should not preclude the use of statins in the prevention of cardiovascular disease. The evidence is clear: statins substantially reduce IHD events (by 61%), and prevent stroke by 17% overall, through the prevention of non-fatal strokes with little effect on the risk of fatal stroke. Any possible excess of haemorrhagic stroke is greatly outweighed by the protective effect against IHD events and thromboembolic stroke.

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Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials

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ELPS

This is an abridged version; the full version is on bmj.com

Abstract

Objective To determine the average reduction in blood pressure, prevalence of adverse effects, and reduction in risk of stroke and ischaemic heart disease events produced by the five main categories of blood pressure lowering drugs according to dose, singly and in combination.

Design Meta-analysis of 354 randomised double blind placebo controlled trials of thiazides, β blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, and calcium channel blockers in fixed dose.

Subjects 40 000 treated patients and 16 000 patients given placebo.

Main outcome measures Placebo adjusted reductions in systolic and diastolic blood pressure and prevalence of adverse effects, according to dose expressed as a multiple of the standard (recommended) doses of the drugs.

Results All five categories of drug produced similar reductions in blood pressure. The average reduction was 9.1 mm Hg systolic and 5.5 mm Hg diastolic at standard dose and 7.1 mm Hg systolic and 4.4 mm Hg diastolic (20% lower) at half standard dose. The drugs reduced blood pressure from all pretreatment levels, more so from higher levels; for a 10 mm Hg higher blood pressure the reduction was 1.0 mm Hg systolic and 1.1 mm Hg diastolic greater. The blood pressure lowering effects of different categories of drugs were additive. Symptoms attributable to thiazides, β blockers, and calcium channel blockers were strongly dose related; symptoms caused by ACE inhibitors (mainly cough) were not dose related. Angiotensin II receptor antagonists caused no excess of symptoms. The prevalence of symptoms with two drugs in combination was less than additive. Adverse metabolic effects (such as changes in cholesterol or potassium) were negligible at half standard dose.

Conclusions Combination low dose drug treatment increases efficacy and reduces adverse effects. From the average blood pressure in people who have strokes (150/90 mm Hg) three drugs at half standard dose are estimated to lower blood pressure by 20 mm Hg systolic and 11 mm Hg diastolic and thereby reduce the risk of stroke by 63% and ischaemic heart disease events by 46% at age 60-69.

Introduction

Lowering systolic blood pressure by 10 mm Hg or diastolic blood pressure by 5 mm Hg reduces the risk of stroke by about 35% and that of ischaemic heart disease (IHD) events by about 25% at age 65.[1–3] This applies across all levels of blood pressure in Western populations, not only in "hypertension."[1–7] Blood pressure lowering drugs should be more widely used,[6 7] but which drugs are most appropriate, whether combina-

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Table 1 Efficacy: average reductions* in blood pressure over 24 hours (treated minus placebo) according to category of drug and dose

Category of drug†	Fall in blood pressure (mm Hg) (95% CI)			Half standard *v* standard: proportional difference (%)
	Half standard dose	Standard dose	Twice standard dose	
Systolic blood pressure				
Thiazides	7.4 (6.6 to 8.2)	8.8 (8.3 to 9.4)	10.3 (9.4 to 11.2)	16
β blockers	7.4 (6.6 to 8.3)	9.2 (8.6 to 9.9)	11.1 (10.2 to 12.0)	20
ACE inhibitors	6.9 (6.1 to 7.8)	8.5 (7.9 to 9.0)	10.0 (9.5 to 10.4)	19
Angiotensin II receptor antagonists	7.8 (7.1 to 8.6)	10.3 (9.9 to 10.8)	12.3 (11.7 to 12.8)	24
Calcium channel blockers	5.9 (5.2 to 6.6)	8.8 (8.3 to 9.2)	11.7 (11.0 to 12.3)	33
All categories: average	7.1 (6.8 to 7.5)	9.1 (8.8 to 9.3)	10.9 (10.7 to 11.2)	22
Diastolic blood pressure				
Thiazides	3.7 (3.2 to 4.2)	4.4 (4.0 to 4.8)	5.0 (4.4 to 5.7)	16
β blockers	5.6 (5.0 to 6.2)	6.7 (6.2 to 7.1)	7.8 (7.1 to 8.4)	16
ACE inhibitors	3.7 (3.2 to 4.2)	4.7 (4.4 to 5.0)	5.7 (5.4 to 6.0)	21
Angiotensin II receptor antagonists	4.5 (4.2 to 4.8)	5.7 (5.4 to 6.0)	6.5 (6.2 to 6.8)	21
Calcium channel blockers	3.9 (3.5 to 4.4)	5.9 (5.6 to 6.2)	7.9 (7.5 to 8.3)	34
All categories: average	4.4 (4.2 to 4.6)	5.5 (5.4 to 5.7)	6.5 (6.3 to 6.7)	20

