1·24 (1·15–1·33)	1·14 (0·98–1·32)	–8·4 (–27·0 to 7·4)	0·32
Stroke	1·18 (0·99–1·39)	1·06 (0·92–1·22)	–11·3 (–38·1 to 10·3)	0·33
Myocardial infarction	1·01 (0·88–1·16)	1·13 (0·98–1·31)	10·7 (–8·2 to 26·2)	0·25
CAPPP[4]				
Cardiovascular mortality	0·80 (0·58–1·09)	0·99 (0·81–1·22)	19·8 (–16·1 to 44·6)	0·24
Cardiovascular events	1·10 (0·95–1·27)	1·23 (1·03–1·46)	10·3 (–11·5 to 27·9)	0·33
Stroke	1·29 (1·03–1·61)	1·14 (0·96–1·34)	–13·4 (–49·0 to 13·8)	0·37
Myocardial infarction	1·01 (0·80–1·26)	1·21 (1·02–1·44)	17·0 (–9·8 to 37·2)	0·19
HOPE[7]				
Cardiovascular mortality	0·73 (0·62–0·86)	0·86 (0·74–0·99)	14·4 (–5·7 to 30·6)	0·15
Cardiovascular events	0·76 (0·67–0·85)	0·82 (0·75–0·91)	8·4 (–6·2 to 21·0)	0·24
Stroke	0·68 (0·52–0·86)	0·77 (0·69–0·85)	11·1 (–12·3 to 29·6)	0·32
Myocardial infarction	0·79 (0·69–0·90)	0·85 (0·77–0·93)	7·2 (–8·6 to 20·6)	0·35
NORDIL[9]				
Cardiovascular mortality	1·16 (0·89–1·50)	1·00 (0·81–1·22)	–16·1 (–60·8 to 16·2)	0·37
Cardiovascular events	1·04 (0·91–1·20)	1·24 (1·04–1·47)	15·5 (–4·8 to 31·9)	0·13
Stroke	0·81 (0·65–1·01)	1·14 (0·97–1·35)	28·8 (6·8 to 45·5)	0·01
Myocardial infarction	1·19 (0·95–1·48)	1·22 (1·02–1·46)	3·0 (–28·1 to 26·5)	0·83
PART2/SCAT[12,15]				
Cardiovascular mortality	0·47 (0·21-0·98)	0·83 (0·73–0·95)	43·3 (–19·8 to 73·2)	0·14
Cardiovascular events	0·64 (0·44-0·94)	0·78 (0·70–0·86)	17·3 (–22·8 to 44·3)	0·35
Myocardial infarction	0·63 (0·38-1·05)	0·80 (0·73–0·88)	21·2 (–31·1 to 52·7)	0·36

*Odds ratio reported in the published articles. †Mean odds ratio (95% CI) predicted by metaregression lines (figures 4 and 5). ‡Difference between predicted minus observed odds ratio (95% CI) expressed in percent of predicted odds ratio. §Significance of difference between observed and predicted odds ratios.

Table 4: **Observed odds ratios and odds ratios predicted by differences in systolic blood pressure in metaregression**

than their counterparts given old classes of drugs (figure 2): odds ratio 0·80 (0·65–0·99, p=0·04), but this result did not lead to significant heterogeneity among studies including calcium-channel blockers.

After exclusion of ALLHAT,[10] overall cardiovascular risk did not differ between patients randomised to diuretics or β-blockers compared with those allocated initial treatment with calcium-channel blockers or ACE inhibitors (figure 1). However, in patients randomised to calcium-channel blockers, reduction in risk of stroke was greater (difference 13·5%, 1·3–24·2, p=0·03, figure 2), but reduction in risk of myocardial infarction was less (19·2%, 3·5–37·3%, p=0·01, figure 2) than in those in whom treatment was started with old drugs. In patients given ACE inhibitors, risk reductions were similar for stroke and for myocardial infarction (figure 2).

In trials leading to significant heterogeneity,[4,10] or with significant differences in overall risk of cardiovascular events[10] or cause-specific cardiovascular complications,[4,9,10] there were differences in achieved systolic pressure between groups of 2 mm Hg or more (table 1). Therefore, we decided to investigate further the relation between odds ratios expressing benefit and achieved blood pressure differences by use of most of the published evidence.

