ClinicalEvidence

Primary prevention of CVD: treating hypertension

Search date December 2007

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ABSTRACT

INTRODUCTION: Hypertension (persistent diastolic blood pressure of 90 mm Hg or greater and systolic blood pressure 140 mm Hg or greater) affects 20% of the world's adult population, and increases the risk of cardiovascular disease, end-stage renal disease, and retinopathy. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of different antihypertensive drugs for people with hypertension? What are the effects of dietary modification for people with hypertension? We searched: Medline, Embase, The Cochrane Library, and other important databases up to December 2007 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 21 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: a low-salt diet, antihypertensive drugs, calcium supplements, fish oil supplements, magnesium supplements, and potassium supplements.

QUESTIONS

INTERVENTIONS

Key points

- Hypertension (persistent diastolic blood pressure of 90 mm Hg or greater and systolic blood pressure 140 mm Hg or greater) affects 20% of the world's adult population, and increases the risk of cardiovascular disease, end-stage renal disease, and retinopathy.

  Risk factors for hypertension include age, sex, race/ethnicity, genetic predisposition, diet, physical inactivity, obesity, and psychological and social characteristics.

- No antihypertensive drug has been found to be more effective than the others at reducing all-cause mortality, cardiovascular mortality, or MI.

  Apparent differences in outcomes with different antihypertensive drugs may be due to different levels of blood pressure reduction.

  Diuretics may be more effective than ACE inhibitors, calcium channel blockers, and alpha-blockers at reducing heart failure.

  Beta-blockers may be as effective as diuretics at reducing stroke, but calcium channel blockers may be even more effective than beta-blockers or diuretics.

  ACE inhibitors may be more effective than calcium channel blockers for prevention of coronary heart disease.

  Choice of second-line antihypertensive agent should be based on other co-morbidities and likely adverse effects as we don't know which is the most likely to reduce cardiovascular events.

- We found no RCT evidence assessing whether dietary modification reduces morbidity or mortality from hypertension compared with a normal diet.

  Advice to reduce dietary intake of salt to below 50 mmoles daily and fish oil supplementation may reduce systolic blood pressure by approximately 1 to 5 mm Hg and reduce diastolic blood pressure by 1 to 3 mm Hg in people with hypertension.

  We do not know whether supplementation with potassium, magnesium, or calcium is effective in reducing blood pressure.

  Potassium supplementation should not be used in people with kidney failure, or in people taking drugs that can increase potassium levels.

Combinations of potassium plus calcium, potassium plus magnesium, and calcium plus magnesium may be no more effective than no supplementation in reducing blood pressure.

DEFINITION

Hypertension, a clinically important elevation in blood pressure, is usually defined in adults as a diastolic blood pressure of 90 mm Hg or greater, or a systolic blood pressure of 140 mm Hg or greater. [1] [2] The WHO defines grade 1 hypertension as surgery blood pressures ranging from 140 to 159 mm Hg systolic or 90 to 99 mm Hg diastolic, grade 2 hypertension as pressures of 160 to 179 mm Hg systolic or 100 to 109 mm Hg diastolic, and grade 3 hypertension as pressures 180 mm Hg or greater systolic and 110 mm Hg diastolic. [1] Systematic reviews have consistently shown that treating essential hypertension (namely the elevation of systolic and diastolic blood pressures, in isolation or combination, with no secondary underlying cause) with antihypertensive drugs, reduces fatal and non-fatal stroke, cardiac events, and total mortality compared with placebo in those with severe hypertension or high cardiovascular risk owing to age or other co-morbid risk factors. [3] [4] [5] This review therefore focuses on the effects of treating essential hypertension with different pharmacological agents and also examines the effect of treating hypertension with non-pharmacological agents compared with placebo. **Diagnosis:** It is usually recommended that clinicians diagnose hypertension only after obtaining at least two elevated blood pressure readings at each of at least two separate visits over a period of at least 1 week. [2] This recommendation follows the pattern of blood pressure measurement in the RCTs of antihypertensive treatment, and represents a compromise between reliable detection of elevated blood pressure and clinical practicality.

INCIDENCE/ PREVALENCE

Coronary heart disease is a major cause of morbidity and mortality throughout the world. [6] It is a leading cause of disability and rising healthcare costs, and it is responsible for 13% of deaths worldwide. Most of this burden of heart disease can be linked to several "traditional" risk factors, including age, sex, increasing blood pressure, increasing cholesterol, smoking, diabetes, and left ventricular hypertrophy. [7] Of these, hypertension is most common, affecting 20% of the world adult population. [8] The relative risk of adverse events associated with hypertension is continuous and graded. [9] The absolute risk of adverse outcomes from hypertension depends on the presence of other cardiovascular risk factors, including smoking, diabetes, and abnormal blood lipid levels, as well as the degree of blood pressure elevation. [10] Even modest elevations in blood pressure in young adulthood are associated with increased risk of cardiovascular events in middle age. [11]

AETIOLOGY/ RISK FACTORS

Identified risk factors for hypertension include age, sex, genetic predisposition, diet, physical inactivity, obesity, and psychological and social characteristics. [12] In addition, certain ethnic groups, such as non-Hispanic black people, are at higher risk of hypertension. [13]

PROGNOSIS

People with hypertension have a two to four times increased risk of stroke, MI, heart failure, and peripheral vascular disease than those without hypertension. [9] Additionally, they have an increased risk of end-stage renal disease, retinopathy, and aortic aneurysm. [14] [15] [16] The absolute risk of adverse outcomes from hypertension depends on other cardiovascular risk factors and on the degree of blood pressure elevation (see incidence/prevalence section). [10]

AIMS OF INTERVENTION

To reduce morbidity and mortality from hypertension, with minimum adverse effects.

OUTCOMES

Incidence of fatal and non-fatal cardiovascular events (including coronary, cerebrovascular, renal, and heart failure). Surrogate outcomes include changes in levels of individual risk factors, such as blood pressure, which we reported when morbidity and mortality-related outcomes were not available.

METHODS

Clinical Evidence search and appraisal December 2007. The following databases were used to identify studies for this systematic review: Medline 1966 to December 2007, Embase 1980 to December 2007, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2007, Issue 4. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and National Institute for Health and Clinical Excellence (NICE). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributors for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, at least single blinded, and containing more than 20 individuals of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. This review includes people with hypertension but with no diagnosis of coronary heart disease. RCTs consisting wholly

of people with diabetes were excluded (see our review of diabetes: treating hypertension). In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 20). The categorisation of the evidence (high, moderate, low, very low) reflects the quality of the evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. Further details of how we perform the GRADE evaluation and the scoring system we use can be found on our website (www.clinicalevidence.com).

QUESTION What are the effects of different antihypertensive drugs for people with hypertension?

OPTION ANTIHYPERTENSIVE DRUGS VERSUS EACH OTHER

Mortality

Antihypertensive drugs compared with each other We don't know whether different antihypertensive groups differ in their effectiveness in reducing mortality. Many systematic reviews compared combinations of drug classes versus each other rather than individual groups versus each other (low-quality evidence).

Cardiovascular events

Antihypertensive drugs compared with each other We don't know whether different antihypertensive groups differ in their effectiveness in reducing cardiovascular events. Many systematic reviews compared combinations of drug classes versus each other rather than individual groups versus each other (low-quality evidence).

End-stage renal disease

Antihypertensive drugs compared with each other Renin–angiotensin system inhibitors seem more effective at reducing end-stage renal disease in people with hypertension compared with other antihypertensive drugs (moderate-quality evidence).

For GRADE evaluation of interventions for primary prevention of CVD: treating hypertension, see table, p 20 .

Benefits:

We found three systematic reviews, which between them found 22 RCTs comparing different classes of antihypertensive drugs versus each other across a wide spectrum of cardiovascular outcomes. Identified RCTs predominantly assessed the effects of older antihypertensive drugs (diuretics and beta-blockers) versus newer antihypertensive single drugs (calcium channel blockers, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], or alpha-blockers). [17] [18] [19]

The first review (search date 2003, 15 RCTs, 120,574 people with hypertension) compared older antihypertensive drugs (diuretics and beta-blockers) versus newer drugs, including calcium channel blockers, ACE inhibitors, ARBs, and alpha-blockers, both as a group and as individual drug classes. [17] The review included RCTs that enrolled people with CVD. In most of the RCTs identified, more than 80% of the people enrolled did not have CVD.

