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BMJ 2009;338;b1665;
doi:10.1136/bmj.b1665

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Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies

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Cite this as: *BMJ* 2009;338:b1665
doi:10.1136/bmj.b1665

ABSTRACT

Objectives To determine the quantitative efficacy of different classes of blood pressure lowering drugs in preventing coronary heart disease (CHD) and stroke, and who should receive treatment.

Design Meta-analysis.

Data source Medline (1966-2007).

Study selection Randomised trials of blood pressure lowering drugs recording CHD events and strokes. 108 trials studied differences in blood pressure between study drug and placebo (or control group not receiving the study drug) ("blood pressure difference trials"), and 46 trials compared drugs ("drug comparison trials"). Seven trials with three randomised groups fell into both categories. The results were interpreted in the context of those expected from the largest published meta-analysis of cohort studies, totalling 958 000 people.

Participants 464 000 people defined into three mutually exclusive categories: participants with no history of vascular disease, a history of CHD, or a history of stroke.

Results In the blood pressure difference trials β blockers had a special effect over and above that due to blood pressure reduction in preventing recurrent CHD events in people with a history of CHD: risk reduction 29% (95% confidence interval 22% to 34%) compared with 15% (11% to 19%) in trials of other drugs. The extra effect was limited to a few years after myocardial infarction, with a risk reduction of 31% compared with 13% in people with CHD with no recent infarct ($P=0.04$). In the other blood pressure difference trials (excluding CHD events in trials of β blockers in people with CHD), there was a 22% reduction in CHD events (17% to 27%) and a 41% (33% to 48%) reduction in stroke for a blood pressure reduction of 10 mm Hg systolic or 5 mm Hg diastolic, similar to the reductions of 25% (CHD) and 36% (stroke) expected for the same difference in blood pressure from the cohort study meta-analysis, indicating that the benefit is explained by blood pressure reduction itself. The five main classes of blood pressure lowering drugs (thiazides, β blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers) were similarly effective (within a few percentage

points) in preventing CHD events and strokes, with the exception that calcium channel blockers had a greater preventive effect on stroke (relative risk 0.92, 95% confidence interval 0.85 to 0.98). The percentage reductions in CHD events and stroke were similar in people with and without cardiovascular disease and regardless of blood pressure before treatment (down to 110 mm Hg systolic and 70 mm Hg diastolic). Combining our results with those from two other studies (the meta-analyses of blood pressure cohort studies and of trials determining the blood pressure lowering effects of drugs according to dose) showed that in people aged 60-69 with a diastolic blood pressure before treatment of 90 mm Hg, three drugs at half standard dose in combination reduced the risk of CHD by an estimated 46% and of stroke by 62%; one drug at standard dose had about half this effect. The present meta-analysis also showed that drugs other than calcium channel blockers (with the exception of non-cardioselective β blockers) reduced the incidence of heart failure by 24% (19% to 28%) and calcium channel blockers by 19% (6% to 31%).

Conclusions With the exception of the extra protective effect of β blockers given shortly after a myocardial infarction and the minor additional effect of calcium channel blockers in preventing stroke, all the classes of blood pressure lowering drugs have a similar effect in reducing CHD events and stroke for a given reduction in blood pressure so excluding material pleiotropic effects. The proportional reduction in cardiovascular disease events was the same or similar regardless of pretreatment blood pressure and the presence or absence of existing cardiovascular disease. Guidelines on the use of blood pressure lowering drugs can be simplified so that drugs are offered to people with all levels of blood pressure. Our results indicate the importance of lowering blood pressure in everyone over a certain age, rather than measuring it in everyone and treating it in some.

INTRODUCTION

Despite the widespread use of blood pressure lowering drugs and the results of many randomised trials,^{1-20w1-}

^{w162} uncertainty remains about which drugs to use and who to treat. Five questions encapsulate this uncertainty. Firstly, do β blockers have a special effect over and above lowering blood pressure in preventing coronary heart disease (CHD) events in people with a history of CHD? This view is widely held but such an effect has not been shown directly or quantified. We aimed to answer this question from an analysis of all relevant trials, and then to answer four further questions after excluding CHD events in trials of β blockers in people with a history of CHD if they did have a special effect. Secondly, does the effect of blood pressure lowering drugs in preventing CHD and stroke differ in people with and without a history of cardiovascular disease (that is, is there a different effect in secondary and primary prevention)? Thirdly, does blood pressure reduction alone explain the effect of blood pressure lowering drugs in preventing CHD and stroke? There are claims of additional non-blood pressure lowering (so called pleiotropic) effects of drugs.^{7 8 13w135 w136 w139} Selected trial data have been used to suggest that each of the five main classes of blood pressure lowering drugs (thiazides, β blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers) has a greater preventive effect,^{1-13 w126 w129} and each a lesser preventive effect,^{9-20w126 w135} than other drugs. Clinical guidelines tend to reflect the view that differences in efficacy exist.²¹⁻²³ Fourthly, should the use of blood pressure lowering drugs be limited to people with "high" blood pressure and not given to those at high risk of cardiovascular disease who have a lower blood pressure? A corollary is whether blood pressure should be reduced to a limited extent only, a treat to target approach.^{9-11 21-24} Although cohort (prospective observational) studies do not show a lower blood pressure limit below which risk ceases to decline ("the lower the better"),²⁵⁻²⁷ this has not been shown in randomised trials across a wide range of blood pressure. Finally, what is the quantitative effect of taking one or

more blood pressure lowering drugs in lowering blood pressure and preventing CHD events and stroke according to dose, pretreatment blood pressure, and age? To date no such quantitative summary of effect, taking account of these determining factors, has been made.

We answered these questions using the results from 147 randomised trials of blood pressure lowering drugs and CHD events (n=22 000) and stroke (n=12 000), examined in the context of the results from the largest meta-analysis of epidemiological cohort studies of blood pressure and CHD and stroke.²⁵ Previous meta-analyses of randomised trials of blood pressure lowering drugs and cardiovascular disease included fewer than 40 trials.^{1-20 28} We also quantified the effect of blood pressure lowering drugs on the incidence of heart failure and on cancer mortality, other non-vascular mortality, and all cause mortality.

METHODS

The database search (by MRL) used Medline (1966 to December 2007; any language) to identify randomised trials of blood pressure lowering drugs in which CHD events or strokes were recorded (irrespective of whether blood pressure reduction was considered the mechanism of action). Search terms were "anti-hypertensive agents" or "hypertension" or "diuretics, thiazide" or "adrenergic beta-antagonists" or "angiotensin-converting enzyme inhibitors" or "receptors, angiotensin/antagonists & inhibitors" or "tetrazoles" or "calcium channel blockers" or "vasodilator agents" or the names of all blood pressure lowering drugs listed in the *British National Formulary* as keywords or text words. Limits were Medline publication type "clinical trial" or "controlled clinical trial" or "randomized controlled trial" or "meta-analysis". We also searched the Cochrane Collaboration and Web of Science databases and the citations in trials and previous meta-analysis and review articles.

