Primary prevention: hypertension

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Antihypertensive drugs *v* each other

Antihypertensive drugs versus each other

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Summary

Systematic reviews found no significant difference in the ability of diuretics and other antihypertensive agents to reduce total mortality, cardiovascular mortality, and myocardial infarction. Compared with diuretics, however, angiotensin converting enzyme (ACE) inhibitors were less effective in reducing rates of stroke; alpha-blockers were less effective in reducing combined cardiovascular events; and ACE inhibitors, calcium channel blockers, and alpha-blockers were less effective in reducing heart failure. Calcium channel blockers and angiotensin receptor blockers reduced stroke more than older antihypertensive drugs (beta-blockers and diuretics), which in combination with findings from a meta-analysis comparing diuretics versus these agents suggests that these agents are more effective than beta-blockers at reducing stroke. One systematic review additionally found that calcium channel blockers were more effective at reducing stroke and less effective in reducing heart failure than ACE inhibitors. Some of these differential effects may be mediated by differences in blood pressure among treatment groups.

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Benefits

We found three systematic reviews, which compared 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, or alpha-blockers) across a wide spectrum of cardiovascular outcomes. [17] [18] [19] We found two systematic reviews that looked specifically at stroke and coronary heart disease [20] or renal outcomes. [21] The first review (search date 2003, 15 RCTs, 120 574 people with hypertension) compared older antihypertensive drugs (diuretics and beta-blockers) versus single newer drugs, including calcium channel blockers, ACE inhibitors, angiotensin receptor blockers, and alpha-blockers. [17] It found no significant difference in older and newer single drug treatments for total mortality (OR 0.98, 95% CI 0.94 to 1.02), cardiovascular mortality (OR 1.00, 95% CI 0.95 to 1.07), or myocardial infarction (OR 1.00, 95% CI 0.95 to 1.06; no significant heterogeneity for these 3 outcomes). However, newer drug treatments were significantly different than older treatments for other outcomes. There was a trend towards reduced stroke with calcium channel blockers (9 RCTs, 67 435 people; OR 0.92, 95% CI 0.84 to 1.01). However, calcium channel blockers significantly increased congestive heart failure (8 RCTs, 65 101 people; OR 1.33, 95% CI 1.22 to 1.44). ACE inhibitors significantly increased stroke (5 RCTs, 46 553 people; OR 1.10, 95% CI 1.01 to 1.20). Angiotensin receptor blockers significantly reduced stroke (2 RCTs, 14 130 people; OR 0.76, 95% CI 0.65 to 0.88) and cardiovascular events (OR 0.86, 95% CI 0.77 to 0.95). Alpha-blockers were associated with increased congestive heart failure (1 RCT, 24 335 people; AR: 5.4% with alpha-blocker *v* 2.8% with older antihypertensive drugs; OR and 95% CI displayed graphically as significant), cardiovascular events (AR: 17.6% with alpha-blocker *v* 14.7% with older antihypertensive drugs; OR and 95% CI displayed graphically as significant), and slightly increased stroke (AR: 2.7% with alpha-blocker *v* 2.3% with older antihypertensive drugs; OR and 95% CI displayed graphically, significance not clear) compared with older antihypertensive drugs. An accompanying meta-regression suggested many of these differences may be attributable to difference in blood pressure among treatment groups. The second review (search date 2003, 16 RCTs, 10 RCTs included in the first review, 101 288 people enrolled on the basis of hypertension or elevated cardiovascular risk) also compared older (beta-blockers and diuretics) versus newer (calcium channel blockers and ACE inhibitors) antihypertensive drugs. [18] It found similar results to the first review. It found no significant difference between calcium channel blockers and older antihypertensive drugs in overall mortality (9 RCTs, 68 449 people; RR 0.99, 95% CI 0.95 to 1.04), or cardiovascular mortality (RR 1.05, 95% CI 0.97 to 1.13). However, it found that calcium channel blockers significantly increased congestive heart failure (7 RCTs, 53 159 people; RR 1.33, 95% CI 1.21 to 1.41), but tended to reduce stroke, although this reduction was of borderline significance (RR 0.93, 95% CI 0.86 to 1.00). There was no significant difference between ACE inhibitors and older antihypertensive drugs in overall mortality (6 RCTs, 47 430 people; RR 1.00, 95% CI 0.95 to 1.05), or cardiovascular mortality (RR 1.03, 95% CI 0.95 to 1.11). However, it found that there was a trend towards increased stroke with ACE inhibitors (5 RCTs, 46 553 people; RR 1.09, 95% CI 1.00 to 1.18). Outcome differences were again related to differences in blood pressure, except in the case of congestive heart failure. The third review (search date 2002, 42 RCTs, 14 RCTs included in first review, 192 478 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, angiotensin receptor blockers, 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. [19] The review found no significant difference between diuretics and beta-blockers in total mortality (OR 0.99, 95% CI 0.91 to 1.07). There was a trend towards reduced cardiovascular disease mortality (OR 0.93, 95% CI 0.81 to 1.07), stroke (OR 0.90, 95% CI 0.76 to 1.06), congestive heart failure (OR 0.83, 95% CI 0.68 to 1.01), and coronary heart disease (OR 0.87, 95% CI 0.74 to 1.04) with diuretics compared with beta-blockers, although this did not reach significance. Diuretics significantly reduced cardiovascular disease events compared with beta-blockers (OR 0.89, 95% CI 0.80 to 0.98). Additionally, diuretics reduced congestive heart failure compared with calcium channel blockers (OR 0.74, 95% CI 0.67 to 0.81); reduced stroke (OR 0.86, 95% CI 0.77 to 0.97) and congestive heart failure (OR 0.88, 95% CI 0.80 to 0.96) compared with ACE inhibitors; and reduced congestive heart failure (OR 0.51, 95% CI 0.43 to 0.60) and cardiovascular events (OR 0.84, 95% CI 0.75 to 0.93) compared with alpha-blockers. There was a trend towards increased stroke with diuretics compared with angiotensin receptor blockers (OR 1.20, 95% CI 0.93 to 1.55). One more recent review (search date 2004, 16 RCTs, 14 RCTs included in the first review, 114 143 people) focusing only on coronary heart disease and stroke outcomes in people receiving calcium channel blockers or ACE inhibitors (compared with diuretics, beta-blockers, or both) supported the above findings. [20] It found no significant difference between ACE inhibitors and older antihypertensive drugs in coronary heart disease (OR 0.97, 95% CI 0.90 to 1.05) or stroke (OR 1.09, 95% CI 0.96 to 1.24). It found no significant difference between calcium channel blockers and older antihypertensive drugs in coronary heart disease (OR 1.02, 95% CI 0.96 to 1.09). It found that calcium channel blockers reduced stroke (OR 0.92, 95% CI 0.85 to 0.99). Another recent review examining only renal outcomes showed a reduction in end stage renal disease (ESRD) with ACE inhibitors and angiotensin receptor blockers compared with other newer and older antihypertensive medications collectively (search date 2005, 13 RCTs, 37 089 people; 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.