The second review (search date 2002, 19 RCTs, 150,590 people) compared low-dose diuretics (starting with 12.5–25.0 mg/day of chlorthalidone or hydrochlorothiazidine or equivalent and titrating upwards) versus beta-blockers and single newer antihypertensive drugs (calcium channel blockers, ACE inhibitors, ARBs, and alpha-blockers) using network meta-analysis, a technique that includes both direct and indirect comparisons between studies while preserving the effects of trial randomisation. [18]

The third review (search date 2006, 13 RCTs, 91,561 people) compared beta-blockers versus placebo and other drug classes used in the treatment of hypertension (calcium channel blockers, diuretics, ACE inhibitors, and ARBs). [19]

We also found two further systematic reviews that looked specifically at stroke and coronary heart disease (CHD) [20] and renal outcomes. [21]

Antihypertensive drugs versus each other:
One review comparing older versus newer antihypertensive drugs found that older antihypertensive drugs were associated with a significantly lower incidence of heart failure compared with newer antihypertensive drugs (see table 1, p 16). [17] The review reported significant heterogeneity among studies in this analysis (P = 0.001 or less). An accompanying meta-regression suggested that the source of heterogeneity among studies may be a difference in blood pressure among treatment groups. The review found no significant difference between older and newer single-drug treatments in all-cause mortality, cardiovascular mortality, MI, or stroke (see table 1, p 16). The review reported significant heterogeneity among RCTs in analysis of all cardiovascular events and stroke (P = 0.001 or less for both outcomes).

Three reviews found no significant difference in cardiovascular mortality between older antihypertensive drugs (diuretics or beta-blockers; assessed either in combined analysis or as individual drug class) and calcium channel blockers. [17] [18] [19] One review found no significant difference in all-cause mortality and stroke between calcium channel blockers and older antihypertensive drugs (assessed as a group), [17] and a second review found no significant difference between calcium channel blockers and diuretics alone for the same outcomes. [18] The review comparing beta-blockers versus calcium channel blockers found that beta-blockers were associated with a significantly higher rate of all-cause mortality (see table 1, p 16). [19] One review (search date 2004, 14 RCTs, 114,143 people) focusing only on CHD and stroke outcomes in people receiving calcium channel blockers or ACE inhibitors (compared with diuretics, beta-blockers, or both) found different results for the outcome of stroke. [20] The review found that older antihypertensive drugs significantly increased stroke compared with calcium channel blockers (see table 1, p 16). The review included additional RCTs in its meta-analysis, but did not report absolute numbers. The review comparing beta-blockers versus calcium channel blockers found similar results. It found that beta-blockers were associated with a significantly higher rate of stroke (see table 1, p 16). [19]

One review found that older antihypertensive drugs significantly reduced congestive heart failure compared with calcium channel blockers (see table 1, p 16). [17] The review comparing diuretics alone versus calcium channel blockers found similar results, with diuretics associated with a significant reduction in cardiovascular events (all types) and congestive heart failure (see table 1, p 16). [18] However, the review comparing beta-blockers versus calcium channel blockers found that beta-blockers significantly increased CVD compared with calcium channel blockers. [19] Reviews found no significant difference between calcium channel blockers and either diuretics alone [18] or beta-blockers alone in CHD. [19] The review focusing on only CHD and stroke outcomes found no significant difference between calcium channel blockers and older antihypertensive drugs in CHD (see table 1, p 16). [20] One review found no significant difference in rates of MI between older antihypertensive drugs and calcium channel blockers. [17]

One review [19] included a key RCT [22] comparing the effects of a beta-blocker-based regimen (atenolol plus bendroflumethiazide [a diuretic]) versus a calcium channel blocker-based regimen (amlodipine plus perindopril [an ACE inhibitor]) in its meta-analysis. We therefore report the results from the RCT separately. The second drug (diuretic or ACE inhibitor) was added as required, to reach prespecified blood pressure targets. The RCT found that the calcium channel blocker-based regimen significantly reduced total mortality, CVD mortality, and stroke (see table 1, p 16). There was a trend towards improvement in both the primary outcome of combined non-fatal MI (including silent MI) and fatal CHD and the secondary outcome of congestive heart failure with the calcium channel blocker-based regimen. This trend did not reach significance, even though blood pressures were significantly lower with the calcium channel blocker-based regimen (mean difference over 5.5 years' follow-up: 2.7 mm Hg systolic blood pressure, 1.9 mm Hg diastolic blood pressure; P less than 0.0001 for both). Although 80% of people were on the primary assigned treatment, less than 55% of people were on combination treatment throughout the trial.

Two reviews found that, compared with ACE inhibitors, older antihypertensive drugs (assessed either as combined analysis or diuretics alone) significantly decreased stroke compared with ACE inhibitors (see table 1, p 16). [17] [18] However, the review focusing on only CHD and stroke outcomes found no significant difference in stroke between ACE inhibitors and older antihypertensive drugs (see table 1, p 16). [20] A third review found that diuretics significantly reduced congestive heart failure and cardiovascular events compared with ACE inhibitors. [18] However, another review found no significant difference between older antihypertensive drugs and ACE inhibitors in congestive heart failure. [17] None of the reviews found a significant difference between older antihypertensive drugs (assessed either as combined analysis or diuretics or beta-blockers alone) and ACE inhibitors in mortality, cardiovascular mortality, MI, CVD, or CHD. [17] [18] [20]

One review found that, compared with ARBs, older antihypertensive drugs significantly increased stroke (see table 1, p 16). [17] However, the review comparing diuretics versus ARBs found no significant difference in stroke between groups, although the rate of stroke was higher with diuretics.

[18] Both reviews found no significant difference between groups in various other outcomes (mortality, cardiovascular mortality, MI, heart failure, CVD events, and CHD). [17] [18]

The review assessing the effects of beta-blockers versus other antihypertensive drugs found that beta-blockers significantly increased the risk of stroke compared with renin–angiotensin system inhibitors. [19] The review identified only two RCTs (1635 people) comparing ACE inhibitors versus beta-blockers and one RCT (9193 people) comparing ARBs versus beta-blockers. Owing to the small number of RCTs identified, the review combined data for the drug classes targeting the renin–angiotensin system for comparison versus beta-blockers. [19] The review found no significant difference between beta-blockers alone and renin–angiotensin system inhibitors in mortality, cardiovascular mortality, CVD, or CHD. [19]

One review (search date 2005, 13 RCTs, 37,089 people) examining only renal outcomes found a significant reduction in end-stage renal disease (ESRD) with renin–angiotensin system inhibitors (ACE inhibitors or ARBs combined in analysis) compared with other antihypertensive (no further information given on drug classes included) medications collectively (304/11,065 [3%] with renin–angiotensin system inhibitor *v* 525/26,024 [2%] with other antihypertensive drugs; RR 0.87, 95% CI 0.75 to 0.99). [21] The effect on ESRD was found to be directly related to the reduction in blood pressure, with greater reduction in blood pressure associated with greater reduction in ESRD.

Two reviews found that, compared with alpha-blockers, older antihypertensive drugs (assessed either as combined analysis or diuretics alone) were associated with lower rates of congestive heart failure and stroke (see table 1, p 16), [17] [18] although the result for stroke did not reach significance in one review [18] and significance was not assessed in the other. [17] One review found that diuretics were associated with a significantly lower rate of cardiovascular events compared with alpha-blockers. [18] Rates of mortality, cardiovascular mortality, MI, and CHD were similar for older antihypertensive drugs and alpha-blockers (see table 1, p 16). [17] [18] One review found that diuretics significantly reduced cardiovascular events compared with beta-blockers (see table 1, p 16). [18]

Two reviews found no significant difference between diuretics and beta-blockers in various outcomes (all-cause mortality, cardiovascular mortality, stroke, congestive heart failure, CVD, and CHD; see table 1, p 16) although the risk of each outcome was lower with diuretics than with beta-blocker. [18] [19] One review found significant heterogeneity among RCTs in relation to stroke (P = 0.01) and CHD (P = 0.03). [19] In the case of stroke, the review suggested that variation in the type of beta-blocker assessed in the trials may be a source of heterogeneity. The review noted that subgroup analysis showed a significant increase in risk of stroke with non-selective beta-blockers (propranolol: RR 2.28, 95% CI 1.31 to 3.95; absolute numbers not reported). However, there was no significant difference in stroke between cardioselective beta-blockers and diuretics (atenolol or metoprolol: RR 1.00, 95% CI 0.74 to 1.33).