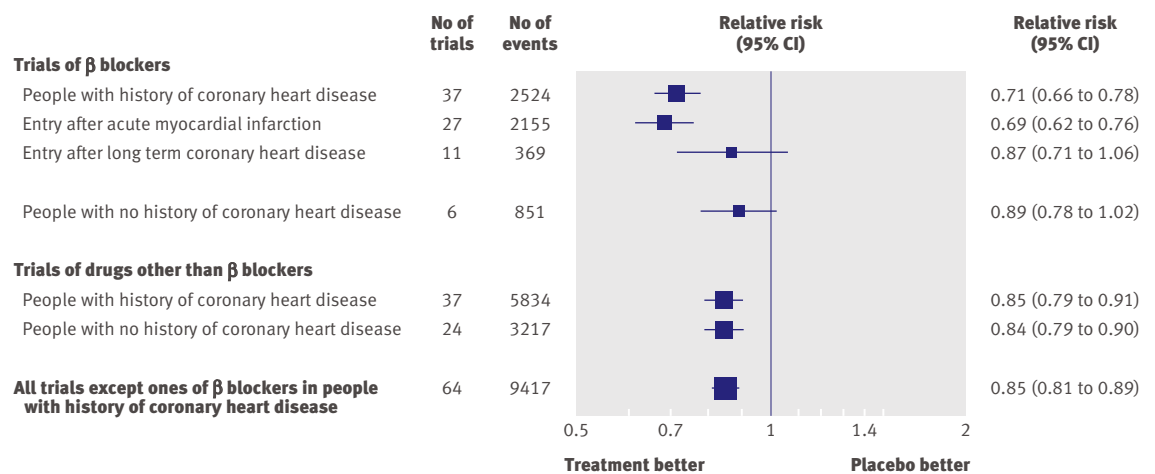


Fig 1 | Relative risk estimates of coronary heart disease events in single drug blood pressure difference trials according to drug (β blockers or other), presence of CHD, and for β blockers according to acute myocardial infarction on entry. (Totals are less than the sum of the individual categories because some trials include more than one category; see web extra figures 1a-e for individual trial results and summary estimates)

We excluded non-randomised trials and trials in which treated groups but not control groups had other interventions as well as blood pressure reduction, such as cholesterol reduction. We excluded trials in patients with chronic renal failure because these patients typically have high blood pressure and high rates of cardiovascular disease and their response to standard blood pressure lowering therapy may differ from other people. We also excluded trials in which fewer than five CHD events and strokes were recorded or the duration of treatment was less than six months, as these data would contribute little to the overall results and substantially increase the complexity of the analyses. Randomised trials were otherwise included irrespective of participants' age, disease status, blood pressure before treatment, or use of other drugs.

Data extraction

We recorded the numbers of participants having one or more CHD events (defined as fatal or non-fatal myocardial infarction or sudden cardiac death but excluding "silent" infarcts) and one or more strokes (haemorrhagic and ischaemic strokes could not be distinguished). We also recorded the numbers of participants with a new diagnosis of heart failure or an exacerbation of existing heart failure based on new hospital admissions or death from the disorder. Two authors (MRL and NJW) independently recorded data, with differences resolved by discussion. Outcomes were recorded regardless of whether participants took their allocated tablets (intention to treat analysis). Change in blood pressure in the trials (value on entry minus the average value during the trial in the treated group, minus the same change in the control group) was recorded on an intention to treat basis by determining the numbers of participants in the treated and in the control groups who stopped attending the clinics (so that their blood pressure reduction was no longer recorded) and taking the difference in blood pressure between them to be zero after they left the trial.

Categories of trial

The trials were divided into three predefined categories according to whether the recruitment was based on participants having no history of cardiovascular disease, a history of CHD (acute myocardial infarction, coronary artery disease without recent infarction, or heart failure), or a history of stroke (or other cerebrovascular disease). In the trials of participants with no history of vascular disease, blood pressure was usually high, variably defined, and a treat to target approach was used, typically based on one drug with the dose increased before the addition of other drugs to reach the target blood pressure. The control groups were allocated to usual care. In the trials of participants with a history of CHD there was generally no selection by blood pressure and no blood pressure target; treated patients were allocated a specified drug in fixed dose, varied only to avoid adverse effects. In the

trials of participants with a history of stroke most followed the treat to target approach, some followed the specified drug approach. In trials of participants who had acute myocardial infarction on entry sudden deaths while in hospital were not recorded because it was not our objective to assess the efficacy of the drugs in reducing mortality in the period immediately after infarction; the CHD events and heart failure episodes we recorded were either those designated as reinfarction or those occurring after hospital discharge. Similarly in trials of participants who had heart failure on entry, sudden deaths were not recorded (as ischaemia and worsening heart failure could not be distinguished as causes). In trials of participants with CHD and who had acute myocardial infarction or heart failure on entry,^{29,30} many of the strokes recorded were likely to have been embolic (thrombus formation on an acute infarct or in a dilated left ventricle) and therefore not preventable by blood pressure reduction, so the estimate of the reduction in stroke was taken from the trials in which participants had coronary artery disease without recent infarction or heart failure.

We also categorised the trials into "blood pressure difference trials" and "drug comparison trials." (Details of each trial are given in web extra tables 1i-iii and 2.) The blood pressure difference trials were those designed to achieve a difference in blood pressure between randomised groups who were given and were not given the study drugs to show the effect of this difference on the incidence of CHD events and stroke. Ninety two of the 108 trials in this category were placebo controlled, but in 16 the control group was not given a placebo. Additional blood pressure lowering drugs were commonly used in the different groups in each trial—for example, in trials comparing an angiotensin converting enzyme inhibitor with placebo in people with CHD, participants in both groups might also receive β blockers or calcium channel blockers, whereas in trials in which a treat to target approach was used, add-on drugs were given if necessary in both actively treated and placebo treated participants to reach their blood pressure targets (the target being lower for treated participants than for placebo participants). Through their design the blood pressure difference trials ensured that the intervention groups were more intensively treated. Trials were regarded as single drug trials if the difference between the groups in the mean number of drugs prescribed per participant (study drug included) was less than 1.5 (in the event 1.0 on average, and as combination drug trials if the mean number of drugs prescribed per participant was 1.5 or greater (2.0 on average).

Drug comparison trials were those that compared two blood pressure lowering drugs with each other. Although additional drugs could be used in either group there was no intention to achieve a different blood pressure reduction in one group compared with another. These trials therefore tested for effects of a drug that were unrelated to lowering blood pressure. In two drug comparison trials of three drugs^{w129 w147} each of the three pairwise comparisons was

Table 1 | Randomised trials of blood pressure lowering drugs according to category of trial (see web extra tables 1i-iii and 2 for details of individual trials)

Trial category and clinical history of participants on entry	No of trials	No of participants	Mean age on entry (years)	Mean duration (years)	No of disease events recorded			Range of mean pretreatment blood pressure in individual trials (mm Hg)	
					Coronary heart disease	Stroke	Heart failure	Systolic	Diastolic
Blood pressure difference trials									
No vascular disease ^{*w1-w33}	27	108 297	62	4.5	3429	2843	582	132-186	72-119
Coronary heart disease†:									
Trials of β blockers ^{w34-w72}	37	38 892	57	1.7	2524	20	3198	112-149	72-92
Trials of other drugs ^{w73-w112}	37	85 395	62	3.6	5815	964	6831	113-141	70-86
Stroke‡ ^{w1 w7 w9 w29 w30 w113-w121}	13*	16 085	64	3.1	567	1593	13	132-186	72-115
All blood pressure difference trials ^{w1-w121}	108	248 445	62	3.5	12 324	5420	10 624	112-186	70-119
Drug comparison trials									
All trial categories¶ ^{w13-w17 w26 w34 w82 w122-w162}	46	230 491	67	4.5	10 357	6862	7317	123-194	71-108
All trials	147§	464 164§	64	4.0	22 115§	12 034§	17 890§	112-194	70-119

*In the event 3% of participants had a history of myocardial infarction and 3% of stroke.