Beta-blockers versus calcium channel blockers:

We found one subsequent RCT (19 257 people with hypertension and ≥ 3 other cardiovascular risk factors, including people with known cardiovascular disease) 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]). [22] The second drug (diuretic or ACE inhibitor) was added as required, to reach prespecified blood pressure targets. It found that the calcium channel blocker based regimen reduced total mortality (HR 0.89, 95% CI 0.81 to 0.99), cardiovascular disease mortality (HR 0.76, 95% CI 0.65 to 0.90), and stroke (HR 0.77, 95% CI 0.66 to 0.89). There was a trend toward improvement in both the primary outcome of combined non-fatal myocardial infarction (including silent myocardial infarction) and fatal coronary heart disease (HR 0.90, 95% CI 0.79 to 1.02) and the secondary outcome of congestive heart failure (HR 0.84, 95% CI 0.66 to 1.05) 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 < 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.

Angiotensin converting enzyme (ACE) inhibitors versus calcium channel blockers:

We found one systematic review (search date 2003) comparing ACE inhibitors versus calcium channel blockers. [18] It found no significant difference between ACE inhibitors and calcium channel blockers in total mortality (6 RCTs, 25 756 people with hypertension; RR 1.04, 95% CI 0.98 to 1.10); cardiovascular mortality (5 RCTs, 25 103 people; RR 1.03, 95% CI 0.94 to 1.13); or coronary heart disease (5 RCTs, 25 103 people; RR 0.96, 95% CI 0.88 to 1.04). However, ACE inhibitors significantly decreased heart failure (4 RCTs, 20 702 people; RR 0.82, 95% CI 0.73 to 0.92; blood pressure 1/1 mm Hg higher in ACE inhibitor group) and significantly increased stroke (5 RCTs, 25 103 people; RR 1.12, 95% CI 1.01 to 1.25; blood pressure 1/1 mm Hg higher in ACE inhibitor group) compared with calcium channel blockers.

