Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data

*The Blood Pressure Lowering Treatment Trialists' Collaboration**

Summary

Background We aimed to investigate whether the benefits of blood pressure-lowering drugs are proportional to baseline cardiovascular risk, to establish whether absolute risk could be used to inform treatment decisions for blood pressure-lowering therapy, as is recommended for lipid-lowering therapy.

Methods This meta-analysis included individual participant data from trials that randomly assigned patients to either blood pressure-lowering drugs or placebo, or to more intensive or less intensive blood pressure-lowering regimens. The primary outcome was total major cardiovascular events, consisting of stroke, heart attack, heart failure, or cardiovascular death. Participants were separated into four categories of baseline 5-year major cardiovascular risk using a risk prediction equation developed from the placebo groups of the included trials (<11%, 11–15%, 15–21%, >21%).

Findings 11 trials and 26 randomised groups met the inclusion criteria, and included 67 475 individuals, of whom 51 917 had available data for the calculation of the risk equations. 4167 (8%) had a cardiovascular event during a median of 4·0 years (IQR 3·4–4·4) of follow-up. The mean estimated baseline levels of 5-year cardiovascular risk for each of the four risk groups were 6·0% (SD 2·0), 12·1% (1·5), 17·7% (1·7), and 26·8% (5·4). In each consecutive higher risk group, blood pressure-lowering treatment reduced the risk of cardiovascular events relatively by 18% (95% CI 7–27), 15% (4–25), 13% (2–22), and 15% (5–24), respectively (p=0·30 for trend). However, in absolute terms, treating 1000 patients in each group with blood pressure-lowering treatment for 5 years would prevent 14 (95% CI 8–21), 20 (8–31), 24 (8–40), and 38 (16–61) cardiovascular events, respectively (p=0·04 for trend).

Interpretation Lowering blood pressure provides similar relative protection at all levels of baseline cardiovascular risk, but progressively greater absolute risk reductions as baseline risk increases. These results support the use of predicted baseline cardiovascular disease risk equations to inform blood pressure-lowering treatment decisions.

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Introduction

The merits of using an individual's predicted absolute risk of cardiovascular disease to inform treatment decisions for the prevention of cardiovascular disease, rather than using only the level of one cardiovascular disease risk factor, have been recognised for decades.[1–3] Most countries and cardiovascular societies now regard this evidence as sufficient to recommend that lipid-lowering treatment should be based on patients' predicted cardiovascular disease risk rather than LDL cholesterol concentrations.[3–6] Blood pressure-lowering treatment recommendations, however, are still based mainly on blood pressure levels.[7–9] The American Heart Association and the American College of Cardiology are the most recent organisations to switch to cardiovascular disease risk-based cholesterol treatment guidelines, and a Cholesterol Treatment Trialists' (CTT) Collaboration meta-analysis using individual participant data from statin trials[10] was influential in their decision to move away from treatment thresholds based mainly on LDL cholesterol concentrations. That meta-analysis involved retrospectively calculating a baseline 5-year vascular risk for all participants, which enabled the investigators to estimate the relative and absolute benefits of lipid lowering in different baseline risk categories. The findings clearly show that baseline vascular risk is a major determinant of the absolute benefits of statin treatment (figure 1).

The Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) has investigated the effects of blood pressure lowering on cardiovascular events in major patient subgroups, defined using individual patient data. The available data now provide a unique opportunity to compare the effects of blood pressure-lowering drugs in subgroups of patients at different levels of baseline absolute risk of cardiovascular events, in much the same way as has been done for lipid-lowering therapy in the CTT meta-analysis.[10]

We postulated that the relative cardiovascular disease risk reductions achieved with blood pressure-lowering therapy would be similar across population groups with different levels of baseline cardiovascular disease risk, and therefore that the absolute risk reductions would be greater for subgroups with higher levels of baseline cardiovascular disease risk. We aimed to test this hypothesis by doing a meta-analysis of individual patient data.