†In the event 90% of participants had a proved coronary heart disease, 8% had heart failure not caused by coronary heart disease, 1% had peripheral arterial or cerebrovascular disease, and 1% had no known vascular disease.

‡All participants had stroke or other cerebrovascular disease.

§"All trials" totals are less than column totals because six trials with two randomised treatment groups and one placebo group, included both as blood pressure difference trials and drug comparison trials, ^{w11-w14 w29 w82} are counted twice; a seventh such trial is counted three times; and participants in five trials of stroke on entry were subgroups in five predominantly "no vascular disease" trials^{w5} (see web extra table 1iii).

¶Participants had no vascular disease in most drug comparison trials; see web extra table 2.

recorded separately. In both trial categories, additional drugs of a class allocated to one randomised group could not be used in the other.

Statistical analysis

All statistical analyses were done using Stata software. We combined relative risk estimates of disease events from individual trials using a random effects model³¹ (which avoids assuming that participants in the individual trials in the meta-analysis are sampled from populations in which the intervention has the same quantitative effect). Summary relative risk estimates from blood pressure difference trials were standardised to a blood pressure reduction of 10 mm Hg systolic or 5 mm Hg diastolic, by raising the relative risk estimate in each trial to the appropriate power (10 divided by the observed reduction in systolic blood

pressure or 5 divided by the observed reduction in diastolic pressure)—for example, if the relative risk was 0.7 and the reduction in systolic blood pressure was 8 mm Hg, the standardised relative risk estimate was 0.64 (0.7^{1.25}, since 10/8=1.25). If reductions in both systolic and diastolic blood pressures were reported (as in most trials), we took the average of the two risk estimates (more strongly predictive than either alone²⁵). As the reduction in blood pressure was not reported in most trials of people with a history of CHD, we estimated the average reduction from the average blood pressure before treatment and the average drug dose (as a multiple of standard dose^{32,33}), using results from a meta-analysis in which the effect of pretreatment blood pressure and dose on blood pressure reduction was quantified.³² The estimated blood pressure reduction was 5.9 mm Hg systolic and 3.1 mm Hg diastolic,

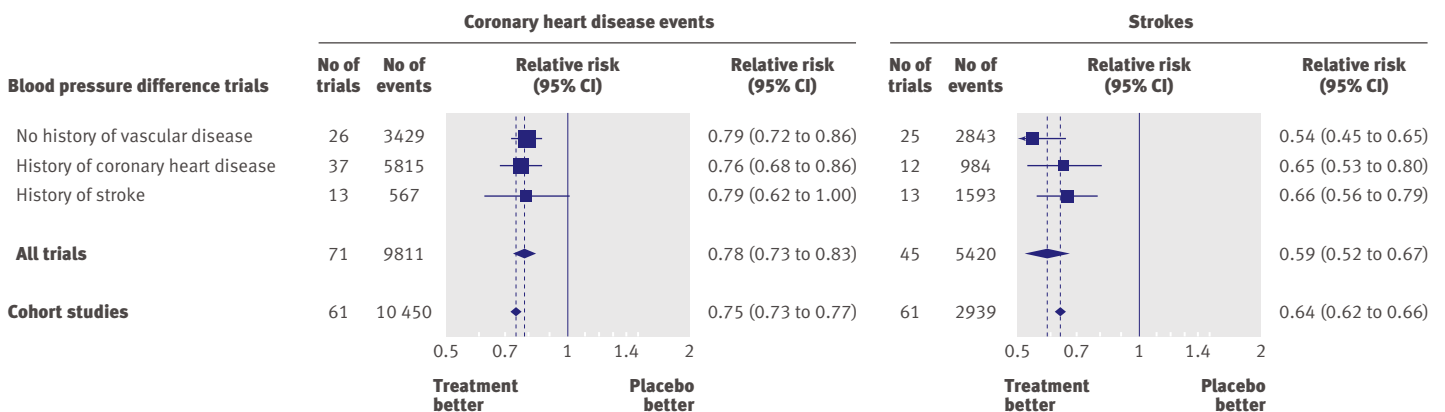


Fig 2 | Relative risk estimates of coronary heart disease events and stroke for a blood pressure reduction of 10 mm Hg systolic or 5 mm Hg diastolic in the blood pressure difference trials and in epidemiological cohort studies. (Total number of trials is fewer than the sum of the three categories as five included participants with and without vascular disease; see web extra figures 2a-f for individual trial results and summary estimates)

Table 2 | Summary relative risk estimates (95% confidence intervals) for coronary heart disease (CHD) events and stroke from randomised blood pressure difference trials observed and standardised to a blood pressure reduction of 10 mm Hg systolic and 5 mm Hg diastolic

Clinical history of participants on entry	No of trials	Observed		Standardised for blood pressure reduction	
		CHD events	Stroke	CHD events	Stroke
No vascular disease	27	0.84 (0.79 to 0.90)	0.64 (0.56 to 0.73)	0.79 (0.72 to 0.86)	0.54 (0.45 to 0.65)
CHD*	37	0.85 (0.79 to 0.91)	0.77 (0.68 to 0.87)	0.76 (0.68 to 0.86)	0.65 (0.53 to 0.80)
Stroke	13†	0.85 (0.73 to 1.00)	0.76 (0.68 to 0.85)	0.79 (0.62 to 1.00)	0.66 (0.56 to 0.79)
All trials*	72	0.84 (0.81 to 0.88)	0.70 (0.65 to 0.76)	0.78 (0.73 to 0.83)	0.59 (0.52 to 0.67)

*Summary estimates omitting CHD events (but not strokes) in trials of β blockers in patients with a clinical history of CHD (heterogeneity for CHD, $\chi^2=0.02$, $df=2$, $P=0.99$; heterogeneity for stroke, $\chi^2=2.0$, $df=2$, $P=0.37$).

†Includes subgroups of participants with stroke on entry from five predominantly "no vascular disease" trials so total is less than the sum of the individual categories^{WS} (see web extra table 1iii).

close to the median reduction in the 27 trials in which blood pressure reduction was reported, which was 6 mm Hg systolic and 3 mm Hg diastolic.