ACE=angiotensin converting enzyme.
*Estimates are average over 24 hours from combining separate peak and trough estimates.
†Examples of standard daily dose of one drug in each category: bendroflumethazide 2.5 mg, atenolol 50 mg, lisinopril 10 mg, valsartan 80 mg, amlodipine 5 mg. See www.smd.qmul.ac.uk/wolfson/bpchol for standard doses of all drugs.

tions of drugs should be used routinely, and whether lower doses than those currently used are preferable is not known. We report a systematic review of randomised placebo controlled trials of the five main categories of blood pressure lowering drugs to answer these questions.

Methods

We sought randomised placebo controlled trials that recorded the change in blood pressure in relation to a specified fixed dose of any thiazide, β blocker, angiotensin converting enzyme (ACE) inhibitor, angiotensin II receptor antagonist, or calcium channel blocker. We searched the Medline, Cochrane Collaboration, and Web of Science databases. Details of the search procedure are on www.smd.qmul.ac.uk/wolfson/bpchol. We used the same set of 354 trials identified and reported in our monograph on the quantification of standard dose blood pressure treatment.[7] In this paper we examine the effect of dose and combination treatment on efficacy and adverse effects. With the exceptions below we included all double blind trials, irrespective of the age or diseases of the participants. Most participants had high blood pressure (typically 90-110 mm Hg diastolic), but trials of people with non-vascular conditions (such as thiazides for renal stones) provided evidence of efficacy at lower blood pressures.

We excluded trials with no placebo group, less than two weeks' duration, titrating dose so that different patients received different doses, treating some control patients, testing drugs only in combination with other drugs, with non-randomised order of treatment and placebo periods in crossover trials, with most participants black (because of their different responses to some blood pressure lowering drugs[8]), or recruiting patients with heart failure, acute myocardial infarction, or other cardiovascular disorders. We included 354 trials.[w1-w343]

We defined the efficacy of a drug as the reduction in systolic and diastolic blood pressure for a specified dose, expressed as the change in the treated group minus that in the placebo group. We categorised reductions in blood pressure as "peak" (2-6 hours after the last dose) or "trough" (22-26 hours). In combining trial data we specified equivalent daily doses of different drugs as the "usual maintenance dose" in reference pharmacopoeias.[9–11] We call this the standard dose. We fitted random effects regression models (separately for systolic and diastolic blood pressure) relating change in blood pressure in each treatment arm to category of drug, dose (expressed as a proportion of the standard dose), usual pretreatment blood pressure, whether blood pressure measurements were peak or trough, and average age.

We estimated adverse effects attributable to the drugs as the difference in prevalence between treated and placebo groups in respect of the numbers of participants reporting one or more symptoms in trials recording all symptoms that might be drug related (313 of the 354 trials, 88% of all participants in the 354 trials) and the numbers of participants who stopped taking the tablets because of symptoms (305 trials, 84% of all participants). We excluded headache because published evidence, and our own analysis, shows that fewer treated patients than patients on placebo report it. Adverse metabolic effects recorded were changes in serum cholesterol and its subfractions, potassium, glucose, and uric acid.

We analysed data on whether the combined effect of two drugs of different categories was additive with respect to blood pressure reduction and adverse effects. Within the 354 trials 50 trials (119 comparisons) tested the effect of drugs of two different categories separately and in combination.

Results

The 354 trials included 791 treatment groups, testing different drugs or different doses of the same drug, with about 40 000 participants receiving treatment and 16 000 receiving placebo. See www.smd.qmul.ac.uk/wolfson/bpchol and www.bmj.com for tables giving further information on the 354 individual trials and the standard doses and costs of the drugs.