Blood pressure reduction

The 27 studies in our metaregression included 136 124 patients. These studies consisted of nine actively controlled trials (table 1);[3–6,8–10,14,16] HOT,[26] in which different levels of blood pressure control were investigated; three placebo-controlled trials in isolated systolic hypertension;[39–41] three placebo-controlled trials in normotensive or hypertensive patients at high cardiovascular risk;[7,12,15] and 11 older trials testing efficacy of antihypertensive drugs against no treatment. The characteristics of these 11 trials have been reviewed.[17,18,20,21,24,25]

The metaregression line between odds of an event and differences in systolic pressure between study groups was linear for cardiovascular mortality (figure 4) and curvilinear for all cardiovascular events (figure 4), stroke (figure 5), and myocardial infarction including sudden death (figure 5). Blood pressure at baseline contributed less to explained variance than blood pressure differences during follow-up (table 3). Consequently, adjustment of metaregression lines for baseline systolic pressure did not substantially alter their position.

Systolic pressure differences seen in individual studies are shown in table 1 and figures 4 and 5. Blood pressure after enrolment was reported at near mean[5,10,12,30–33,49] or median[40,41] follow-up in ten trials, at end of follow-up in four,[6,7,36,63] and as average of whole follow-up in 13.[3,8,9,15,16,26,28,29,34,35,37–39] In addition to ALLHAT,[10] CAPPP,[4] and NORDIL[9] (table 1), differences in achieved systolic pressure, diastolic pressure, or both between study groups (reference minus experimental drug) were significant in hypertension trials that included less treated[26,27] or untreated[28–41] controls, and in MIDAS (difference −3·5 [systolic]/about 0 [diastolic] mm Hg),[3] HOPE (−3·3/−1·0 mm Hg),[7] PART2 (−5/−4 mm Hg),[12] and SCAT (−4/−2 mm Hg).[15] For MIDAS[3] combined with NICS[5] and VHAS,[63] systolic/diastolic differences were −1·8/about 0 mm Hg. For PART2[12] combined with SCAT,[15] these differences were −4·6/−3·1 mm Hg. Differences between observed odds ratios and those predicted by metaregression lines (table 4) were not significant apart from in NORDIL,[9] in which risk of stroke was lower in patients on diltiazem than on old drugs despite systolic pressure that was 3·1 mm Hg higher on diltiazem (figure 5 and table 4). ALLHAT[10] and HOPE[7] were large trials (table 1) with significant differences in on-treatment systolic pressure between randomised groups. STONE[34] and Syst-China[41] used alternate non-randomised allocation of consecutive patients to placebo on active treatment. Sensitivity analyses in which ALLHAT[10] and HOPE,[7] or STONE[34] and Syst-China[41] were excluded only slightly changed the position of the regression lines and their 95% CIs, and therefore did not alter the results shown in table 4.

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Discussion

Our main finding was that results of outcome trials for antihypertensive drugs can be explained by blood pressure differences between randomised groups. All antihypertensive drugs had similar long-term efficacy and safety. Our results show the desirability of lowering blood pressure as much as possible to achieve the greatest reduction in cardiovascular complications. These findings are in accord with, and add to, earlier reports.[17,18] Indeed, in older patients with isolated systolic hypertension,[17] lowering systolic blood pressure by 10 mm Hg and diastolic pressure by 4 mm Hg reduced risk of stroke and myocardial infarction by 30% and 23%, respectively. In patients with predominantly diastolic hypertension,[18] corresponding benefits produced by a 5–6 mm Hg decline in diastolic pressure were 38% and 16%, respectively.

Because in most trials study groups were similar at entry, we did not need to adjust for characteristics of patients in our metaregression. Furthermore, blood pressure at entry explained little additional variance. After adjustment for baseline blood pressure, our conclusions remained unaltered. The stage of follow-up at which we assessed blood pressure differences depended on what was reported in the studies. However, our inclusion criteria specified a minimum follow-up of 2 years. In most trials, blood pressure differences between study groups were already at their greatest at 6 months of follow-up. Moreover, our metaregression results suggested that for fatal and non-fatal outcomes combined, a substantial part of drug benefit was already achieved by modest 5 mm Hg differences in systolic pressure. Almost all possible benefit of antihypertensive treatment was seen at systolic pressure gradients of about 15 mm Hg. However, these results should be interpreted cautiously. Indeed, these differences in systolic pressure do not represent absolute declines in blood pressure, because they were expressed relative to blood pressure changes in controls. Furthermore, the 5357 patients randomised in trials in which systolic difference exceeded 15 mm Hg represented only 3·9% of patients included in our metaregression analysis. We also did not define a priori the hypothesis of a curvilinear relation between odds ratios and achieved differences in systolic pressure.