Methods

Study eligibility

The methods used have been reported previously,[11] and only the main components are summarised here. In

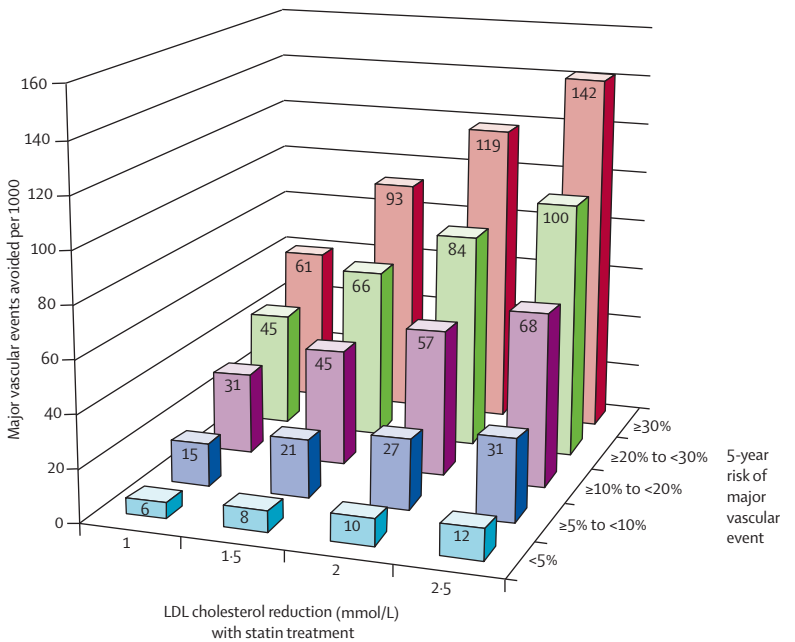

Figure 1: **Predicted 5-year benefits of LDL cholesterol reductions with statin treatment at different levels of risk**
Reprinted from the Cholesterol Treatment Trialists' (CTT) Collaborators' meta-analysis,[10] by permission of Elsevier.

brief, trials were eligible if they met the original inclusion criteria specified in the protocol,[11] and were part of the subset of studies that randomly allocated patients to either a blood pressure-lowering drug or placebo, or to a more intensive or less intensive blood pressure regimen. Trials had to have a minimum of 1000 patient-years of planned follow-up in each randomised group, and should not have presented their main results before the protocol was finalised in July, 1995.

Outcomes

The primary outcome was a composite of total major cardiovascular events,[11] consisting of stroke (non-fatal stroke or death from cerebrovascular disease), coronary heart disease (non-fatal myocardial infarction or death from coronary heart disease including sudden death), heart failure (resulting in death or admission to hospital), or cardiovascular morbidity. Secondary outcomes were stroke, coronary heart disease, heart failure, cardiovascular mortality, and total mortality. Only the first event for an individual was used for the analysis of each outcome, but an individual who had more than one outcome type could contribute to analyses of more than one individual outcome.

Risk stratification

Participants were stratified to different levels of predicted absolute risk based on covariates and events recorded in the BPLTTC dataset. The risk equations were determined by fitting Weibull models with shared frailty for each trial simultaneously to the placebo groups of all available trials that had time-to-event data. The variables included age, sex, body-mass index, systolic and diastolic blood pressures, other antihypertensive treatment, current smoking, diabetes, and history of cardiovascular disease. Interaction terms for age and sex, age and smoking, age and diabetes, age and history of cardiovascular disease, and age and other antihypertensive treatment were also included. These models were developed to balance the desire for a good model fit with the availability of risk factor data. Blood lipids were not included because these data were absent for most of the trials. Separate equations were developed for each of the six prespecified outcomes. We used data from ten trials that included 14 633 individuals (in placebo groups) for whom the following events were recorded: 1526 total cardiovascular events, 744 strokes, 367 heart failure events, and 611 coronary heart disease events. Data for cardiovascular deaths (n=691) and deaths from any cause (n=991) were available for 14 224 people in nine trials. 5-year risks, rather than 10-year risks, were calculated because 5 years was closer to the median follow-up of participants.