Predicting the trial results on CHD and stroke from epidemiological studies and trials of drugs on blood pressure

Effect of blood pressure lowering drugs in lowering blood pressure according to dose

These estimates are taken from a meta-analysis of 354 short term randomised placebo controlled trials of blood pressure lowering drugs in fixed dose,³² which showed that the five main classes of blood pressure lowering drugs produce similar reductions in blood pressure when taken at standard dose or at the same multiple of standard dose. It also showed that the blood pressure lowering effect of the drugs increased with dose and with pretreatment blood pressure, and reported regression equations that quantified the reduction in blood pressure from one drug according to pretreatment blood pressure. From the average blood pressure of 154 mm Hg systolic and 97 mm Hg diastolic one drug at standard dose lowered blood pressure by 9.1 mm Hg systolic and 5.5 mm Hg diastolic on average.

At lower or higher pretreatment blood pressures the blood pressure reduction decreased (or increased) by 0.10 mm Hg systolic and 0.11 mm Hg diastolic per mm Hg decrease (or increase) in pretreatment blood pressure. The estimated effect of one drug at standard dose in lowering blood pressure from a pretreatment blood pressure P is therefore $[9.1+0.10(P-154)]$ systolic and $[5.5+0.11(P-97)]$ diastolic. So for example the reduction in blood pressure was 8.7 mm Hg systolic from a pretreatment value of 150 mm Hg, 4.7 mm Hg diastolic from a pretreatment value of 90 mm Hg. The estimated blood pressure reduction for two or three drugs at standard dose was calculated by applying these equations to each drug in turn, allowing for the effect of the first in lowering pretreatment blood pressure for the second, and the second for the third. In the above example the pretreatment blood pressure for the second drug would be 141.3 (150-8.7) mm Hg systolic and 85.3 (90-4.7) mm Hg diastolic.

Using drugs at half standard dose, taking dose and pretreatment blood pressure into account, it was estimated in the meta-analysis of 354 trials that one, two, and three drugs at half standard dose reduced a pretreatment systolic pressure of 150 mm Hg by 6.7 mm

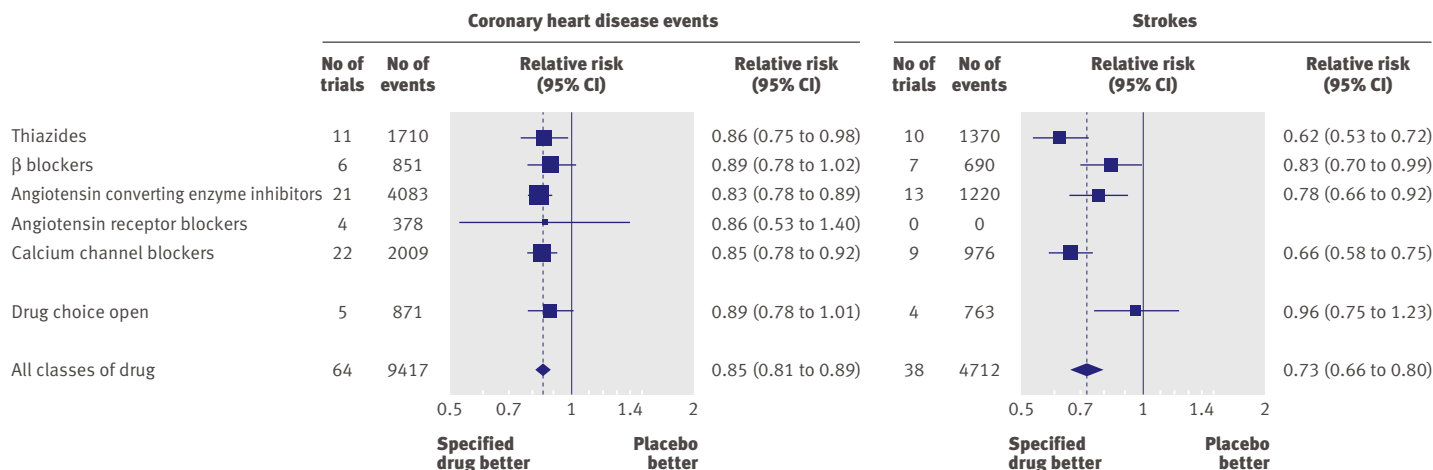


Fig 3 | Relative risk estimates of coronary heart disease events and stroke in single drug blood pressure difference trials according to class of drug (excluding CHD events in trials of β blockers in people with history of coronary heart disease). (Totals are less than the sum of the individual categories because some trials include more than one category; see web extra figures 3a-i for individual trial results and summary estimates)

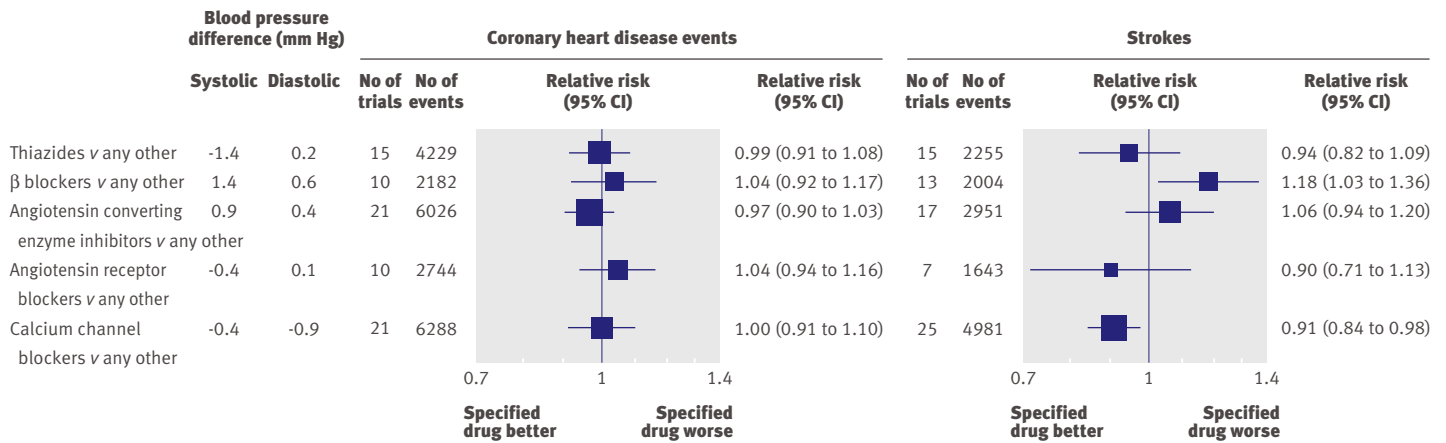


Fig 4 | Relative risk estimates of coronary heart disease events and stroke in 46 drug comparison trials comparing each of the five classes of blood pressure lowering drug with any other class of drug (excluding CHD events in trials of β blockers in people with a history of coronary heart disease; see web extra figures 4a-j for individual trial results and summary estimates)