Angiotensin receptor blockers versus calcium channel blockers:

We found one RCT (15 313 people with hypertension, and with other cardiovascular risk factors, with and without cardiovascular disorders) comparing the effects of the angiotensin receptor blocker, valsartan, with the effects of the calcium channel blocker, amlodipine. [23] Participants could receive additional hydrochlorothiazide and other antihypertensive drugs as needed to achieve adequate blood pressure control. It found no significant difference in the primary outcome of first cardiac event between treatments (HR 1.04, 95% CI 0.94 to 1.15). Cardiac events included sudden cardiac death, fatal or non-fatal myocardial infarction, death associated with recent myocardial infarction, 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 myocardial infarction. However, the RCT found significantly increased myocardial infarction (HR 1.19, 95% CI 1.02 to 1.38), and trends toward increased stroke (HR 1.15, 95% CI 0.98 to 1.35) and reduced congestive heart failure (HR 0.89, 95% CI 0.77 to 1.03) with valsartan. These results may be confounded by differential use of alpha-blockers as ancillary treatments (24.4% in the valsartan group *v* 18.3% in the amlodipine group; statistical assessment not performed). More people in the valsartan group received the highest dose of the allocated antihypertensive drug plus hydrochlorothiazide plus other antihypertensive drugs (figures not reported). Additionally, blood pressure was lower with amlodipine (mean difference from 6 months to study end: about 2.0/1.6 mm Hg; P < 0.001 at all time points). [23]

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Harms

None of the systematic reviews reported on harms. [17] [18] [19] [20] [21] We found two other reviews addressing harms of antihypertensive drugs compared with placebo. [4] [24] 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, angiotensin receptor blockers, diuretics, and beta-blockers alone or in combination (including 40 000 treated people and 16 000 controls). It found that adverse effects varied significantly among different antihypertensive drugs compared with placebo. [4] It found that standard doses of beta-blockers, calcium channel blockers, and diuretics significantly increased adverse effects compared with placebo (proportion with adverse effects with beta-blockers: 7.5%, 95% CI 4% to 11%; with calcium channel blockers: 8.3%, 95% CI 4.8% to 11.8%; with diuretics: 9.9%, 95% CI 6.6% to 13.2%). The 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 angiotensin II receptor antagonists or ACE inhibitors and placebo (proportion with adverse effects with angiotensin II receptor antagonists: 0%, 95% CI –5.4% to +5.4%; with ACE inhibitors: +3.9%, 95% CI –0.5% to +8.3%). Withdrawal from treatment owing to adverse effects occurred in at least 1% of people taking any antihypertensive drug. [4] For standard doses, see web table A. The second review, focused only on quality of life concerns with beta-blockers (e.g. depressive symptoms, fatigue, and sexual dysfunction), and included RCTs in people with myocardial infarction, heart failure, or hypertension. [24] It found that beta-blockers increased fatigue compared with placebo (search date 2001, 10 RCTs, 17 682 people; AR: 33.4% with beta-blocker *v* 30.4% with placebo; RR 1.15, 95% CI 1.05 to 1.26). However, it found no increase in depressive symptoms (7 RCTs, 10 662 people; AR: 20.1% with beta-blocker *v* 20.5% with placebo; RR 1.12, 95% CI 0.89 to 1.41) or sexual dysfunction (6 RCTs, 14 897 people; AR: 21.6% with beta-blocker *v* 17.4% with placebo; RR 1.10, 95% CI 0.96 to 1.25) with beta-blockers.

Beta-blockers versus calcium channel blockers:

There was no significant difference between the amlodipine based regimen and the atenolol based regimen in discontinuations owing to adverse events (25% overall, figures not reported by treatment group, difference reported as not significant, P value not reported). [22] However, significantly more people taking atenolol discontinued treatment owing to severe adverse events (2% with amlodipine based regimen *v* 3% with atenolol based regimen; $P < 0.0001$).

Angiotensin receptor blockers versus calcium channel blockers:

The RCT found that peripheral oedema was significantly more common with amlodipine than with valsartan (32.9% with amlodipine *v* 14.9% with valsartan; $P < 0.0001$). Valsartan significantly increased dizziness (14.3% with amlodipine *v* 16.5% with valsartan; $P < 0.0001$) and headache (12.5% with amlodipine *v* 14.7% with valsartan; $P < 0.0001$) compared with amlodipine. [23]

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Comment

Clinical guide:

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

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