For each equation we divided the sample into four risk groups using three cutoff points that separated the number of cardiovascular disease events into equal quarters. This step was done to maximise the precision of the estimated treatment effects for each risk group.

Intervention versus control

Data from four sets of comparisons were included in these analyses: angiotensin-converting enzyme (ACE)-inhibitor-based treatment versus placebo; calcium channel blocker-based treatment versus placebo; diuretic-based treatment versus placebo; and more intensive versus less intensive blood pressure-lowering regimens. To maximise power we combined these four sets of comparisons for our main analyses. Results of previous analyses have shown that most of the treatment effect reported for these comparisons is determined by the blood pressure reduction achieved with rather little attributable to drug-specific effects.[12,13] We did not include studies that compared drug classes because the differences in blood pressure levels between randomised groups in those studies were generally small and differences in protection were more likely to be due to drug-specific effects.[12,13]

The average achieved blood pressure differences between randomised groups varied for each risk subgroup. To control for these differences and to enable direct comparisons between the effects of blood pressure lowering in each risk group we did subsidiary analyses in which we standardised relative risk reductions in each risk subgroup to a 5 mm Hg systolic blood pressure reduction. To control for baseline blood pressures, in a second set of analyses we standardised the risk reductions to a 5% systolic blood pressure reduction. Hence, these models estimated the effect of lowering blood pressure by 5 mm Hg or 5% in each of the four risk groups.

	Patient groups defined by 5-year risk of CVD*				Total sample (n=51 917)
	<11% risk (n=25 480)	11–15% risk (n=12 544)	15–21% risk (n=8287)	>21% risk (n=5606)	
Baseline characteristics					
Female participants	55·4%	40·5%	32·3%	21·9%	44·5%
Age, years	59·4 (6·7)	67·8 (7·4)	72·0 (8·1)	75·1 (7·6)	65·1 (9·4)
Smoking	10·4%	18·1%	18·8%	24·5%	15·1%
Previous CVD	11·3%	23·2%	40·7%	70·2%	25·4%
Previous BP drug treatment	45·4%	59·0%	68·5%	77·6%	55·9%
Diabetes	29·5%	44·7%	46·9%	59·1%	39·1%
BMI, kg/m²	28·3 (4·9)	27·6 (4·7)	27·0 (4·5)	26·8 (4·2)	27·8 (4·8)
Total cholesterol, mM	5·7 (1·5)	5·5 (1·4)	5·4 (1·3)	5·2 (1·3)	5·6 (1·5)
HDL cholesterol, mM	1·45 (0·74)	1·35 (0·57)	1·33 (0·53)	1·27 (0·43)	1·37 (0·62)
SBP, mm Hg	155 (21)	159 (21)	162 (21)	165 (21)	158 (21)
DBP, mm Hg	94 (14)	90 (13)	89 (12)	88 (12)	92 (13)
Estimated 5-year CVD risk	6·0% (2·0)	12·1% (1·5)	17·7% (1·7)	26·8% (5·4)	11·7% (7·5)
CVD events during follow-up	1042 (4·1%)	1042 (8·3%)	1042 (12·6%)	1041 (18·6%)	4167 (8·0%)
Stroke	1·8%	3·9%	5·6%	7·6%	3·6%
Coronary heart disease	1·8%	3·4%	4·8%	6·8%	3·2%
Heart failure	0·6%	1·5%	3·1%	5·1%	1·7%
Cardiovascular death	1·2%	3·3%	5·9%	10·1%	3·4%
Death	2·6%	6·2%	9·0%	15·8%	5·9%
Observed 5-year CVD risk in placebo groups	6·5%	13·2%	20·6%	24·8%	11·5%

Data are % or mean (SD). CVD=cardiovascular disease. BP=blood pressure. BMI=body-mass index. SBP=systolic blood pressure. DBP=diastolic blood pressure. *Baseline levels of CVD risk were estimated using a risk equation derived from the Blood Pressure Lowering Treatment Trialists' Collaboration dataset.