In HOPE[7,62] around 90% of patients had previous cardiovascular complications. Treatment with ramipril reduced cardiovascular mortality and incidence of stroke, myocardial infarction, and congestive heart failure.[7] Systolic pressure differed by 3·3 mm Hg between ramipril and placebo groups.[7] Endothelial actions of ramipril[62] have been suggested as stabilisers of atherosclerotic plaques in the large arteries.[64] ACE inhibitors have proven benefit in patients with heart failure[65] or dysfunction of the left ventricle.[66] However, our results suggest that in fact blood pressure could have accounted for most—if not all—benefits seen in HOPE patients allocated ramipril. Furthermore, results of two further placebo-controlled trials of ACE inhibition in high-risk patients[12,15] also did not significantly deviate from benefits predicted by differences in systolic pressure between randomised groups.

Two large Scandinavian trials[4,6] also did not produce any evidence that ACE inhibitors would provide better cardiovascular protection than diuretics, β-blockers, or both. By contrast, risk of stroke was 18% higher in patients randomised to initial treatment with captopril than in those given old drugs.[4] Interpretation of these results is difficult, because at randomisation blood pressure was already 2·2/1·7 mm Hg higher in patients in the captopril group[4,57] and the blood pressure gradient was maintained during follow-up. After extrapolation of results from the Framingham Heart Study and the second National Health and Nutrition Examination Survey,[19] researchers speculated that a 2 mm Hg difference in blood pressure could account for a 15% difference in stroke risk, but they could not exclude the possibility that old drugs were more effective in prevention of stroke.[4] Our results suggest that less blood pressure control on captopril could explain the higher risk of stroke.[4]

Patients randomly assigned doxazosin had higher rates of stroke and congestive heart failure than those on chlorthalidone.[10] The investigators suggested that participants' blood pressure differences were sufficient to explain the higher incidence of stroke on doxazosin, but that these differences could account for only a 10–20% increase in occurrence of heart failure—not a doubling of the rate.[10] Our metaregression analysis results showed that the blood pressure gradient was indeed sufficient to explain the higher risk of stroke on doxazosin. Furthermore, before randomisation, 90% of the patients were on antihypertensive drugs, presumably diuretics in many instances. Thus, ALLHAT not only tested doxazosin versus chlorthalidone, but also tested stopping versus continuing a diuretic in a group of hypertensive patients, of whom a considerable proportion must have been at high risk of heart failure. These factors probably explain why Kaplan-Meier curves for heart failure started to diverge immediately after randomisation.[10] The most important point, however, is that doxazosin achieved similar results to chlorthalidone for the primary outcome, which was coronary heart disease, despite poorer blood pressure control on doxazosin.[10]

The results of our quantitative overview of actively controlled trials in hypertension showed that calcium-channel blockers and ACE inhibitors reduced fatal and non-fatal outcomes as effectively as diuretics or β-blockers. Compared with older drug classes, calcium-channel blockers and ACE inhibitors gave the same overall protection against cardiovascular complications, but calcium-channel blockers provided more reduction in risk of stroke and less reduction in risk of myocardial infarction. With metaregression, we showed that diltiazem compared with diuretics, β-blockers, or both, decreased risk of stroke despite higher systolic pressure. Furthermore, stroke results were not heterogeneous between NORDIL[9] and other actively controlled studies with calcium-channel blockers.[3,5,6,8,63] Nevertheless, these cause-specific results must be interpreted with caution because confidence intervals were wide, and because results might be attributable not only to the drugs under study, but also to characteristics of patients.[67] Selective recruitment of middle-aged patients with type 2 diabetes,[53] older high-risk hypertensive patients,[8] and elderly patients with isolated systolic hypertension[39,40,56,59] probably explains why rates of myocardial infarction varied from 6·3[8] to 32·2[56] cases per 1000 patient-years,

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and why results for prevention of myocardial infarction were contradictory.

Our overview should be interpreted within the context of its limitations. As in all meta-analyses that start from published summary statistics, we achieved less standardisation than is attainable in quantitative overviews based on individual patients' data. Thus, not only participants' characteristics, but also the definition and validation of endpoints in individual trials might have affected our estimates of risk in treated and untreated patients. Masked validation in open trials[4,6,9,16,26,28,49] does not remove the possibility that previous knowledge of treatment allocation resulted in selective over-reporting or under-reporting of events. Furthermore, we chose not to combine weaker coronary endpoints such as angina pectoris with myocardial infarction, sudden death, or both. Conversely, to allow interpretation of ALLHAT results[10] against the background of all available evidence, we included heart failure in all cardiovascular events, which can also be looked upon as a weaker clinical endpoint. Finally, our analysis does not indicate to what extent blood pressure should be lowered. This issue remains unsettled because the studies that we analysed did not account for systolic pressure or pulse pressure,[26,49] or had blood pressure targets that were too high.[27] Additionally, individual tailoring of antihypertensive drugs compared with fixed selection, titration, and combination of treatments was not investigated in any trial.