We found one RCT (15,313 people with hypertension, and with other cardiovascular risk factors, with and without cardiovascular disorders) comparing the ARB valsartan versus the calcium channel blocker amlodipine. [23] People could receive additional hydrochlorothiazide and other antihypertensive drugs as needed to achieve adequate blood pressure control. The RCT found no significant difference between treatments in the primary outcome of first cardiac event (see table 1, p 16). Cardiac events included sudden cardiac death, fatal or non-fatal MI, death associated with recent MI, death during or after percutaneous coronary procedures or coronary artery bypass graft, death from coronary heart failure, coronary heart failure requiring admission to hospital, or emergency procedures to prevent MI. However, the RCT found that valsartan significantly increased MI compared with amlodipine. The RCT found no significant difference between treatments in stroke or congestive heart failure, although there was a trend towards increased risk of stroke and decreased risk of heart failure with valsartan. These results may be confounded by differential use of alpha-blockers as ancillary treatments (24% in the valsartan group *v* 18% in the amlodipine group; statistical assessment not performed). A larger proportion of people in the valsartan group received the highest dose of the allocated antihypertensive drug plus hydrochlorothiazide plus other antihypertensive drugs (figures not reported). [23]

Harms:

Antihypertensive drugs versus each other:

Most of the systematic reviews gave information on adverse effects. [17] [24] [18] [20] [21] We found two other reviews addressing harms of antihypertensive drugs compared with placebo. [4] [25] The first review (search date 2001, 354 RCTs in people with hypertension with and without cardiovascular disorders) reported on the adverse effects of calcium channel blockers, ACE inhibitors, ARBs, diuretics, and beta-blockers alone or in combination (including 40,000 treated people and 16,000 controls). [4] It found that adverse effects varied significantly among different antihypertensive drugs compared with placebo. It found that standard doses of beta-blockers, calcium channel blockers, and diuretics significantly increased adverse effects compared with placebo (results presented as

difference between antihypertensive and placebo groups in proportion of people with an adverse effect: beta-blockers: 7.5%, 95% CI 4% to 11%; calcium channel blockers: 8.3%, 95% CI 4.8% to 11.8%; diuretics: 9.9%, 95% CI 6.6% to 13.2%; absolute numbers not reported). Adverse effects included cold extremities, fatigue, and nausea with beta-blockers; flushing, ankle oedema, and dizziness with calcium channel blockers; and dizziness, impotence, nausea, and muscle cramps with diuretics. However, the review found no significant increase in adverse effects between standard doses of ARBs or ACE inhibitors and placebo (ARBs: 0%, 95% CI –5.4% to +5.4%; ACE inhibitors: +3.9%, 95% CI –0.5% to +8.3%). At least 1% of people taking any antihypertensive drug withdrew from treatment owing to adverse effects. [4]

The second review focused on only quality-of-life adverse effects associated with beta-blockers (e.g., depressive symptoms, fatigue, and sexual dysfunction), and included RCTs in people with MI, heart failure, or hypertension. [25] It found that beta-blockers significantly increased fatigue compared with placebo (search date 2001, 10 RCTs, 17,682 people; 3038/9108 [33%] with beta-blocker *v* 2610/8574 [30%] with placebo; RR 1.15, 95% CI 1.05 to 1.26). However, it found no significant difference between beta-blockers and placebo in depressive symptoms or sexual dysfunction (depressive symptoms: 7 RCTs, 10,662 people; 1094/5450 [20.1%] with beta-blocker *v* 1070/5212 [20.5%] with placebo; RR 1.12, 95% CI 0.89 to 1.41; as reported in review; sexual dysfunction: 6 RCTs, 14,897 people; 1386/6430 [22%] with beta-blocker *v* 1477/8467 [17%] with placebo; RR 1.10, 95% CI 0.96 to 1.25).

The third review found no significant difference between beta-blockers and calcium channel blockers in rate of withdrawal caused by adverse effects (2 RCTs, 21,591 people: 427/10,775 [4%] with beta-blocker *v* 354/10,816 [3%] with calcium channel blocker; RR 1.20, 95% CI 0.71 to 2.04). [19] The review found that beta-blockers were associated with a significantly higher rate of withdrawal due to adverse effects compared with renin–angiotensin system inhibitors (2 RCTs, 9951 people: 951/4946 [19%] with beta-blocker *v* 687/5005 [14%] with renin–angiotensin system inhibitor; RR 1.41, 95% CI 1.29 to 1.54). [19] The third review found that beta-blockers were associated with a significantly higher rate of withdrawal due to adverse effects compared with diuretics (3 RCTs, 11,566 people: 874/5845 [15%] with beta-blocker *v* 490/5721 [9%] with diuretic; RR 1.86, 95% CI 1.39 to 2.50). [19]

The RCT comparing amlodipine versus valsartan found that peripheral oedema was significantly more common with amlodipine compared with valsartan (2492/7576 [33%] with amlodipine *v* 1135/7622 [15%] with valsartan; P less than 0.0001). Valsartan significantly increased dizziness and headache compared with amlodipine (dizziness: 1083/7576 [14%] with amlodipine *v* 1257/7622 [17%] with valsartan; P less than 0.0001; headache: 947/7576 [13%] with amlodipine *v* 1120/7622 [15%] with valsartan; P less than 0.0001). [23]

Comment:

Clinical guide:

In broad terms, results suggest that there is no difference between diuretics, calcium channel blockers, and ACE inhibitors as the optimal first-step treatment in hypertension-related morbidity and mortality. Various factors could influence choice of first-line treatment in those with hypertension. A meta-analysis (21 RCTs, 145,811 people) indicates that beta-blockers may not be the most effective first-line treatment for those aged over 60 years. [26] The review found that, compared with placebo, beta-blockers significantly reduced major cardiovascular outcomes in younger patients (under 60 years; RR 0.86, 95% CI 0.74 to 0.99) but not in older patients (over 60 years; RR 0.89, 95% CI 0.75 to 1.05). Beta-blockers also demonstrated efficacy similar to other antihypertensive agents in people under 60 years old (RR 0.97, 95% CI 0.88 to 1.07) but not in people aged over 60 years (RR 1.06, 95% CI 1.01 to 1.10): the increased risk of cardiovascular outcomes with beta-blockers compared with other antihypertensive drugs found in older patients was particularly marked for stroke. Other factors that may influence choice of first-line treatment include sex and ethnicity. A subgroup analysis of one RCT found that lisinopril (an ACE inhibitor) was associated with a significantly higher rate of stroke in women (RR 1.45, 95% CI 1.17 to 1.79) and in black people (RR 1.51, 95% CI 1.22 to 1.86) compared with amlodipine (calcium channel blocker). [27] Some of these effects may have been explained by poorer blood pressure control in the lisinopril arm.

Diuretics should be used as first-line treatment for treatment of high blood pressure in most older people. Their superior effect compared with other drugs in reviews (even if mediated by blood pressure), in combination with their low cost to patients, argues for their use in this capacity. In people at high risk of stroke, however, calcium channel blockers can be considered as first-line treatment. There is no strong evidence to guide the choice of second-line treatment for hypertension. In our opinion, choice of additional agents should be guided by the potential for benefit to co-morbidities and the potential to incur known harms.

QUESTION What are the effects of dietary modification in people with hypertension?

OPTION FISH OIL SUPPLEMENTATION

Blood pressure
Compared with placebo Fish oil supplements in large doses may be more effective at lowering blood pressure (very low-quality evidence).

Note
We found no direct information from RCTs about the effects of fish oil on morbidity or mortality in people with hypertension.

For GRADE evaluation of interventions for primary prevention of CVD: treating hypertension, **see table, p 20 .**

Benefits:

Mortality or morbidity:
We found no systematic review or RCTs examining the effects on morbidity or mortality of fish oil supplementation in people with hypertension.

Blood pressure:
We found one systematic review (search date 2001, 36 RCTs, 2114 people, 50% with hypertension) comparing the effects of fish oil (median 3.7 g/day, range 0.2–15 g/day, as capsules, mostly eicosapentaenoic acid and docosahexaenoic acid) versus no supplements or "placebo" on blood pressure. [28] The review performed a separate analysis in people with hypertension (defined as blood pressure 140/90 mm Hg or greater). It found that fish oil supplements significantly reduced blood pressure compared with placebo in people with hypertension (mean difference in systolic blood pressure: –3.65 mm Hg, 95% CI –5.73 mm Hg to –1.58 mm Hg; mean difference in diastolic blood pressure: –2.51 mm Hg, 95% CI –3.70 mm Hg to –1.33 mm Hg). Benefits were independent of the dose of fish oil, although only one trial reported fish oil doses consistent with the doses habitual in Western diets (under 250 mg/day).

Harms:
The review gave no information on adverse effects. [28] An earlier systematic review (search date not reported; published 1993) of RCTs and controlled clinical trials found that belching, bad breath, fishy taste, and abdominal pain occurred in about one third of people taking high doses of fish oil. [29]

Comment:
The RCTs were of short duration (under 12 weeks) and used high doses of fish oil (median 3.7 g/day). Such high intake may be difficult to maintain in westernised populations, in which habitual intake of fish oil is below 250 mg/day (1 oily fish meal/week).