Efficacy

Single drugs

See bmj.com for dose-response relations for the five categories of blood pressure lowering drug for systolic pressure (the plots for diastolic pressure were similar). The straight lines fit the data well. Table 1 shows the average reductions in blood pressure over 24 hours produced by half standard, standard, and twice standard doses of the five categories of drug. Within each dose category the reductions were remarkably similar for different categories of drugs; few statistically significant differences existed, and no category of drug was materially more effective than another. Reductions with half standard dose were about 20% less than those with standard dose.

The individual drugs within each of the five categories produced similar reductions in blood pressure. Some drugs may be more effective than others, but any differences are small, and in the absence of any prior hypothesis we could not identify them. The cheaper drugs within each category were as effective as the more expensive ones.

Figure 1 shows that the drugs significantly lowered blood pressure from all pretreatment levels, although the reduction was greater from a higher level. For each 10 mm Hg increase in pretreatment blood pressure, the reduction in blood pressure with one drug at standard dose increased on average by 1.0 (95% confidence interval 0.7 to 1.2) mm Hg systolic and 1.1 (0.8 to 1.4) mm Hg diastolic. The blood pressure reductions shown in table 1 apply to the average pretreatment blood pressure in all the trials of 154 mm Hg systolic and 97 mm Hg diastolic.

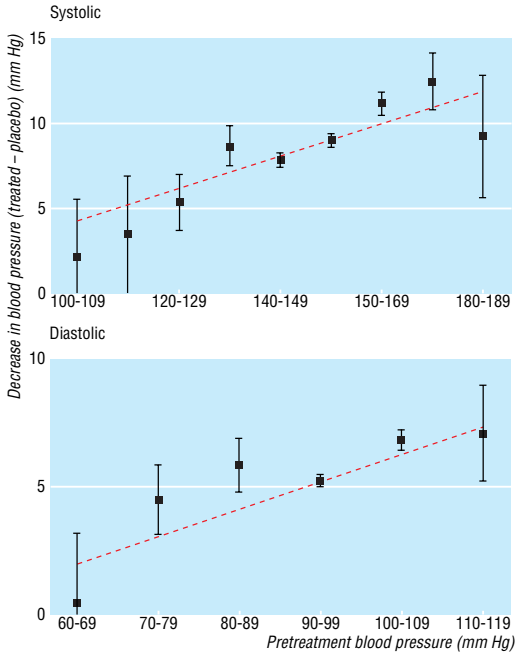

Fig 1 Average reduction in blood pressure (adjusted for the change in the placebo group; with 95% confidence intervals) according to the usual pretreatment blood pressure, from the results of 354 randomised trials, with the best fitting line

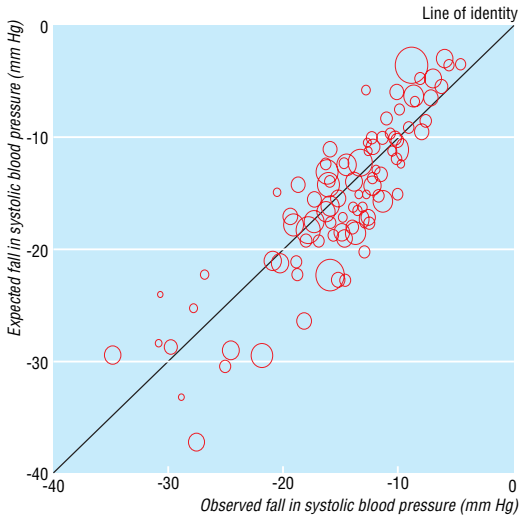

Fig 2 Trials testing two blood pressure lowering drugs separately and in combination: observed placebo adjusted reduction in systolic blood pressure (treated minus placebo) with two drugs used in combination plotted against the expected reduction in blood pressure from adding the reductions produced by each drug alone. The area of each symbol is inversely proportional to the variance in the trial it represents. Adapted from Law et al[7]

Combinations of drugs

Fifty trials (including 119 placebo controlled comparisons) compared drugs from two categories, separately and together. Figure 2 shows the observed reductions in blood pressure with two drugs taken together plotted against the expected reductions from adding the reductions produced by each drug alone. Overall the points lie close to the 45° line of identity between observed and expected. The sum of the average reductions in blood pressure is close to the observed effect of the two drugs used in combination, indicating an additive effect (see bmj.com). The 119 comparisons tested six of the 10 possible combinations of two drugs and showed an additive effect. Although no trial has studied the effect of three drugs in combination, the additive effect of many combinations of two drugs suggests that the effect of three drugs in combination would also be additive.