In conclusion, in trials in hypertension and high-risk patients, blood pressure gradients largely accounted for most differences in outcome. These findings emphasise the desirability of blood pressure control. On average, all antihypertensive drugs have similar long-term efficacy and safety. Compared with diuretics and β-blockers, calcium-channel blockers might protect more against stroke than myocardial infarction, resulting in an overall cardiovascular benefit similar to that of old classes of antihypertensive drugs. The hypothesis that in the reviewed studies ACE inhibitors might affect outcome beyond their blood-pressure-lowering effects remains unproved. On the contrary, in the PROGRESS trial,[68] monotherapy with perindopril lowered systolic pressure by 5 mm Hg more than placebo, but unexpectedly[69] did not reduce the risk of cardiovascular events or stroke recurrence.

Contributors

Jan Staessen and Ji-Guang Wang extracted data and wrote the manuscript. Ji-Guang Wang did statistical calculations with the help of Lutgarde Thijs and Jan Staessen. All authors reviewed the manuscript and approved the final version.

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Appendix

ABCD (Appropriate Blood Pressure Control in Diabetes trial);[53] ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial);[10,58] ATMH (Australian Trial in Mild Hypertension);[35] CAPPP (Captopril Prevention Project);[4,57] EWPHE (trial conducted by the European Working Party on High Blood Pressure in the Elderly);[30,55] HEP (trial of hypertension in elderly patients in primary care);[28] HDFP (Hypertension Detection and Follow-Up Program);[49] HOPE (Heart Outcomes Prevention Evaluation Study);[7,62] HOT (Hypertension Optimal Treatment trial);[26] HOT M *vs* H (Hypertension Optimal Treatment trial—85 *vs* 90 mm Hg as target diastolic pressure);[26] HOT L *vs* H (Hypertension Optimal Treatment trial—80 *vs* 90 mm Hg as target diastolic pressure);[26] HSCS (Hypertension-Stroke Cooperative Study);[36] INSIGHT (International Nifedipine GITS Study—Intervention as a Goal in Hypertensive Treatment);[8] MIDAS (Multicenter Isradipine Diuretic Atherosclerosis Study);[3] MIDAS/NICS/VHAS (combined results of MIDAS,[3] NICS,[5] and VHAS[63]); MRC1 (Medical Research Council trial of treatment of mild hypertension);[33] MRC2 (Medical Research Council trial of treatment of hypertension in older adults);[32] NORDIL (Nordic Diltiazem Study);[9] NICS (National Intervention Cooperative Study in Elderly Hypertensives);[5] OSLO (Oslo Study on the Treatment of Mild Hypertension);[29] PART2 (Prevention of Atherosclerosis with Ramipril Trial);[12] PART2/SCAT (combined results of PART2[12] and SCAT[15]); RCT70-80 (combined results of 4 smaller trials published from 1970 through 1980, including HSCS,[36] OSLO,[29] USPHS,[37] and VACS[38]); SCAT (Simvastatin/Enalapril Coronary Atherosclerosis Trial);[15] SHEP (Systolic Hypertension in the Elderly Program);[39,56] STONE (Shanghai Trial of Nifedipine in the Elderly);[34] STOP1 (Swedish Trial in Old Patients with hypertension);[31] STOP2 (Swedish Trial in Old Patients with hypertension-2);[6] STOP2/ACEIs (angiotensin-converting enzyme inhibitor arm of STOP2);[6] STOP2/CCBs (calcium-channel blocker arm of STOP2);[6] Syst-China (Systolic Hypertension in China trial);[41,61] Syst-Eur (Systolic Hypertension in Europe trial);[40,59,60] UKPDS (UKPDS Hypertension in Diabetes Study);[16,27] UKPDS C *vs* A (UKPDS Hypertension in Diabetes Study–captopril *vs* atenolol);[16] UKPDS L *vs* H (UKPDS Hypertension in Diabetes Study—low *vs* high on-treatment blood pressure);[27] USPHS (United States Public Health Service Hospitals Cooperative Study);[37] VACS (Veterans Administration Cooperative Study in patients with diastolic blood pressure averaging 90–114 mm Hg);[38] VHAS (Verapamil in Hypertension and Atherosclerosis Study).[63]

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