Clinical guide:
Evidence suggests that fish oil supplements in doses of 3 to 4 g daily can be used to lower blood pressure. Given their modest effect, however, it is unlikely that fish oil capsules alone can be used for adequate blood pressure control in most people with hypertension.

OPTION LOW-SALT DIET

Blood pressure
Compared with usual salt intake Low-salt diets seem more effective at reducing blood pressure compared with usual diets in people with hypertension (moderate-quality evidence).

Note
We found no direct information from RCTs about the effects of actual dietary sodium reduction (rather than advice to reduce sodium) on morbidity or mortality in people with hypertension.

For GRADE evaluation of interventions for primary prevention of CVD: treating hypertension, **see table, p 20 .**

Benefits:

Mortality or morbidity:
We found no systematic review or RCTs examining the effect of actual sodium reduction (rather than advice to reduce sodium) on morbidity or mortality in people with hypertension.

Blood pressure:
We found one systematic review (search date 2005, 20 RCTs, 802 people with hypertension), which assessed the effect of actual salt reduction on blood pressure. [30] It found that a 78 mmol reduction in daily salt intake (range –117 mmol to –53 mmol) significantly reduced blood pressure

over a median 5 weeks (range 4 weeks to 1 year; mean difference in systolic blood pressure: –5.06 mm Hg, 95% CI –5.81 mm Hg to –4.31 mm Hg; mean difference in diastolic blood pressure: –2.70 mm Hg, 95% CI –3.16 mm Hg to –2.24 mm Hg). [30] Importantly, one RCT included in the review (412 people with systolic/diastolic blood pressure over 120/80 mm Hg, mean age 48 years, duration 30 days) directly assessed the relationship between sodium and blood pressure levels. [31] People were assigned to receive prepared food with three different target levels of sodium intake (150, 100, and 50 mmol/day [8.6, 5.7, and 2.9 g/day]) in a crossover design. [31] The RCT found that, for people eating a typical American diet, those in the lowest salt-intake group (i.e., those with the greatest salt restriction) had significantly reduced systolic (mean difference –6.7 mm Hg, 95% CI –8.0 mm Hg to –5.4 mm Hg; P less than 0.001) and diastolic (mean difference –3.5 mm Hg, 95% CI –4.3 mm Hg to –2.6 mm Hg; P less than 0.001) blood pressures compared with those with the highest salt intake. Although the greatest effect of salt reduction occurred after 1 week, blood pressures continued to decline throughout the duration of the study, suggesting that effects may be greater with longer-term follow-up. [32]

Harms: The review gave no information on adverse effects. [30] We found no other evidence of harms of a low-salt diet.

Comment: Small RCTs tended to report larger reductions in systolic and diastolic blood pressure than larger RCTs. This may be explained by publication bias or less-rigorous methodology in small RCTs.

Clinical guide:
Low-salt diets (50 mmol/day or less) should be encouraged for all people with hypertension based on good-quality evidence that salt restriction reduces blood pressure.

OPTION CALCIUM SUPPLEMENTATION

Blood pressure
Compared with placebo or no supplementation Calcium supplements may reduce systolic blood pressure by small amounts, but we don't know whether calcium supplementation reduces diastolic blood pressure (very low-quality evidence).

Calcium plus potassium supplementation compared with placebo Calcium plus potassium supplementation may be no more effective at reducing systolic and diastolic blood pressure at 24 weeks (low-quality evidence).

Calcium plus magnesium supplementation compared with placebo Calcium plus magnesium supplementation may be no more effective at reducing systolic and diastolic blood pressure at 24 weeks (low-quality evidence).

Note
We found no direct information from RCTs about the effects of calcium supplementation on morbidity or mortality in people with hypertension.

For GRADE evaluation of interventions for primary prevention of CVD: treating hypertension, see table, p 20 .

Benefits:

Calcium supplementation versus placebo or no supplementation:
Mortality or morbidity:
We found no systematic review or RCTs examining the effects of calcium supplementation on morbidity or mortality in people with primary hypertension.

Blood pressure:
We found two systematic reviews (search date 2003) [33] [34] assessing the effects of calcium supplementation on blood pressure. The reviews had different inclusion criteria, included different RCTs in their meta-analysis, and found slightly different results, and so we discuss both reviews. The first review included clinical trials and RCTs with a minimum length of follow-up of 2 weeks (range of follow-up of identified RCTs was 2–208 weeks). The second review specified a minimum follow-up of 8 weeks, and systolic blood pressure of 140 mm Hg or greater or diastolic blood pressure of 85 mm Hg or greater with no known primary cause. [34] The review excluded RCTs in which changes were made to antihypertensive drugs received during the course of the trial.

The first review (40 RCTs, 2492 people) assessed the effects of calcium supplementation on blood pressure. [33] Meta-analysis of RCTs in people with hypertension (defined by the review as initial blood pressure of 140/90 mm Hg or greater) found that, compared with placebo or no treatment, calcium supplementation (mean daily dose of 1200 mg) significantly reduced systolic and diastolic blood pressure at 2–208 weeks (23 RCTs, 764 people with hypertension: mean difference in change in systolic blood pressure from baseline: –2.17 mm Hg, 95% CI –3.78 mm Hg to –0.55 mm Hg;

mean difference in change in diastolic blood pressure from baseline: –0.95 mm Hg, 95% CI –1.89 mm Hg to –0.01 mm Hg).

The second review in people with hypertension (13 RCTs [all of which were identified by the first review], 485 people) found that, compared with control (placebo, no treatment, or usual care), calcium supplementation significantly reduced systolic blood pressure at 8 to 15 weeks (mean difference –2.53 mm Hg, 95% CI –4.45 mm Hg to –0.60 mm Hg). [34] However, the review found no significant difference between groups in diastolic blood pressure at 8 to 15 weeks (mean difference –0.81 mm Hg, 95% CI –2.07 mm Hg to +0.44 mm Hg). The review reported moderate heterogeneity among RCTs in the analyses of diastolic blood pressure (P = 0.06 for diastolic blood pressure; level of statistical significance for heterogeneity not specified). Sensitivity analyses suggested the poor quality of the identified RCTs (unclear level of blinding and non-reporting of standard deviation of results) was a source of heterogeneity. Percentage of people with CVD was zero in most RCTs, but some RCTs did not report the proportion of people with CVD. Subgroup analyses based on calcium dose and baseline blood pressure found similar results for treatment effect, which suggested that dose of calcium and baseline blood pressure were not contributing to the heterogeneity. The review commented that, because of the poor quality of the RCTs, results of the meta-analysis should be interpreted with caution.

Calcium plus magnesium supplementation versus placebo:
We found one systematic review (search date 2003), [35] identified one four-arm RCT (140 people with hypertension, mean baseline systolic and diastolic blood pressures of 139 mm Hg and 90 mm Hg, respectively) assessing the effects of supplementation with mineral combinations on blood pressure. [36] The RCT compared potassium (60 mmol) plus calcium (25 mmol; 29 people) versus potassium plus magnesium (15 mmol; 31 people) versus calcium plus magnesium (34 people) versus placebo (31 people): see potassium supplementation, p 11 option for data on comparisons involving potassium. The RCT found no significant difference between supplementation with calcium plus magnesium and placebo in change from baseline in either systolic (mean difference +2.1 mm Hg, 95% CI –1.8 mm Hg to +6.0 mm Hg) or diastolic (mean difference +2.2 mm Hg, 95% CI –1.0 mm Hg to +5.4 mm Hg) blood pressure at 24 weeks.

Calcium plus potassium supplementation versus placebo:
See benefits of potassium supplementation, p 11 .

Harms:

Calcium supplementation versus placebo or no supplementation:
The first review gave no information on adverse effects. [33] The second systematic review found no significant difference between calcium supplementation and control in proportion of people withdrawing from a trial or in rate of gastrointestinal adverse effects, including diarrhoea (withdrawal from trial: 3 RCTs, 161 people: any reason for withdrawal: 5/87 [6%] with calcium supplementation *v* 5/74 [7%] with control; RR 0.96, 95% CI 0.30 to 3.08; rate of gastrointestinal adverse effects, including diarrhoea: 3 crossover RCTs, 178 people: 7/89 [8%] with calcium supplementation *v* 8/89 [9%] with control; RR 0.82, 95% CI 0.31 to 2.14). [34]

Calcium plus magnesium supplementation versus placebo:
The RCT gave no information on adverse effects. [36]

Calcium plus potassium supplementation versus placebo:
See harms of potassium supplementation, p 11 .

Comment:

Data relating specifically to people with hypertension are limited by few studies with small sample sizes and short durations.

Clinical guide:
Calcium supplements should not routinely be used to lower blood pressure given the availability of other agents that have demonstrated effectiveness.