***Table*: Characteristics of patient groups defined by different baseline levels of cardiovascular risk**

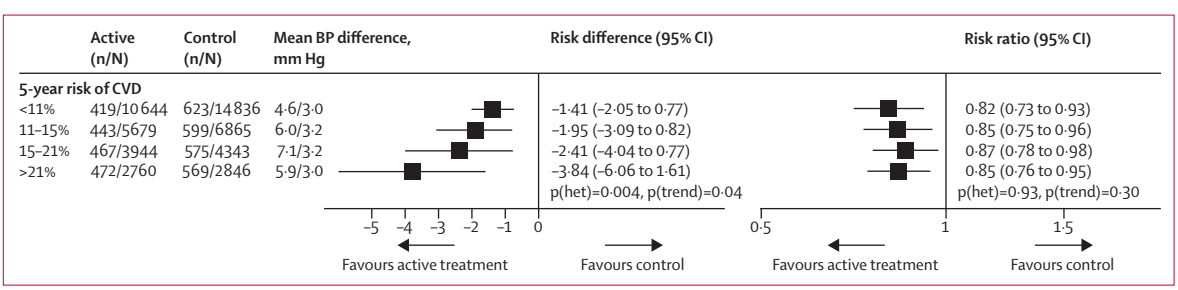

***Figure 2*: Effects of blood pressure reduction on absolute and proportional risks of cardiovascular disease for patient groups defined by different baseline levels of cardiovascular risk**

Total sample, n=51 917. n/N is the number of cases/number at risk. BP difference is the difference between active and control groups in treatment-induced reduction in systolic/diastolic blood pressures. BP=blood pressure. CVD=cardiovascular disease. het=heterogeneity.

Statistical analyses

We investigated calibration for all equations by plotting observed 5-year risks against expected 5-year risks for all equations. For each risk group in each trial, the achieved blood pressure lowering was calculated as the difference in mean blood pressure change from baseline to 12 months between the randomised treatment groups. Overall blood pressure reduction within risk groups was then obtained by combining these data across trials using inverse variance weighted fixed-effects meta-analysis.

Standard inverse variance-weighted meta-analysis was used to estimate crude summary risk ratios for each risk group across the included studies. We also estimated risk differences and numbers needed to treat using the recommended[14] approach of applying the pooled risk ratios to the mean absolute 5-year risk levels in each patient group, with symmetrical 95% CIs for the risk differences calculated as $(p1-p2) \pm 1{\cdot}96 \times \sqrt{((p1 \times (1-p1)/n1) + (p2 \times (1-p2)/n2))}$, with p1 being treated 5-year risks and p2 control 5-year risks with n1 the number of treated patients and n2 the number of controls. Summary estimates standardised to a 5 mm Hg or 5% reduction in systolic blood pressure were derived from risk ratios, achieved systolic blood pressure lowering, and baseline systolic blood pressures using established methods.[10,15] We also estimated