Table 2 shows the expected reduction in blood pressure with one, two, and three blood pressure lowering drugs used at half standard dose. The reductions are adjusted from those in table 1 to a usual pretreatment blood pressure of 150/90 mm Hg, which cohort studies show is about average in people who have a stroke or IHD event.[7] The reductions with two and three drugs are based on the additive effect but adjusted for the lower pretreatment blood pressure for each successive drug (fig 2). Three drugs together would be expected to lower blood pressure by about 20 mm Hg systolic and 11 mm Hg diastolic.

Adverse effects

Single drugs

See bmj.com for plots showing the difference in prevalence of participants who experienced symptoms between treated and placebo groups according to dose. The dose-response relation is clear for thiazides, β blockers, and calcium channel blockers. Table 3, based on the straight lines on the plots, shows

Table 2 Efficacy: blood pressure lowering effects of drugs when used at half standard dose separately and in combination

	Blood pressure reduction* (95% CI)		
	One drug	Two drugs	Three drugs
Systolic blood pressure (mm Hg)	6.7 (6.1 to 7.2)	13.3 (12.4 to 14.1)	19.9 (18.5 to 21.3)
Diastolic blood pressure (mm Hg)	3.7 (3.1 to 4.3)	7.3 (6.2 to 8.3)	10.7 (9.1 to 12.4)

*Reductions in blood pressure adjusted to a usual pretreatment blood pressure of 150/90 mm Hg, the average blood pressure in people aged 50-69 years who have a stroke or ischaemic heart disease event.[7]

that thiazides and calcium channel blockers caused symptoms infrequently (2.0% and 1.6%) at half standard dose but commonly (9.9% and 8.3%) at standard dose (P (for trend) <0.001). β blockers caused symptoms in 5.5% of patients at half standard dose and in 7.5% at standard dose (P=0.04). Cough (3.9%) was virtually the only symptom with ACE inhibitors and did not vary with dose, a finding consistent with earlier studies.[12 13] No excess of symptoms occurred at standard dose or half standard dose of angiotensin II receptor antagonists.[7] Thiazides were the only drugs to affect sexual function, a finding confirmed in a large long term trial.[14] The prevalence of symptoms sufficiently severe to stop treatment (treated minus placebo) was 0.8% (0.3% to 1.4%) for β blockers, 0.1% for thiazides and ACE inhibitors, and zero for angiotensin II receptor antagonists and (at half standard dose) calcium channel blockers.

The metabolic effects of thiazides were dose dependent (see bmj.com). The increase in serum cholesterol was 1% at half standard dose, 3% at standard dose, and 5% at twice standard dose. The increase was in the very low density lipoprotein subfraction, which is associated only weakly with atherogenesis. Thiazides at half standard dose also had a small effect in decreasing serum potassium (– 6%), increasing blood glucose (1%), and increasing serum uric acid (9%). Even at standard doses the loss of total body potassium is small (about 200 mmol/l) and does not increase the risk of cardiac arrhythmia.[7 15–19] The increase in blood glucose is reversible, with no excess risk of overt diabetes.[20 21] From the association between serum uric acid and gout reported in a cohort study of men, the 9% average increase in uric acid at half standard dose would be expected to increase the incidence of gout from a background incidence of about 1.5 per 1000 per year to 2.4 per 1000 per year (an absolute increase of under 1 per 1000 per year).[22 23] Gout is less common in women,[23] and the absolute increase would be about 1 per 10 000 per year.

Insufficient data were available to examine the effect by dose for the other four drug categories.[7] In six trials of β blockers total serum cholesterol decreased by 3%. β blockers produced a 2% (1% to 4%) increase in serum potassium on average (10 trials) and no significant change in blood glucose or uric acid.[7] ACE inhibitors and angiotensin II receptor antagonists increase serum potassium because of their effect on aldosterone: in 18 trials of either the average increase was 3% (2% to 5%). Calcium channel blockers did not increase blood glucose.