OPTION MAGNESIUM SUPPLEMENTATION

Blood pressure
Compared with placebo or no supplements Magnesium supplementation may be no more effective at reducing systolic blood pressure in people with hypertension, but we don't know whether magnesium supplementation is more effective at reducing diastolic blood pressure (very low-quality evidence).

Magnesium plus potassium supplementation compared with control Magnesium plus potassium supplementation seems no more effective than control (placebo, no treatment, or usual care) at reducing blood pressure at 24 to 28 weeks (moderate-quality evidence).

Magnesium plus calcium supplementation compared with placebo Magnesium plus calcium supplementation may be no more effective at reducing blood pressure at 24 weeks (low-quality evidence).

Note
We found no direct information from RCTs about the effects of magnesium supplementation on morbidity or mortality in people with hypertension.

For GRADE evaluation of interventions for primary prevention of CVD: treating hypertension, see table, p 20 .

Benefits:

Magnesium versus placebo or no supplementation:
Mortality or morbidity:
We found no systematic review or RCTs examining the effects of magnesium supplementation on morbidity or mortality.

Blood pressure:
We found two systematic reviews, which between them identified 18 RCTs assessing the effects of supplementation with magnesium on blood pressure. [37] [38] The reviews had different inclusion criteria, included different RCTs in their meta-analyses, and found slightly different results, and so we discuss both reviews. The first review included RCTs of any length of follow-up (range of follow-up of identified RCTs was 3–24 weeks), and RCTs in which concomitant antihypertensive medication was administered. [37] The second review specified a minimum follow-up of 8 weeks, and systolic blood pressure of 140 mm Hg or greater or diastolic blood pressure of 85 mm Hg or greater with no known primary cause. The review excluded RCTs in which changes were made to antihypertensive drugs received during the course of the trial. [38]

The first review (search date 2001, 20 RCTs, 1220 people with and without hypertension and with normal magnesium) compared the effects of magnesium supplementation versus placebo on blood pressure. [37] The review performed a separate analysis of RCTs in people with hypertension (14 RCTs, 467 people, hypertension defined as average baseline systolic blood pressure over 140 mm Hg or diastolic blood pressure over 90 mm Hg). It found no significant difference between magnesium supplementation (increase of 10 mmol/day) and placebo at 3 to 24 weeks in reduction in systolic blood pressure (mean difference in change in systolic blood pressure from baseline: –3.3 mm Hg, 95% CI –6.8 mm Hg to +0.1 mm Hg) or diastolic blood pressure (mean difference in change in diastolic blood pressure from baseline –2.3 mm Hg, 95% CI –5.6 mm Hg to +1.0 mm Hg).

The second review in people with hypertension (search date 2003, 12 RCTs, 545 people), which identified the first review, [37] found that, compared with control (placebo, no treatment, or usual care), magnesium supplementation significantly reduced diastolic blood pressure at 8 to 26 weeks (12 RCTs [3 of crossover design], 671 people: mean difference –2.15 mm Hg, 95% CI –3.40 mm Hg to –0.90 mm Hg). [38] However, the review found no significant difference between groups in systolic blood pressure at 8 to 26 weeks (mean difference –1.26 mm Hg, 95% CI –3.99 mm Hg to +1.47 mm Hg). Percentage of people with CVD was zero in most RCTs, but some RCTs did not report the proportion of people with CVD. The review reported significant heterogeneity among RCTs in the analyses of systolic and diastolic blood pressure (P = 0.003 for systolic blood pressure and P = 0.03 for diastolic blood pressure). The review reported that subgroup analyses indicated heterogeneity was unlikely to be the result of variation in magnesium dose, baseline blood pressure, methods of measuring blood pressure, or proportion of men enrolled. Potential sources of heterogeneity that could not be subjected to subgroup analysis were use of antihypertensive medication and level of dietary sodium or magnesium.

Magnesium plus potassium versus control:
See benefits of potassium supplementation, p 11 .

Magnesium plus calcium versus control:
See benefits of calcium supplementation, p 8 .

Harms:

Magnesium versus placebo or no supplementation:
The first systematic review gave no information on adverse effects. [37] The second systematic review found no significant difference between magnesium supplementation and control in proportion of people experiencing an adverse effect or in rate of gastrointestinal adverse effects (any adverse effect: 6 RCTs, 330 people: 21/181 [12%] with magnesium supplementation *v* 19/149 [13%] with control; RR 0.89, 95% CI 0.63 to 1.25; gastrointestinal adverse effects: 3 RCTs, 245 people: 11/138 [8%] with magnesium supplementation *v* 7/107 [7%] with control; RR 0.83, 95% CI 0.35 to 1.96). [38]

Magnesium plus potassium versus control:
See harms of potassium supplementation, p 11 .

Magnesium plus calcium versus control:
See harms of calcium supplementation, p 8 .

Comment: Larger studies with higher-dose magnesium supplementation are still needed.

Clinical guide:
Magnesium supplementation has no current role in the treatment of hypertension.

OPTION POTASSIUM SUPPLEMENTATION

Blood pressure
Compared with placebo or no supplementation We don't know whether potassium supplementation is more effective than placebo or no supplementation at reducing blood pressure (low-quality evidence).

Potassium plus calcium supplementation compared with placebo Potassium plus calcium supplementation may be no more effective at reducing systolic and diastolic blood pressure at 24 weeks (low-quality evidence).

Potassium plus magnesium supplementation compared with control Potassium plus magnesium supplementation seems no more effective than control (placebo, no treatment, or usual care) at reducing systolic and diastolic blood pressure at 24 to 28 weeks (moderate-quality evidence).

Adverse effects
Potassium supplements can increase serum potassium and need regular monitoring.

Note
We found no direct information from RCTs about the effects of potassium supplementation on morbidity or mortality in people with hypertension.

For GRADE evaluation of interventions for primary prevention of CVD: treating hypertension, **see table, p 20 .**

Benefits:

Potassium supplementation versus placebo or no supplementation:
Mortality or morbidity:
We found no systematic review or RCTs examining the effects of potassium supplementation on morbidity or mortality in people with primary hypertension.

Blood pressure:
We found two systematic reviews (search dates 1995 [39] and 2003), [40] and one additional RCT [41] assessing the effects of potassium supplementation on blood pressure. The reviews had different inclusion criteria, included different RCTs in their meta-analyses, and found different results, and so we discuss both reviews. The first review included open-label RCTs of any length of follow-up (range of follow-up of identified RCTs was 4 days to 3 years), and RCTs in which concomitant antihypertensive medication was administered, with the caveat that additional treatments were equal in treatment and control groups. [39] The second review specified a minimum follow-up of 8 weeks, and systolic blood pressure of 140 mm Hg or greater or diastolic blood pressure of 85 mm Hg or greater with no known primary cause. [40] The review excluded RCTs in which changes were made to antihypertensive drugs received during the course of the trial.

The first review (search date 1995, 21 RCTs, 1560 adults with hypertension, and 12 RCTs, 1005 people with normal blood pressure, age range across RCTs of 19–79 years), which was identified by the second review, [40] assessed the effects of potassium supplementation in the prevention and treatment of hypertension. [39] Meta-analysis of RCTs in people with hypertension (baseline systolic and diastolic blood pressure not specified) found that, compared with placebo or no treatment, potassium supplementation significantly reduced systolic and diastolic blood pressure at 4 days to 24 weeks (20 RCTs, 1512 people with hypertension: mean difference in change in systolic blood pressure from baseline –4.4 mm Hg, 95% CI –6.6 mm Hg to –2.2 mm Hg; mean difference in change in diastolic blood pressure from baseline –2.5 mm Hg, 95% CI –4.9 mm Hg to –0.1 mm Hg). The mean reduction in systolic and diastolic blood pressure was larger in people with hypertension than those with blood pressure in the normal range. The authors of the review recommended potassium supplementation for the treatment of hypertension.

The second review (search date 2003, 6 RCTs [all of which were identified by the first review], 483 people with hypertension) found no significant difference between potassium supplementation and control (placebo, no treatment, or usual care) in reduction in systolic or diastolic blood pressure at

8 to 16 weeks, although the absolute mean difference between groups for both outcomes was large (5 RCTs, 398 people: systolic blood pressure: mean difference –11.25 mm Hg, 95% CI –25.18 mm Hg to +2.68 mm Hg; diastolic blood pressure: WMD –5.03 mm Hg, 95% CI –12.47 mm Hg to +2.42 mm Hg). [40] The review reported significant heterogeneity among RCTs in the analyses of systolic and diastolic blood pressure (P less than 0.0001 for both analyses). The review reported that the heterogeneity was unlikely to be the result of variation in methods of measuring blood pressure, and suggested unreported differences in study population (e.g., dietary potassium intake) as a source of heterogeneity. Percentage of people with CVD was zero in most RCTs, but some RCTs did not report the proportion of people with CVD. The authors of the review also commented that follow-up of some of the RCTs included in the meta-analysis may have been too short to draw conclusions on the effectiveness of potassium supplementation.