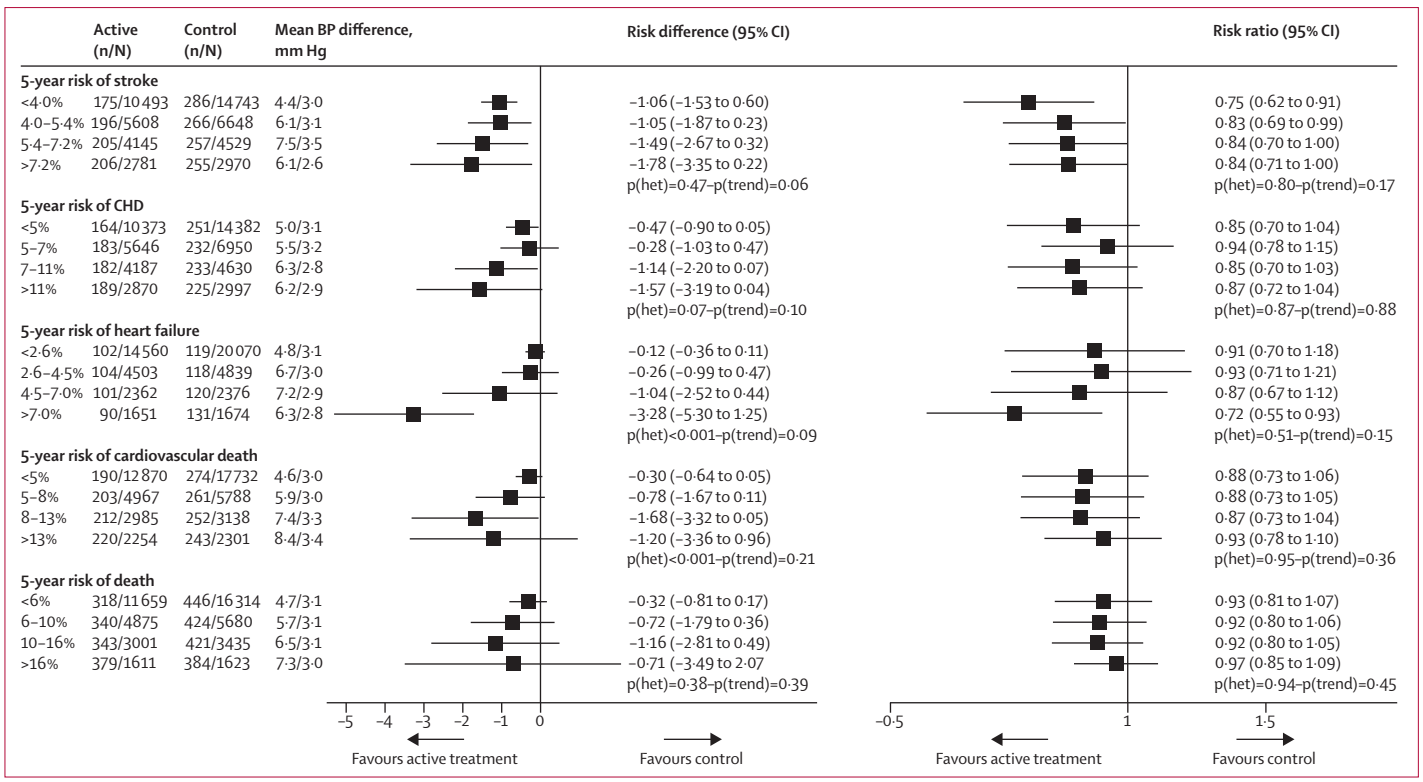

***Figure 3*: Effects of blood pressure reduction on absolute and proportional risks of coronary heart disease, stroke, heart failure, cardiovascular mortality, and all-cause mortality for patient groups defined by different baseline levels of risk of those outcomes**

Sample for coronary heart disease, heart failure, and cardiovascular death analyses, n=52 035; for stroke, n=51 917; and for death, n=48 198. n/N is the number of cases/number at risk. BP difference is the difference between active and control groups in treatment-induced reduction in systolic/diastolic blood pressures. CHD=coronary heart disease. CVD=cardiovascular disease. het=heterogeneity.

See Online for appendix

number of avoidable cardiovascular events by treating 1000 patients for 5 years in each of the four risk groups by four levels of systolic and diastolic blood pressure reduction, by combining meta-regression-obtained relative risk reductions per mm Hg blood pressure lowering with observed 5-year risks in placebo groups.

We used fixed-effects models as our primary means of analysis, such that very small subgroups of trials were not given undue weight, and we fitted random effects models as sensitivity analyses. In secondary analyses, we also investigated active drug versus placebo studies separately from more versus less blood pressure reduction studies, and a subsample of people with baseline systolic blood pressure of at least 140 mm Hg or diastolic blood pressure of at least 90 mm Hg. We used Stata version 13 for all analyses.