Hg, 13.3 mm Hg, and 19.9 mm Hg, respectively, and reduced a pretreatment diastolic pressure of 90 mm Hg by 3.7 mm Hg, 7.3 mm Hg, and 10.7 mm Hg, respectively (allowing for the effect of one drug in lowering pretreatment blood pressure for the next; table 4).³² These blood pressure reductions decreased (or increased) by an estimated 0.078 mm Hg systolic and 0.088 mm Hg diastolic, per mm Hg decrease (or increase) in pretreatment blood pressure per drug, 22% and 20% lower, respectively, than the changes at standard dose (0.10 mm Hg and 0.11 mm Hg.³² The blood pressure reductions from one, two, and three drugs at half standard dose were $[R+n \times 0.078(P-150)]$ systolic and $[R+n \times 0.088(P-90)]$ diastolic, where R is the blood pressure reduction at 150 mm Hg systolic or 90 mm Hg diastolic (given above), n is the number of drugs, and P is the pretreatment blood pressure

Expected reduction in disease events for a specified reduction in blood pressure

The associations between systolic and diastolic blood pressure and CHD events and stroke were taken from the largest published meta-analysis of 61 cohort (prospective observational) studies.²⁵ This showed that in every age group cardiovascular mortality plotted on a logarithmic scale against blood pressure on an arithmetic scale is well fitted by straight lines, indicating a constant proportional change in risk for a specified change in blood pressure from any level of pretreatment blood pressure. Age specific slopes of the lines (regression coefficients) were published, permitting the calculation of the predicted proportional reduction in disease events for any age and blood pressure difference. For an age specific regression slope, S (see web extra table 3), and decrease in blood pressure, d, the relative risk is $S^{d/20}$ for systolic pressure and $S^{d/10}$ for diastolic pressure. The following examples illustrate the calculations. At age 60-69, the relative risk of stroke is 0.43 (57% decrease) for a 20 mm Hg decrease in systolic blood pressure. For a blood pressure decrease

twice as great (40 mm Hg), the relative risk of 0.43 effectively applies twice (0.43×0.43 , or 0.43^2), which is 0.18 (an 82% decrease). For a reduction in blood pressure half as great, by symmetry the relative risk is $\sqrt{0.43}$, or $0.43^{1/2}$, which is 0.66 (a 34% decrease). For a 30 mm Hg decrease in blood pressure the relative risk is $0.43^{1.5}$ (since $30/20=1.5$), which is 0.28 (a 72% decrease). The sloping lines in the lower portion of figure 6 reflect these regression coefficients for stroke and CHD events in the age groups 50-59, 60-69, and 70-79 years.

The effect of blood pressure lowering drugs in reducing the risk of CHD events and stroke can therefore be estimated according to the reduction in systolic or diastolic blood pressure (or the average of the two), from the regression slope, S, and the decrease in blood pressure, d, from the above equations. As an example, the effect of three drugs at half standard dose in preventing stroke in people aged 60-69 with a pretreatment systolic blood pressure of 180 mm Hg systolic is estimated as: decrease in systolic blood pressure = $[19.9 + (3 \times 0.078 \times (180 - 150))] = 26.9$ mm Hg, and relative risk of stroke = $0.43^{26.9/20} = 0.32$ (a 68% decrease).

RESULTS

Overall, 147 trial reports were included in the analysis: 108 were blood pressure difference trials and 46 drug comparison trials (seven trial reports with two treatment groups and a placebo group fell into both categories, treatment versus placebo and one treatment versus the other). Table 1 summarises the trials (see web extra tables 1i-iii and 2 for individual data from the trials). Forest plots of individual trial results are presented in 55 web extra figures (available at www.wolfson.qmul.ac.uk/bptrial/) and the summary relative risk estimates and results for heterogeneity testing are shown in web extra table A. Results on CHD events and stroke are presented first, according to the five questions posed in the introduction, followed by results on heart failure and all cause mortality.

Table 3 | Estimates of preventive effect of taking one or more blood pressure lowering drugs on coronary heart disease (CHD) events and stroke according to pretreatment systolic blood pressure, age, number of drugs, and dose (as multiple of standard³³)

Pretreatment systolic blood pressure (mm Hg)	Estimated reduction in systolic blood pressure (mm Hg)*	Relative risk of CHD events by age (years)					Relative risk of stroke by age (years)				
		40-49	50-59	60-69	70-79	80-89	40-49	50-59	60-69	70-79	80-89
One drug half standard dose:											
180	9.0	0.72	0.73	0.76	0.79	0.83	0.63	0.65	0.68	0.73	0.83
170	8.3	0.74	0.75	0.78	0.81	0.85	0.66	0.67	0.71	0.75	0.85
160	7.5	0.77	0.77	0.79	0.83	0.86	0.68	0.70	0.73	0.77	0.86
150	6.7	0.79	0.79	0.81	0.84	0.87	0.71	0.72	0.75	0.79	0.87
140	5.9	0.81	0.81	0.83	0.86	0.89	0.74	0.75	0.78	0.81	0.89
130	5.1	0.83	0.84	0.85	0.88	0.90	0.77	0.78	0.81	0.84	0.90
120	4.4	0.86	0.86	0.87	0.89	0.92	0.80	0.81	0.83	0.86	0.92
One drug standard dose:											
180	11.7	0.66	0.67	0.70	0.74	0.79	0.55	0.57	0.61	0.67	0.79
170	10.7	0.68	0.69	0.72	0.76	0.81	0.58	0.60	0.64	0.69	0.81
160	9.7	0.71	0.71	0.74	0.78	0.82	0.61	0.63	0.66	0.71	0.82
150	8.7	0.73	0.74	0.76	0.80	0.84	0.64	0.66	0.69	0.74	0.84
140	7.7	0.76	0.77	0.79	0.82	0.86	0.67	0.69	0.72	0.77	0.86
130	6.7	0.79	0.79	0.81	0.84	0.87	0.71	0.72	0.75	0.79	0.87
120	5.7	0.82	0.82	0.84	0.86	0.89	0.75	0.76	0.79	0.82	0.89
Two drugs half standard dose:											
180	18.0	0.53	0.54	0.57	0.63	0.70	0.40	0.42	0.47	0.54	0.70
170	16.4	0.56	0.57	0.60	0.66	0.72	0.43	0.45	0.50	0.57	0.72
160	14.5	0.59	0.60	0.63	0.68	0.74	0.47	0.49	0.53	0.60	0.74
150	13.3	0.62	0.63	0.66	0.71	0.77	0.51	0.53	0.57	0.63	0.77
140	11.7	0.66	0.67	0.70	0.74	0.79	0.55	0.57	0.61	0.67	0.79
130	10.2	0.70	0.70	0.73	0.77	0.82	0.59	0.61	0.65	0.70	0.82
120	8.6	0.74	0.74	0.77	0.80	0.84	0.64	0.66	0.70	0.74	0.84
Two drugs standard dose:											
180	22.2	0.45	0.46	0.50	0.57	0.64	0.32	0.34	0.39	0.46	0.64
170	20.3	0.48	0.49	0.53	0.59	0.67	0.35	0.37	0.42	0.47	0.67
160	18.4	0.52	0.53	0.57	0.62	0.69	0.39	0.41	0.46	0.53	0.69
150	16.5	0.55	0.56	0.60	0.66	0.72	0.43	0.45	0.50	0.56	0.72
140	14.6	0.59	0.60	0.64	0.69	0.75	0.47	0.49	0.54	0.60	0.75
130	12.7	0.64	0.64	0.68	0.72	0.77	0.52	0.54	0.58	0.64	0.77
120	10.8	0.68	0.69	0.72	0.76	0.81	0.58	0.59	0.63	0.69	0.81
Three drugs half standard dose:											
180	26.9	0.38	0.39	0.44	0.50	0.58	0.25	0.27	0.32	0.39	0.58
170	24.6	0.42	0.43	0.47	0.53	0.61	0.28	0.30	0.35	0.43	0.61
160	22.2	0.45	0.46	0.50	0.57	0.64	0.32	0.34	0.39	0.46	0.64
150	19.9	0.49	0.50	0.54	0.60	0.67	0.36	0.38	0.43	0.50	0.67
140	17.6	0.50	0.51	0.55	0.61	0.68	0.37	0.39	0.44	0.54	0.68
130	15.2	0.58	0.59	0.63	0.68	0.74	0.46	0.48	0.53	0.59	0.74
120	12.9	0.63	0.64	0.67	0.72	0.77	0.52	0.54	0.58	0.64	0.77
Three drugs standard dose:											
180	31.7	0.32	0.33	0.38	0.44	0.53	0.20	0.22	0.26	0.33	0.53
170	29.0	0.36	0.37	0.41	0.48	0.56	0.23	0.25	0.29	0.37	0.56
160	26.3	0.39	0.40	0.44	0.51	0.59	0.26	0.28	0.33	0.40	0.59
150	23.6	0.43	0.44	0.48	0.55	0.62	0.30	0.32	0.37	0.44	0.62
140	20.9	0.48	0.49	0.53	0.59	0.66	0.34	0.36	0.41	0.49	0.66
130	18.2	0.52	0.53	0.57	0.63	0.70	0.40	0.42	0.46	0.53	0.70
120	15.5	0.58	0.59	0.62	0.67	0.73	0.45	0.47	0.52	0.59	0.73