The additional RCT (150 adults living in China, aged 35–64 years, blood pressure 130–159/80–94 mm Hg) found that, compared with placebo, supplementation with potassium chloride (60 mmol/day) significantly reduced systolic blood pressure at 12 weeks (mean difference –5 mm Hg, 95% CI –7.88 mm Hg to –2.13 mm Hg). However, it found no significant difference in mean diastolic blood pressure between potassium chloride and placebo (mean difference –0.63 mm Hg, 95% CI –2.49 mm Hg to +1.23 mm Hg). [41]

Potassium plus calcium supplementation versus placebo:
We found one systematic review (search date 2003), [35] which identified one four-arm RCT (140 people with hypertension, mean baseline systolic and diastolic blood pressures of 139 mm Hg and 90 mm Hg, respectively) assessing the effects of supplementation with mineral combinations on blood pressure. [36] The RCT compared potassium (60 mmol) plus calcium (25 mmol; 29 people) versus potassium plus magnesium (15 mmol; 31 people) versus calcium plus magnesium (34 people) versus placebo (31 people): see calcium supplementation, p 8 option for data on comparison of calcium plus magnesium versus placebo (31 people). The RCT found no significant difference between supplementation with potassium plus calcium and placebo in change from baseline in either systolic (mean difference –0.7 mm Hg, 95% CI –4.3 mm Hg to +2.9 mm Hg) or diastolic (mean difference –0.4 mm Hg, 95% CI –2.9 mm Hg to +2.1 mm Hg) blood pressure at 24 weeks.

Potassium plus magnesium supplementation versus placebo:
We found one systematic review (search date 2003, 3 RCTs, 277 people with hypertension) assessing the effects of supplementation with combined potassium plus magnesium on blood pressure. [35] The review found no significant difference between supplementation with potassium plus magnesium and control (placebo, no treatment, or usual care) in reduction in systolic and diastolic blood pressure at 24 to 28 weeks, although there was a difference between groups in favour of mineral supplementation for both outcomes (3 RCTs: systolic blood pressure: mean difference –4.64 mm Hg, 95% CI –9.94 mm Hg to +0.66 mm Hg; diastolic blood pressure: mean difference –3.84 mm Hg, 95% CI –9.47 mm Hg to +1.79 mm Hg). The review reported significant heterogeneity among RCTs in the analyses of systolic and diastolic blood pressure (P = 0.04 for systolic blood pressure; P = 0.001 for diastolic blood pressure). Sources of heterogeneity were baseline characteristics of the people enrolled, methods of assessing blood pressure outcomes, and ingested dose and method of administration of mineral supplements. Sensitivity analysis using alternative reported values, which accounted for missing data, resulted in the change in systolic blood pressure becoming significant (mean difference –5.77 mm Hg, 95% CI –10.53 mm Hg to –1.02 mm Hg): the difference in diastolic blood pressure remained non-significant (mean difference –3.19 mm Hg, 95% CI –7.58 mm Hg to +1.20 mm Hg).

Harms:

Potassium supplementation versus placebo or no supplementation:
The systematic reviews [39] [40] and subsequent RCT [41] gave no information on adverse effects.

Potassium plus calcium supplementation versus placebo:
The RCT gave no information on adverse effects. [36]

Potassium plus magnesium supplementation versus placebo:
The review found no significant difference between supplementation with potassium plus magnesium and control in proportion of people withdrawing from treatment (no further information on reasons for withdrawal given) (2 RCTs, 171 people: 8/85 [9%] with mineral supplement *v* 7/86 [8%] with control; RR 1.06, 95% CI 0.45 to 3.03). [35] The review stated that all three RCTs reported mild adverse effects associated with mineral supplementation, but two RCTs gave no further information on the types of adverse effect. Lack of information on adverse effects precluded pooling of data by the review.

Comment:

Clinical guide:
The evidence for potassium supplementation is variable and depends on the quality of the trials, included population, and length of follow-up. More RCTs of a longer follow-up are required to

clarify this area. Evidence suggests that potassium supplements (60 mmol/day, about the amount found in 5 bananas) may modestly reduce blood pressure. Given their modest effect and their potential for harm if used without follow-up, potassium supplementation should not be used alone or without regular monitoring for blood pressure control and serum potassium levels. Potassium supplementation should not be used in people who already have raised serum potassium levels, such as people with kidney failure or people taking drugs that increase serum potassium.

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Antihypertensive drugs versus each other One systematic review added comparing beta-blockers versus other classes of antihypertensive found no significant difference between beta-blockers and diuretics in various cardiovascular outcomes. [19] The review found that beta-blockers were associated with higher rates of all-cause mortality, stroke, and CVD compared with calcium channel blockers, and with higher rates of stroke compared with renin–angiotensin system inhibitors (angiotensin-converting enzyme [ACE] inhibitors and angiotensin receptor blockers). Categorisation unchanged (Unknown effectiveness) as it remains unclear which antihypertensive drug is more effective.

Calcium supplementation Two systematic reviews added assessing the effects of calcium supplementation on blood pressure found slightly different results. [33] [34] The reviews had different inclusion criteria and included different RCTs in their meta-analysis. Although both reviews found that calcium supplementation improved systolic blood pressure, their results differed slightly for diastolic blood pressure. One review commented that results should be interpreted with caution because of the poor quality of the identified RCTs. [34] One review [35] and one RCT [36] added assessing the effects of combined mineral supplementation on blood pressure found no significant difference between placebo and calcium plus potassium or calcium plus magnesium in change in blood pressure at 24 to 28 weeks. Categorisation unchanged (Unknown effectiveness) owing to poor quality of included evidence.

Magnesium supplementation One systematic review added in people with hypertension found that, compared with control (placebo, no treatment, or usual care), magnesium supplementation reduced diastolic blood pressure at 8 to 26 weeks. [38] However, the review found no significant difference between groups in systolic blood pressure at 8 to 26 weeks. The review reported that overall quality of the trials identified was low, and the results should be interpreted with caution. One review and one RCT added assessing the effects of combined mineral supplementation on blood pressure found no significant difference between placebo and magnesium plus potassium [35] or magnesium plus calcium [36] in change in blood pressure at 24 to 28 weeks. Categorisation unchanged (Unknown effectiveness) owing to poor quality of included evidence.

Potassium supplementation One systematic review added found no significant difference at 8 to 16 weeks between potassium supplementation and placebo in improvement in systolic and diastolic blood pressure, although the difference between groups for both outcomes was large. [40] The authors of the review also commented that follow-up of some of the RCTs included in the meta-analysis may have been too short to draw conclusions on the effectiveness of potassium supplementation. The findings and conclusion reached by the review differ from systematic review evidence previously presented. One review and one RCT added assessing the effects of combined mineral supplementation on blood pressure found no significant difference between placebo and potassium plus calcium [36] or potassium plus magnesium [35] in change in blood pressure at 24 to 28 weeks. Based on evidence added at update, categorisation of potassium supplementation changed to Unknown effectiveness (previously Likely to be beneficial).

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Competing interests: JC has 50% of his salary paid by GlaxoSmithKline. KMO declares that he has no competing interests. MJB has acted as consultant for and given lectures at meetings sponsored by the following companies during the past 5 years: AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Menarini, Merck Sharp & Dohme, Novartis, Pfizer, Sankyo, Sanofi, Servier, and Takeda.