Role of the funding source

This study received no funding. All authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

11 trials and 26 randomised groups met the inclusion criteria (some trials were factorial or included more than two groups), and included 67 475 individuals (appendix).[16–30] Data for the calculation of the risk equations were available for 51 917 patients. The mean estimated baseline absolute 5-year risk of cardiovascular disease events in this sample was 11·7% (7·5), with the four risk groups defined as having estimated 5-year cardiovascular disease risks of less than 11%, 11–15%, 15–21%, and >21%. Characteristics of patients in each of these risk strata are shown in the table. The mean blood pressure difference between active and control groups was 5·4 (95% CI 5·2–5·7)/3·1 (3·0–3·2) mm Hg. During a median follow-up of 4·0 years (IQR 3·4–4·4), 4167 (8·0%) participants developed cardiovascular disease (table). Assessment of the performance of the risk equations is shown in the appendix.

Pharmacological blood pressure reduction produced significant relative risk reductions of cardiovascular disease that were similar across all four risk groups (figure 2; p=0·30 for trend). The magnitude of the absolute risk reduction, as a result, increased in a linear fashion from the lowest risk group to the highest risk group (figure 2; p=0·04 for trend). Giving 1000 patients in each group blood pressure-lowering treatment for 5 years would prevent 14 (95% CI 8–21), 20 (8–31), 24 (8–40), and 38 (16–61) cardiovascular events, respectively. Put another way, the number needed to treat for 5 years to avoid one cardiovascular event decreased with

increasing baseline risk, from 71 (95% CI 49–130) in the lowest risk group, to 51 (32–122) and 41 (25–130) in the second and third risk groups, and down to 26 (17–62) in the highest risk group.

Effect estimates were much less precise for cause-specific vascular outcomes and mortality, but a broadly similar pattern was noted for stroke, coronary heart disease, heart failure, and cardiovascular death (figure 3). For all-cause mortality, absolute risk reductions did not clearly increase with higher baseline risk (figure 3).

Baseline systolic blood pressure was higher, and diastolic blood pressure was lower, in patient groups with a higher baseline level of risk, as expected in view of the increasing mean age with increasing baseline risk (table). The achieved reductions in blood pressure tended to be greater in those with higher baseline systolic blood pressure, although we noted no clear pattern for diastolic blood pressure (figures 2, 3). The pattern of similar relative risk reductions across risk groups but increasing absolute risk reductions with increasing levels of baseline risk, except for mortality, remained in the analyses when standardised to either a 5 mm Hg systolic blood pressure reduction or a 5% systolic blood pressure reduction (appendix). The estimated number of avoidable events increased with increasing blood pressure reduction and higher baseline risk (figure 4).

We noted similar findings in random effects models, and the subsample with baseline systolic blood pressure of at least 140 mm Hg or diastolic blood pressure of at least 90 mm Hg (data not shown). Results of analyses restricted to the trials comparing an active drug to placebo were similar, although analyses based only on the trials that compared more versus less intensive blood pressure-lowering regimens were uninformative because of the small numbers of outcomes recorded (data not shown).

Discussion

In this meta-analysis of more than 50 000 patients, pharmacological blood pressure lowering produced relative reductions in cardiovascular risk that were similar across patient groups with markedly varying levels of baseline estimated cardiovascular risk, while delivering progressively greater absolute risk reductions at higher levels of baseline risk. This same pattern was apparent in a range of subsidiary analyses done on the primary composite cardiovascular outcome after adjusting for differences in baseline and achieved blood pressure levels between the risk groups studied. These findings for blood pressure-lowering treatment are consistent with a similar study of lipid-lowering treatment[10] that has already influenced national lipid-lowering treatment guidelines in the USA and the UK.[3,4]

This analysis objectively shows the effects of blood pressure lowering on proportional and absolute cardiovascular risks in a large dataset stratified by baseline cardiovascular risk.[31,32] Three aspects of the epidemiology of blood pressure and blood pressure lowering presage our findings. First, a continuous positive log-linear association exists between blood pressure and vascular risk as shown in several large observational studies.[33] Second, benefits of drugs that