This table is a numerical expansion of figure 7 (systolic blood pressure). Estimates calculated using a two stage procedure in which the effect of drug treatment in reducing systolic blood pressure was first estimated,³² then the effect of this blood pressure reduction on disease risk.²⁵

*See Methods (section headed "Predicting the trial results.")

Do β blockers have a special effect in preventing CHD events in people with a history of CHD?

Blood pressure difference trials

Figure 1 shows the reduction in CHD events in the 37 blood pressure difference trials of β blockers in people with a history of CHD, comparing β blockers with placebo (32 trials) or with an untreated control group (five trials). CHD events were, on average, reduced by 29% (relative risk 0.71, 95% confidence interval 0.66 to 0.78), significantly greater ($P<0.001$) than the 15% reduction in single drug trials of β blockers in people without a history of CHD and of other classes of drug in people with and without a history of CHD. The greater protective effect of β blockers in people with CHD was explained by a greater effect in the 27 trials that recruited participants at the time of an acute myocardial infarction (within a month in 25 trials and within four months in the other two). The risk reduction for recurrent CHD events in these 27 trials of people with an acute myocardial infarction was 31% (relative risk 0.69, 0.62 to 0.76); the duration of follow-up was short (77% of the events occurred in the first year and 94% in the first two years), so almost all the recurrent events occurred within one or two years of the infarct. Eleven trials remained (not 10 (37–27) because one trial recruited some participants with a recent infarct and some without^{w62}); these recruited participants with a history of CHD but no recent infarct and in these the risk reduction was 13% (relative risk 0.87,

0.71 to 1.06; $P=0.04$ for the difference between the two groups of trials). In these 11 trials about 75% of the participants had had an infarct, but not within the last four months and typically several years before. The 13% risk reduction was similar to the 15% risk reductions in the other categories of single drug trials, whereas the 31% risk reduction after acute myocardial infarction was significantly greater ($P<0.001$). β blockers used for one or two years after an acute myocardial infarction were therefore about twice as effective as β blockers used in other circumstances and about twice as effective as other drugs used in any circumstances (see web figures 1a-e for forest plots of the individual trial results).

Drug comparison trials

The four drug comparison trials of β blockers compared with other drugs in people with CHD but no recent infarct (see web extra table 2) confirmed the absence of a special effect of β blockers in the absence of a recent infarct; the summary relative risk of CHD events was 0.99 (0.82 to 1.20), a relative risk of 1.0 indicating the same risk reduction from β blockers and other drugs.

In view of the special effect of β blockers, CHD events (but not stroke or heart failure) in all 37 blood pressure difference trials and all four drug comparison trials of β blockers in people with CHD were excluded from subsequent analyses according to the prior