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TABLE 1 **Antihypertensive drug treatments versus each other in the treatment of hypertension**

Reference	Outcomes
Diuretics and beta-blockers versus calcium channel blockers, ACE inhibitors, angiotensin receptor blockers, and alpha-blockers	
[17]	**Mortality** OR 0.98, 95% CI 0.94 to 1.02 15 RCTs, 120,574 people: 4489/53,279 (8.4%) with older antihypertensive drugs *v* 5698/67,295 (8.5%) with newer antihypertensive drugs **Cardiovascular mortality** OR 1.00, 95% CI 0.95 to 1.07 15 RCTs, 106,138 people: 2104/50,115 (4.2%) with older antihypertensive drugs *v* 2349/56,023 (4.2%) with newer antihypertensive drugs **Stroke** OR 0.98, 95% CI 0.88 to 1.08 15 RCTs, 119,717 people: 2025/52,853 (3.8%) with older antihypertensive drugs *v* 2530/66,864 (3.8%) with newer antihypertensive drugs **MI** OR 1.00, 95% CI 0.95 to 1.06 15 RCTs, 119,717 people: 2473/52,853 (4.6%) with older antihypertensive drugs *v* 3253/66,864 (4.9%) with newer antihypertensive drugs **Heart failure** OR 1.23, 95% CI 1.03 to 1.47 15 RCTs, 112,446 people: 1529/49,236 (3%) with older antihypertensive drugs *v* 2672/63,210 (4%) with newer antihypertensive drugs ORs represent effect of newer versus older antihypertensive drugs
Diuretics and beta-blockers versus calcium channel blockers	
[17]	**Mortality** OR 0.98, 95% CI 0.92 to 1.03 9 RCTs, 67,435 people: 2367/30,520 (8%) with calcium channel blockers *v* 3303/36,915 (9%) with older antihypertensive drugs **Cardiovascular mortality** OR 1.03, 95% CI 0.95 to 1.11 9 RCTs, 67,435 people: 1191/30,520 (3.9%) with calcium channel blockers *v* 1581/36,915 (4.3%) with older antihypertensive drugs **Stroke** OR 0.92, 95% CI 0.84 to 1.01 9 RCTs, 67,435 people: 971/30,520 (3%) with calcium channel blockers *v* 1329/36,915 (4%) with older antihypertensive drugs **MI** OR 1.02, 95% CI 0.95 to 1.10 9 RCTs, 67,435 people: 1404/30,520 (4.6%) with calcium channel blockers *v* 1933/36,915 (5.2%) with older antihypertensive drugs **Heart failure** OR 1.33, 95% CI 1.22 to 1.44 8 RCTs, 65,101 people: 1111/29,343 (4%) with calcium channel blockers *v* 1215/35,758 (3%) with older antihypertensive drugs ORs represent effect of calcium channel blockers versus older antihypertensive drugs
[20]	**Stroke** 11 RCTs, 91,893 people: OR 0.92, 95% CI 0.85 to 0.99 **Coronary heart disease** 11 RCTs, 91,893 people: OR 1.02, 95% CI 0.96 to 1.09 ORs represent effect of calcium channel blockers versus diuretics and beta-blockers Absolute numbers not reported for either outcome
Diuretics versus calcium channel blockers	
[18]	**Mortality** RR 1.03, 95% CI 0.98 to 1.08 **Cardiovascular mortality** RR 0.95, 95% CI 0.87 to 1.04 **Stroke** RR 1.02, 95% CI 0.91 to 1.14 **Cardiovascular events** RR 0.94, 95% CI 0.89 to 1.00 **Coronary heart disease** RR 0.89, 95% CI 0.76 to 1.01 **Congestive heart failure** RR 0.74, 95% CI 0.67 to 0.81 Absolute numbers not reported for any outcome
Beta-blockers versus calcium channel blockers	

Reference	Outcomes
[19]	**Mortality** RR 1.07, 95% CI 1.00 to 1.14 4 RCTs, 44,825 people: 1768/22,525 (7.8%) with beta-blocker *v* 1637/22,300 (7.3%) with calcium channel blocker **Cardiovascular mortality** RR 1.15, 95% CI 0.92 to 1.46 4 RCTs, 44,825 people: 785/22,525 (3.5%) with beta-blocker *v* 700/22,300 (3.1%) with calcium channel blocker **Stroke** RR 1.24, 95% CI 1.11 to 1.40 3 RCTs, 44,167 people: 637/22,084 (2.9%) with beta-blocker *v* 512/22,083 (2.3%) with calcium channel blocker **Coronary heart disease** RR 1.05, 95% CI 0.96 to 1.15 3 RCTs, 44,167 people: 902/22,084 (4.1%) with beta-blocker *v* 860/22,083 (3.9%) with calcium channel blocker **Cardiovascular disease** RR 1.18, 95% CI 1.08 to 1.29 2 RCTs, 19,915 people: 950/10,059 (9%) with beta-blocker *v* 800/9856 (8%) with calcium channel blocker
[22]	**Mortality** HR 0.89, 95% CI 0.81 to 0.99 738/9639 (8%) with calcium channel blocker *v* 820/9618 (9%) with beta-blocker **Cardiovascular disease mortality** HR 0.76, 95% CI 0.65 to 0.90 263/9639 (3%) with calcium channel blocker *v* 342/9618 (4%) with beta-blocker **Stroke** HR 0.77, 95% CI 0.66 to 0.89 327/9639 (3%) with calcium channel blocker *v* 422/9618 (4%) with beta-blocker **Composite outcome of non-fatal MI (including silent MI) and fatal coronary heart disease** HR 0.90, 95% CI 0.79 to 1.02 429/9639 (5%) with calcium channel blocker *v* 474/9618 (5%) with beta-blocker **Heart failure** HR 0.84, 95% CI 0.66 to 1.05 134/9639 (1%) with calcium channel blocker *v* 159/9618 (2%) with beta-blocker Population: 19,257 people with hypertension and 3 or more other cardiovascular risk factors, including people with known CVD (11% had a history of stroke or transient ischaemic attack and 6% had peripheral vascular disease)
Diuretics and beta-blockers versus angiotensin-converting enzyme inhibitors	
[17]	**Mortality** OR 1.00, 95% CI 0.94 to 1.06 6 RCTs, 47,410 people: 2175/20,626 (10.5%) with ACE inhibitors *v* 3061/26,784 (11.4%) with older antihypertensive drugs **Cardiovascular mortality** OR 1.02, 95% CI 0.94 to 1.11 6 RCTs, 42,272 people: 1365/19,126 (5%) with ACE inhibitors *v* 1539/23,146 (4%) with older antihypertensive drugs **Stroke** OR 1.10, 95% CI 1.01 to 1.20 5 RCTs, 46,553 people: 994/20,195 (5%) with ACE inhibitors *v* 1184/26,358 (4%) with older antihypertensive drugs **MI** OR 0.97, 95% CI 0.90 to 1.04 5 RCTs, 46,553 people: 1216/20,195 (6%) with ACE inhibitors *v* 1805/26,358 (7%) with older antihypertensive drugs **Heart failure** OR 1.04, 95% CI 0.89 to 1.22 5 RCTs, 46,553 people: 917/20,195 (4.5%) with ACE inhibitors *v* 1200/26,358 (4.6%) with older antihypertensive drugs ORs represent effect of ACE inhibitors versus older antihypertensive drugs
Diuretics and beta-blockers versus angiotensin-converting enzyme inhibitors	
[20]	**Stroke** 5 RCTs, 46,553 people: OR 1.09, 95% CI 0.96 to 1.24 **Coronary heart disease** 5 RCTs, 46,553 people: OR 0.97, 95% CI 0.90 to 1.05 ORs represent effect of ACE inhibitor versus diuretics and beta-blockers Absolute numbers not reported for either outcome
Diuretics versus angiotensin-converting enzyme inhibitors	
[18]	**Mortality** RR 1.00, 95% CI 0.95 to 1.05 **Cardiovascular mortality** RR 0.93, 95% CI 0.85 to 1.02 **Stroke** RR 0.86, 95% CI 0.77 to 0.97 **Cardiovascular events** RR 0.94, 95% CI 0.89 to 1.00 **Coronary heart disease** RR 1.00, 95% CI 0.88 to 1.14 **Congestive heart failure** RR 0.88, 95% CI 0.80 to 0.96 Absolute numbers not reported for any outcome