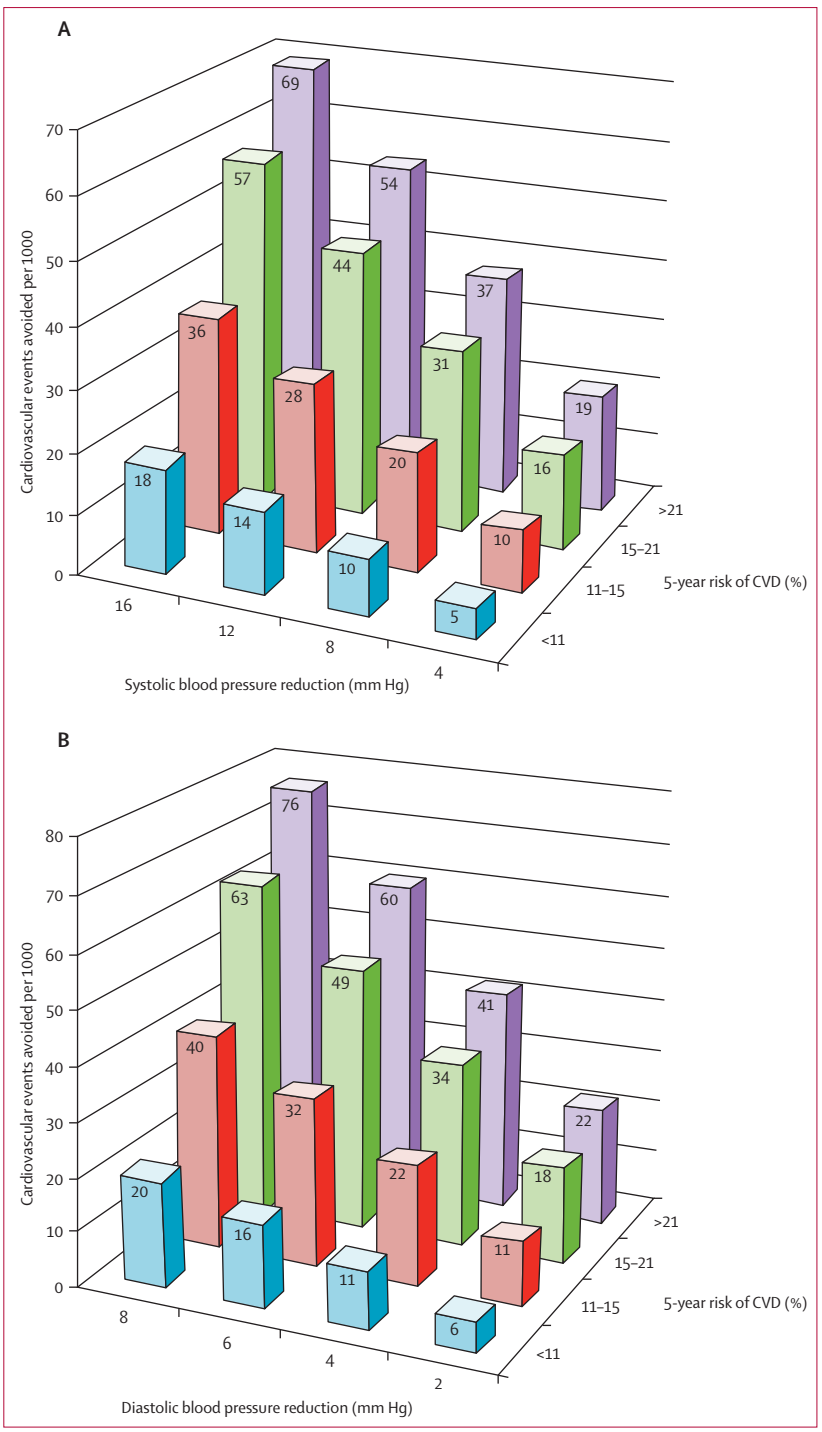

Figure 4: **Avoidable events by baseline risk and extent of blood pressure lowering**
(A) Systolic blood pressure reduction. (B) Diastolic blood pressure reduction. CVD=cardiovascular disease.

lower blood pressure in both hypertensive and non-hypertensive patient groups have been reported in a series of large-scale randomised trials.[15] And third, the absolute benefits of blood pressure lowering have been shown to be greatest in the presence of other vascular risks such as dyslipidaemia, increasing age, diabetes, and male sex.[34]