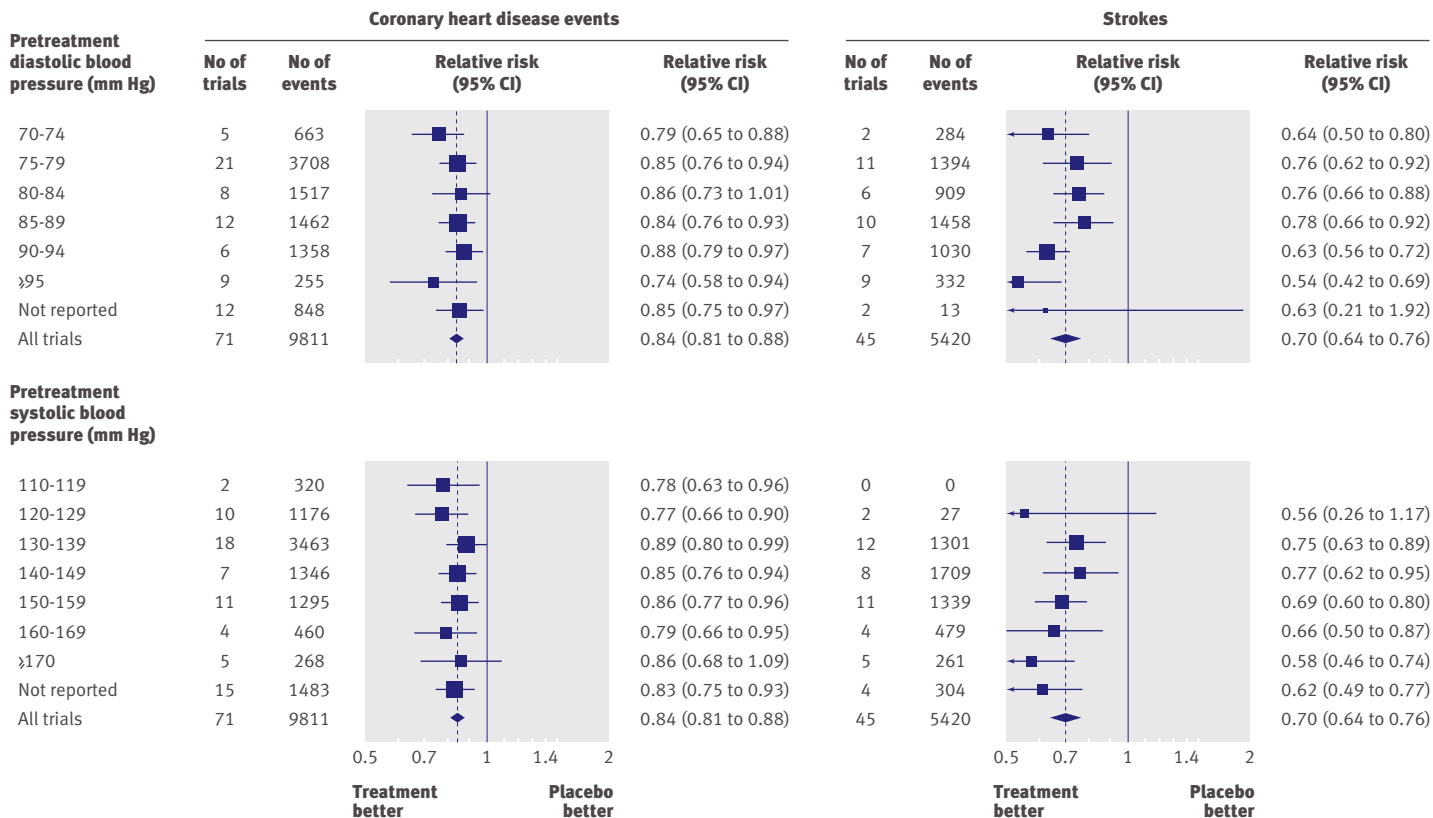


Fig 5 | Relative risk estimates of coronary heart disease events and stroke in blood pressure difference trials according to pretreatment diastolic and systolic blood pressures (taken as average in placebo group over course of trial). (Totals are less than the sum of the individual categories because some trials include more than one category; see web extra figures 5a-l and 6a-m for individual trial results and summary estimates)

Table 4 | Estimates of preventive effect of taking one or more blood pressure lowering drugs on coronary heart disease (CHD) events and stroke according to pretreatment diastolic blood pressure, age, number of drugs, and dose (as multiple of standard³³)³² then the effect of this blood pressure reduction on disease risk.²⁵

Pretreatment diastolic blood pressure (mm Hg)	Estimated reduction in diastolic blood pressure (mm Hg)	Relative risk of CHD events by age (years)					Relative risk of stroke by age (years)				
		40-49	50-59	60-69	70-79	80-89	40-49	50-59	60-69	70-79	80-89
One drug half standard dose:											
110	5.5	0.66	0.70	0.73	0.77	0.82	0.56	0.55	0.61	0.67	0.78
105	5	0.68	0.72	0.75	0.79	0.84	0.59	0.58	0.63	0.69	0.79
100	4.6	0.71	0.74	0.77	0.80	0.85	0.62	0.61	0.66	0.71	0.81
95	4.1	0.73	0.76	0.79	0.82	0.86	0.65	0.64	0.68	0.74	0.83
90	3.7	0.76	0.79	0.81	0.84	0.88	0.68	0.67	0.71	0.76	0.84
85	3.3	0.78	0.81	0.83	0.86	0.89	0.71	0.70	0.74	0.79	0.86
80	2.8	0.81	0.83	0.85	0.87	0.90	0.74	0.74	0.77	0.81	0.88
75	2.4	0.84	0.86	0.87	0.89	0.92	0.78	0.77	0.80	0.84	0.90
One drug standard dose:											
110	6.9	0.59	0.64	0.67	0.72	0.78	0.48	0.47	0.53	0.60	0.73
105	6.4	0.62	0.66	0.69	0.74	0.80	0.51	0.50	0.56	0.63	0.74
100	5.8	0.64	0.68	0.71	0.76	0.81	0.54	0.53	0.59	0.65	0.76
95	5.3	0.67	0.71	0.74	0.78	0.83	0.57	0.57	0.62	0.68	0.78
90	4.7	0.70	0.73	0.76	0.80	0.84	0.61	0.60	0.65	0.71	0.80
85	4.2	0.73	0.76	0.78	0.82	0.86	0.64	0.64	0.68	0.74	0.82
80	3.6	0.76	0.79	0.81	0.84	0.88	0.68	0.68	0.72	0.77	0.85
75	3.1	0.79	0.82	0.84	0.86	0.90	0.72	0.72	0.75	0.80	0.87
Two drugs half standard dose:											
110	10.8	0.44	0.49	0.53	0.60	0.68	0.32	0.31	0.37	0.45	0.61
105	9.9	0.47	0.52	0.56	0.62	0.70	0.35	0.34	0.40	0.48	0.63
100	9.1	0.50	0.55	0.59	0.65	0.72	0.39	0.38	0.44	0.51	0.66
95	8.2	0.54	0.59	0.62	0.68	0.75	0.42	0.41	0.47	0.55	0.69
90	7.3	0.58	0.62	0.65	0.71	0.77	0.46	0.45	0.51	0.59	0.71
85	6.4	0.62	0.66	0.69	0.74	0.80	0.51	0.50	0.56	0.62	0.74
80	5.5	0.66	0.70	0.73	0.77	0.82	0.56	0.55	0.60	0.67	0.77
75	4.7	0.70	0.74	0.76	0.80	0.85	0.61	0.60	0.65	0.71	0.81
Two drugs standard dose:											
110	13.1	0.37	0.42	0.49	0.53	0.63	0.25	0.24	0.30	0.38	0.55
105	12.1	0.40	0.45	0.50	0.56	0.65	0.28	0.27	0.33	0.41	0.57
100	11.0	0.44	0.49	0.53	0.59	0.67	0.31	0.30	0.36	0.45	0.60
95	10.0	0.47	0.52	0.56	0.62	0.70	0.35	0.34	0.40	0.48	0.63
90	8.9	0.51	0.56	0.60	0.65	0.73	0.39	0.38	0.44	0.52	0.66
85	7.9	0.55	0.60	0.63	0.69	0.75	0.44	0.43	0.48	0.56	0.69
80	6.9	0.60	0.64	0.67	0.72	0.78	0.49	0.48	0.53	0.60	0.73
75	5.8	0.64	0.68	0.71	0.76	0.81	0.54	0.53	0.59	0.65	0.76
Three drugs half standard dose:											
110	16.0	0.30	0.35	0.40	0.47	0.57	0.19	0.18	0.23	0.31	0.48
105	14.7	0.33	0.38	0.43	0.50	0.59	0.21	0.21	0.26	0.34	0.51
100	13.3	0.37	0.42	0.46	0.53	0.62	0.25	0.24	0.29	0.38	0.54
95	12.0	0.40	0.46	0.50	0.56	0.65	0.28	0.27	0.33	0.41	0.57
90	10.7	0.45	0.50	0.54	0.60	0.68	0.33	0.32	0.38	0.46	0.61
85	9.4	0.49	0.54	0.58	0.64	0.72	0.37	0.36	0.42	0.50	0.65
80	8.1	0.54	0.59	0.63	0.68	0.75	0.43	0.42	0.48	0.55	0.69
75	6.7	0.60	0.64	0.68	0.72	0.79	0.49	0.48	0.54	0.61	0.73
Three drugs standard dose:											
110	18.6	0.25	0.30	0.34	0.41	0.52	0.14	0.13	0.18	0.26	0.42
105	17.1	0.27	0.33	0.37	0.44	0.54	0.17	0.16	0.21	0.28	0.45
100	15.6	0.31	0.36	0.40	0.47	0.57	0.19	0.19	0.24	0.32	0.49
95	14.2	0.34	0.40	0.44	0.51	0.60	0.23	0.22	0.27	0.35	0.52
90	12.7	0.38	0.44	0.48	0.55	0.64	0.26	0.25	0.31	0.39	0.56
85	11.2	0.43	0.48	0.52	0.59	0.67	0.31	0.30	0.36	0.44	0.60
80	9.7	0.48	0.53	0.57	0.63	0.71	0.36	0.35	0.41	0.49	0.64
75	8.3	0.54	0.58	0.62	0.67	0.74	0.42	0.41	0.47	0.55	0.68