Reference	Outcomes
Beta-blockers versus renin–angiotensin system inhibitors (ACE inhibitors or angiotensin receptor blockers)	
[19]	**Mortality** RR 1.10, 95% CI 0.98 to 1.24 3 RCTs, 10,828 people: 496/5387 (9%) with beta-blocker *v* 455/5441 (8%) with renin–angiotensin system inhibitor **Cardiovascular mortality** RR 1.09, 95% CI 0.92 to 1.29 3 RCTs, 10,828 people: 270/5387 (5.0%) with beta-blocker *v* 253/5441 (4.6%) with renin–angiotensin system inhibitor **Stroke** RR 1.30, 95% CI 1.11 to 1.53 2 RCTs, 9951 people: 326/4946 (7%) with beta-blocker *v* 253/5005 (5%) with renin–angiotensin system inhibitor **Coronary heart disease** RR 0.90, 95% CI 0.76 to 1.06 2 RCTs, 9951 people: 236/4946 (4.8%) with beta-blocker *v* 271/5005 (5.4%) with renin–angiotensin system inhibitor **Cardiovascular disease** RR 1.00, 95% CI 0.72 to 1.38 3 RCTs, 10,828 people: 675/5387 (5.0%) with beta-blocker *v* 625/5441 (4.6%) with renin–angiotensin system inhibitor
Diuretics and beta-blockers versus angiotensin receptor blockers	
[17]	**Mortality** OR 0.91, 95% CI 1.81 to 1.02 (as reported in review) 2 RCTs, 14,130 people: 642/7082 (9%) with alpha-blockers *v* 697/7048 (10%) with older antihypertensive drugs **Cardiovascular mortality** OR 0.89, 95% CI 0.77 to 1.04 2 RCTs, 14,130 people: 3492/7082 (4.9%) with alpha-blockers *v* 386/7048 (5.4%) with older antihypertensive drugs **Stroke** OR 0.76, 95% CI 0.65 to 0.88 2 RCTs, 14,130 people: 321/7082 (5%) with angiotensin receptor blockers *v* 424/7048 (6%) with older antihypertensive drugs **MI** OR 1.08, 95% CI 0.90 to 1.29 2 RCTs, 14,130 people: 268/7082 (3.7%) with angiotensin receptor blockers *v* 251/7048 (3.6%) with older antihypertensive drugs
Diuretics versus angiotensin receptor blockers	
[18]	**Mortality** RR 1.09, 95% CI 0.96 to 1.22 **Cardiovascular mortality** RR 1.07, 95% CI 0.85 to 1.36 **Stroke** RR 1.20, 95% CI 0.93 to 1.55 **Cardiovascular events** RR 1.00, 95% CI 0.85 to 1.18 **Coronary heart disease** RR 0.83, 95% CI 0.59 to 1.16 **Congestive heart failure** RR 0.88, 95% CI 0.66 to 1.16 Absolute numbers not reported for any outcome
Diuretics and beta-blockers versus alpha-blockers	
[17]	**Mortality** 1 RCT, 24,335 people: 514/9067 (5.7%) with alpha-blockers *v* 851/15,268 (5.6%) with older antihypertensive drugs **Stroke** 1 RCT, 24,335 people: 244/9067 (3%) with alpha-blockers *v* 251/15,268 (2%) with older antihypertensive drugs **MI** 1 RCT, 24,335 people: 365/9067 (4.0%) with alpha-blockers *v* 608/15,268 (3.9%) with older antihypertensive drugs **Heart failure** 1 RCT, 24,335 people: 491/9067 (5%) with alpha-blockers *v* 420/15,268 (3%) with older antihypertensive drugs OR and CI displayed graphically for all outcomes
Diuretics versus alpha-blockers	
[18]	**Mortality** RR 0.98, 95% CI 0.88 to 1.10 **Cardiovascular mortality** RR 1.00, 95% CI 0.75 to 1.34 **Stroke** RR 0.85, 95% CI 0.66 to 1.10 **Cardiovascular events** RR 0.84, 95% CI 0.75 to 0.93 **Coronary heart disease** RR 0.99, 95% CI 0.75 to 1.31 **Congestive heart failure** RR 0.51, 95% CI 0.43 to 0.60 Absolute numbers not reported for any outcome

Reference	Outcomes
Beta-blockers versus diuretics	
[18]	**Mortality** RR 0.99, 95% CI 0.91 to 1.07 **Cardiovascular mortality** RR 0.93, 95% CI 0.81 to 1.07 **Stroke** RR 0.90, 95% CI 0.76 to 1.06 **Cardiovascular events** RR 0.89, 95% CI 0.80 to 0.98 **Coronary heart disease** RR 0.87, 95% CI 0.74 to 1.03 **Congestive heart failure** RR 0.83, 95% CI 0.68 to 1.01 RRs represent effect of diuretics versus beta-blockers Absolute numbers not reported for any outcome
[19]	**Mortality** RR 1.04, 95% CI 0.91 to 1.19 5 RCTs, 18,241 people: 388/9195 (4.2%) with beta-blocker *v* 367/9046 (4.1%) with diuretic **Cardiovascular mortality** RR 1.09, 95% CI 0.90 to 1.32 3 RCTs, 17,452 people: 217/8802 (2.5%) with beta-blocker *v* 195/8650 (2.3%) with diuretic **Stroke** RR 1.17, 95% CI 0.65 to 2.09 4 RCTs, 18,135 people: 130/9142 (1.4%) with beta-blocker *v* 108/8993 (1.2%) with diuretic **Coronary heart disease** RR 1.12, 95% CI 0.82 to 1.54 4 RCTs, 18,135 people: 323/9142 (3.5%) with beta-blocker *v* 294/8993 (3.3%) with diuretic **Cardiovascular disease** RR 1.13, 95% CI 0.99 to 1.28 4 RCTs, 18,135 people: 469/9142 (5.1%) with beta-blocker *v* 409/8993 (4.5%) with diuretic
Angiotensin receptor blockers versus calcium channel blockers	
[23]	**First cardiac event** HR 1.04, 95% CI 0.94 to 1.15 810/7649 (10.6%) with valsartan *v* 789/7596 (10.4%) with amlodipine **MI** HR 1.19, 95% CI 1.02 to 1.38 369/7649 (5%) with valsartan *v* 313/7596 (4%) with amlodipine **Stroke** HR 1.15, 95% CI 0.98 to 1.35 322/7649 (4.2%) with valsartan *v* 281/7596 (3.7%) with amlodipine **Congestive heart failure** HR 0.89, 95% CI 0.77 to 1.03 354/7649 (4.6%) with valsartan *v* 400/7596 (5.3%) with amlodipine

TABLE **GRADE evaluation of interventions for primary prevention of CVD: hypertension**

Important outcomes	Mortality (all-cause and cardiovascular), cardiovascular events (MI, stroke, congestive heart failure, and coronary heart disease), renal outcomes, blood pressure, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consis-tency**	**Direct-ness**	**Effect size**	**GRADE**	**Comment**
What are the effects of different antihypertensive drugs for people with hypertension?									
at least 22 (at least 150,590) [17] [18] [19] [20]	Mortality	Antihypertensive drugs *v* each other	4	0	–1	–1	0	Low	Consistency point deducted for statistical heterogeneity among RCTs included in meta-analysis. Directness point deducted for combining drug classes for analysis
at least 23 (at least 169,903) [17] [18] [19] [20] [23]	Cardiovascular events	Antihypertensive drugs *v* each other	4	0	–1	–1	0	Low	Consistency point deducted for statistical heterogeneity among RCTs included in meta-analysis. Directness points deducted for combining drug classes
13 (37,089) [21]	End-stage renal disease	Antihypertensive drugs *v* each other	4	0	0	–1	0	Moderate	Directness point deducted for combining drug classes for analysis
What are the effects of dietary modification for people with hypertension?									
36 (2114) [28]	Blood pressure	Fish oil supplements *v* no supplements or placebo	4	–1	0	–2	0	Very low	Quality point deducted for short follow-up. Directness points deducted for high doses used and broad inclusion criteria
20 (802) [30] [31]	Blood pressure	Salt reduction *v* normal intake	4	–1	+1	–1	0	Moderate	Quality point deducted for methodological flaws. Consistency point added for dose response. Directness point deducted for uncertainty of diagnostic measurement in study
22 (1710) [39] [40] [41]	Blood pressure	Potassium supplementation *v* placebo or no supplementation	4	0	–1	–1	0	Low	Consistency point deducted for statistical heterogeneity among RCTs. Directness point deducted for subgroup analysis in one SR
1 (60) [36]	Blood pressure	Potassium plus calcium supplementation *v* placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point for borderline hypertensive baseline systolic blood pressure
3 (277) [35]	Blood pressure	Potassium plus magnesium supplementation *v* control	4	0	–1	0	0	Moderate	Consistency point deducted for statistical heterogeneity among RCTs
42 (4560) [33] [34]	Blood pressure	Calcium supplementation *v* placebo or no supplementation	4	–1	–1	–1	0	Very low	Quality point deducted for poor follow-up. Consistency point deducted for statistical heterogeneity among RCTs. Directness point deducted for subgroup analysis in one SR
1 (65) [36]	Blood pressure	Calcium plus magnesium supplementation *v* placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point for borderline hypertensive baseline systolic blood pressure
20 (1220) [37] [38]	Blood pressure	Magnesium supplementation *v* placebo or no supplementation	4	0	–2	–1	0	Very low	Consistency points deducted for conflicting results and for statistical heterogeneity among RCTs. Directness point deducted for subgroup analysis in one SR

Important outcomes	Mortality (all-cause and cardiovascular), cardiovascular events (MI, stroke, congestive heart failure, and coronary heart disease), renal outcomes, blood pressure, adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consis-tency	Direct-ness	Effect size	GRADE	Comment

Type of evidence: 4 = RCT; 2 = Observational; 1 = Non-analytical/expert opinion.
Consistency: similarity of results across studies.
Directness: generalisability of population or outcomes.
Effect size: based on relative risk or odds ratio.