Risk-based treatment has been a cornerstone of lipid management for a decade[3,5,35,36] and is recommended in several other clinical settings.[37–39] A previous movement towards blood pressure-lowering treatment on the basis of absolute risk in some prevention guidelines[35,40,41] has come to a halt,[5,7,8] and risk-based approaches to blood pressure management do not seem to be widely used. In part at least, this reluctance to use absolute risk as a basis for decision making might be a result of the absence of direct evidence of effectiveness, which this study should go some way towards addressing. Risk-based blood pressure treatment decisions also have much to recommend them in terms of cost-effectiveness.[42–45]

Strengths of this analysis are the inclusion of a large group of patients with individual-level risk data, and more than 4000 major cardiovascular events, which provided reasonably precise estimates of the effects on the primary outcome for each risk group. The use of data from many studies with different inclusion criteria should make the findings more generalisable[46] and the robustness of the main conclusions to subsidiary methods of analysis further supports the conclusions drawn. The study is, however, limited by the fact that most included patients were hypertensive at baseline, although other trials[22,47] and overviews[15] have provided direct evidence about the benefits of treating high-risk non-hypertensive patients in some settings. Although the numbers of vascular events recorded was reasonably large, the estimates of effect are nonetheless imprecise for most cause-specific outcomes. The study also focuses only on the major benefits and major harms of treatment that might affect measures of cardiovascular events and mortality. Clearly, other less substantive but nonetheless important treatment benefits and risks will also affect treatment decisions. The study is also limited by the relatively short duration of the included studies and we used 5-year absolute risk as the basis of the primary estimates. Most risk prediction equations in clinical use tend to focus on 10-year risks despite the shortage of of any trial data with this length of follow-up. We did not have access to all baseline variables required for common risk equations, and because data were generally missing for a whole study at a time we chose not to make imputations. Instead, to accommodate the absence of this information and to maximise the usefulness of the available dataset we developed our own risk equation using variables available for most studies. Finally, the primary analyses were based on a composite outcome, which could have produced biased results if the proportion of event types varied between risk groups. Reassuringly, the ratios of event types were broadly similar across the risk groups.

In conclusion, this meta-analysis showed that treatment with blood pressure-lowering drugs resulted in similar relative risk reductions irrespective of the baseline level of absolute risk, hence greater absolute risk reduction with higher baseline absolute risk. This finding provides support for the notion that blood pressure-lowering treatment should target those at greatest cardiovascular risk, not just those with the highest blood pressure levels. A risk-based approach is likely to be more cost effective than a blood pressure-based approach, and could simultaneously reduce the numbers of patients needing treatment, and control drug costs, while increasing the numbers of averted strokes and heart attacks.[42–45]

Contributors

JS, RJ, BN, and MW were responsible for the study design. JS did the statistical analysis and created the figures. JS, HA, CB, JE, RJ, KK, DL-J, SM, BN, AP, VP, KR, FT, and MW interpreted the data. JS, RJ, and BN wrote the report. MW gave statistical advice. HA was responsible for data management. HA, CB, JE, KK, DL-J, SM, AP, VP, KR, FT, and MW were responsible for the critical revision of the manuscript for important intellectual content. KR and FT were responsible for project management. JS is the guarantor of the manuscript, and affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Declaration of interests
JS is an advisory board member for Itrim. MW is on a trial advisory committee for Novartis. AP has received drugs for clinical trials and grant funding from Dr Reddy's Laboratories. VP has received honoraria for meeting presentations and/or advisory board participation AbbVie, AstraZeneca, Baxter, Boehringer Ingelheim, Servier, and Vitae, and his employer has received trial funding from Abbvie, Baxter, Janssen, Novartis, Roche, and Servier. BN is on trial steering committees for Janssen, Dr Reddy's Laboratories, and Servier; his institution has received grant funding from Abbvie, Janssen, Novartis, Dr Reddy's Laboratories, Roche, and Servier; and he has received honoraria for meeting presentations from Abbott, AstraZeneca, Novartis, Pfizer, Roche, and Servier. All other authors declare no competing interests.

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