This table is a numerical expansion of figure 6 (diastolic blood pressure). Estimates calculated using a two stage procedure in which the effect of drug treatment in reducing diastolic blood pressure was first estimated,³² then the effect of this blood pressure reduction on disease risk.²⁵

*See Methods (section headed "Predicting the trial results.")

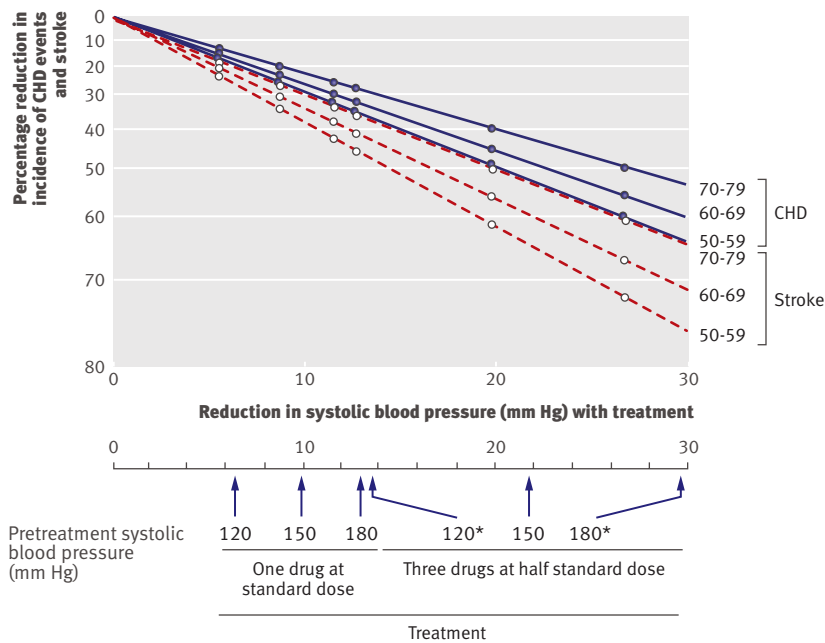


Fig 7 | Reduction in incidence of coronary heart disease (CHD) events and stroke in relation to reduction in systolic blood pressure according to dose and combination of drugs, pretreatment systolic blood pressure, and age. *Blood pressure reductions are more uncertain and hence also reductions in disease incidence

stipulation that we would do so if a special effect was observed, even though post hoc the special effect was limited to a subset (those with acute infarction).

Does the preventive effect of drugs differ in people with and without a history of cardiovascular disease?

The summary relative risk estimates of CHD events and stroke in the blood pressure difference trials, observed and standardised for reduction in blood pressure, were similar in the three categories of trials (no vascular disease, history of CHD, and history of stroke), showing no difference in effect in people with or without vascular disease (table 2, also see web extra figures 2a-f for forest plots of individual trial results). There was no heterogeneity across the trials (table 2) and no special effect of drugs other than β blockers after acute myocardial infarction.

Does blood pressure reduction alone explain the preventive effect of the drugs?

Blood pressure difference trials

Figure 2 shows the relative risk estimates of CHD events and stroke in the blood pressure difference trials, standardised to a blood pressure reduction of 10 mm Hg systolic and 5 mm Hg diastolic, together with the corresponding relative risk estimates derived from the meta-analysis of cohort studies (Prospective Studies Collaboration analysis²⁵), in the age group 60-69 years, the average age at the time of a cardiovascular event in the trials (table 1). The estimates from the trials meta-analysis were a 22% (95% confidence interval 17% to 27%) reduction in CHD events (relative risk 0.78) and a 41% (33% to 48%) reduction in stroke (relative risk 0.59). The cohort study meta-analysis showed a 25% decrease in CHD events (relative risk 0.75) and a 36% decrease in stroke (relative risk 0.64) for the same blood pressure difference of 10 mm Hg systolic, or 5 mm Hg diastolic (results from other cohort study meta-analyses were similar^{26,27}). Thus the reductions in disease events in the trials were similar to those expected from the cohort study results for the same reduction in blood pressure.

After only one year of follow-up (see web extra table 1) the reduction in CHD events was 20% (9% to 29%) and the reduction in stroke was 32% (18% to 44%) for a reduction of 10 mm Hg in systolic blood pressure and 5 mm Hg diastolic, similar to the long term trial results (22% and 41%) and similar to the results expected from the cohort studies (25% and 36%; see fig 2), indicating that the full potential effect of blood pressure reduction is achieved within a year.

Figure 3 shows the reductions in CHD events and stroke in the single drug trials comparing a specified drug with placebo (or with a control group not receiving the study drug in nine trials), separately for each of the five main classes of drug (the only drugs tested in single drug trials). The five classes of drug produced reductions in CHD events and stroke that were similar in magnitude. All the reductions were statistically significant but for angiotensin receptor blockers there were only four trials and hence insufficient statistical power to show an effect. Average differences between

Table 5 | Observed percentage reductions in coronary heart disease (CHD) events and stroke in single and combination drug treatment blood pressure difference trials compared with predicted reductions according to number of drugs, dose, pretreatment blood pressure, and age (60-69 years) (tables 3 and 4), adjusted for proportion of treated participants not taking their allocated tablets (25%)

Category of drug trial†	No of trials*	Average No of drugs per participant	Mean dose (multiple of standard ³³)	Mean pretreatment blood pressure (mm Hg)		No of disease events		Percentage reduction in cardiovascular disease events			
				Systolic	Diastolic	CHD	Stroke	CHD		Stroke	
								Observed in trials (95% CI)	Predicted based on systolic and diastolic	Observed in trials (95% CI)	Predicted based on systolic and diastolic
Single	65	1.0	1.7	140	81	9417	4712	15 (11 to 19)	19 and 17	27 (20 to 34)	25 and 25
Combination	8	2.0	1.2	160	91	394	708	25 (9 to 38)	36 and 34	41 (31 to 50)	45 and 48

*One trial was part single drug and part combined drug therapy,^{w118} hence numbers sum to 73 when there were 72 trials.

†In "single" drug trials the difference between intervention and control groups in average number of drugs taken per participant, taking account of "add-on" therapy in individual trials, was <1.5, in combination drug trials ≥ 1.5 .