Combinations of drugs

Of the 50 placebo controlled trials testing drugs of two different categories separately and in combination, 33 reported adverse effects. In 66 trial arms single drugs caused symptoms in 5.2% (3.6% to 6.6%) of participants on average (prevalence in treated group minus placebo). In 33 trial arms two drugs together caused symptoms in 7.5% (5.8% to 9.3%), which is significantly lower than the value of 10.4% (twice 5.2%) expected with an additive effect (P=0.03). One drug does not therefore potentiate the adverse effects of another. The lower than expected prevalence with two drugs may suggest that some people are more likely than others to either experience or report symptoms.

Discussion

The five categories of drugs produced similar reductions in blood pressure and were effective from all pretreatment levels (fig 1), reinforcing the view that use of blood pressure lowering drugs should be determined by a person's overall level of risk rather than the blood pressure alone.[6] Reduction in blood pressure was only about 20% less at half standard dose than at standard dose, but adverse effects were much less common. Efficacy of drugs in combination was additive, but prevalence of adverse effects was less than additive. Combinations of two or three drugs at low dose are therefore preferable to one or two drugs at standard dose.

Combining the blood pressure reductions from table 2 and estimates of the association between blood pressure and disease events at age 60-69 from the Prospective Studies Collaboration, it follows that one, two, and three drugs used in combination at half standard dose would reduce the risk of stroke by 29%, 49%, and 63% and that of IHD events by 19%, 34%, and 46% respectively.[1–7] Use of one of the three drugs at standard dose (an ACE inhibitor or angiotensin II receptor antagonist because adverse effects were no higher at standard than half standard dose) would reduce the risk of stroke by 66% and that of IHD events by 49%.

All but two of our conclusions are based on direct evidence. No trial directly studied the combined effect

Table 3 Adverse effects of drugs: percentage of people with one or more symptoms attributable to treatment*, according to category of drug and dose, in randomised trials

		Percentage (95% CI) with symptoms (treated minus placebo)†		
Category of drug	No of trials	Half standard dose	Standard dose	Twice standard dose
Thiazides	59	2.0 (–2.2 to 6.3)	9.9 (6.6 to 13.2)	17.8 (11.5 to 24.2)
β blockers	62	5.5 (0.3 to 10.7)	7.5 (4.0 to 10.9)	9.4 (3.6 to 15.2)
ACE inhibitors	96	3.9 (–3.7 to 11.6)	3.9 (–0.5 to 8.3)	3.9 (–0.2 to 8.0)
Angiotensin II receptor antagonists	44	–1.8 (–10.2 to 6.5)	0 (–5.4 to 5.4)	1.9 (–5.6 to 9.3)
Calcium channel blockers	96	1.6 (–3.5 to 6.7)	8.3 (4.8 to 11.8)	14.9 (9.8 to 20.1)

ACE=angiotensin converting enzyme.

*Calculated as difference between treated and placebo groups in proportion of participants who developed one or more symptoms, excluding headaches, which were significantly less common in people receiving treatment.

†Commonest symptoms: thiazides—dizziness, impotence, nausea, muscle cramp; β blockers—cold extremities, fatigue, nausea; ACE inhibitors—cough; calcium channel blockers—flushing, ankle oedema, dizziness.[7]

What is already known on this topic

Blood pressure lowering drugs prevent stroke and heart disease, but whether they are best used in combination, and if so at what dose, is not known

What this study adds

The efficacies of five categories of drug are similar at standard doses and only 20% lower at half standard doses; adverse effects are much less common at half standard dose than at standard dose

The drugs are effective from all pretreatment levels of blood pressure

Reductions in blood pressure with drugs in combination are additive; adverse effects are less than additive

Using three blood pressure lowering drugs in low dose combination would reduce stroke by two thirds and heart disease by half

of three drugs on blood pressure, but an additive effect follows because an additive effect has been shown for many combinations of two drugs. Randomised trials have not tested the combined effect of two or three drugs on the incidence of stroke and IHD events, but the cohort studies show a continuous relation between blood pressure and the risk of these diseases,[1–3] confirmed by randomised trials of single drug treatment from a wide range of pretreatment levels.[4–7]

Three drugs in low dose combination have a large preventive effect, reducing the risk of stroke by two thirds and IHD events by half, with a low prevalence of adverse effects. Low dose combination treatment should be used as a first option in lowering blood pressure, and the indications for using blood pressure lowering drugs should be broadened.

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