Recommendation 10

Should adult patients with high initial systolic blood pressure ≥160 and/or diastolic blood presuure ≥100 be offered as initial therapy any combination treatment compared with any monotherapy?

Critical outcomes: mortality, CV mortality, stroke, health related quality of life, myocardial infarction, hypertensive emergencies, end stage renal disease etc according to the outcome table.

There is no direct evidence that the use of initial combination therapy is more effective in reducing the clinical outcomes compared to the step-up regimens.

There is moderate quality evidence that an initial combination treatment and tight uptitration sequence achieves better BP control (64.7% versus 52.7%; RD 12.0%; 95% CI: 1.5% to 22.4%; P=0.026 at 6 months).

There is good quality evidence from multiple RCT-s that, compared to monotherapy:

- combination therapy achieves greater BP reductions and control rates;
- at least 2/3 of patients (including stage 1 hypertension) need combination therapy to achieve BP control;
- combination therapy with moderate doses of 2 drugs is no more harmful than monotherapy and may reduce specific adverse effects of e.g. CCB-s.

There is good quality evidence from a meta-analysis that the extra BP reduction from combining drugs from 2 different classes is approximately 5 times greater than doubling the dose of 1 drug.

There is good quality evidence froma meta-analysis that the greater effect of combination treatment on BP is seen also in Stage 1 hypertension.

We did not find any meta-analysis investigating the possible superiority of predefined combinations as initial treatment in reducing cardiovascular events. Therefore, there exist no combination that can be currently considered superior to all others. Some RCT-s have been performed focusing on the superiority of certain combinations compared to others:

- a calcium channel blocker+diuretic regimen was shown to be inferior to other combinations for preventing myocardial infarction (odds ratio 1.98, 95% confidence interval 1.37—2.87) but not stroke;
- an ACEI (or ARB)+diuretic combination was not significantly superior for stroke and myocardial infarction prevention compared with diuretic+beta blocker;
- ACCOMPLISH trial (moderate quality evidence) demonstrated that starting a CCB+ACEI in high-risk hypertensive patients significantly reduced the primary composite outcome (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, sudden cardiac arrest, coronary revascularization) by 20% compared with ACEI+HCTZ).

Guidelines

Some of the reviewed guidelines provided recommendations on the initial combination therapy of initially high blood pressure. The recommendations were not explicitly based on synthesis of evidence or RTC.
The 2009 Canadian Hypertension Education Program suggested that a combination of two first-line agents may be considered as initial treatment of hypertension if systolic blood pressure is 20 mmHg above target or if diastolic blood pressure is 10 mmHg above target (evidence grade C).
The Finnish Guidline of Hypertension suggested that if RR values are markedly increased or the patient has high CV risk, combitherapy can be started as first line.
ESC 2007 guideline suggests that a combination of two drugs at low doses should be preferred as first step treatment when initial BP is in the grade 2 or 3 range or total cardiovascular risk is high or very high.

References

Summary (abstract or less)	Full ref
To determine whether a simplified treatment algorithm is more effective than guideline-based management, we studied 45 family practices in southwestern Ontario, Canada, using a cluster randomization trial comparing the simplified treatment algorithm with the Canadian Hypertension Education Program guidelines. The simplified treatment algorithm consisted of the following: (1) initial therapy with a low-dose angiotensin-converting enzyme inhibitor/diuretic or angiotensin receptor blocker/diuretic combination; (2) up-titration of combination therapy to the highest dose; (3) addition of a calcium channel blocker and up-titration; and (4) addition of a non-first-line antihypertensive agent. The proportion of patients treated to target blood pressure (systolic blood pressure <140 mm Hg and diastolic blood pressure <90 mm Hg for patients without diabetes mellitus or systolic blood pressure <130 mm Hg and diastolic blood pressure <80 mm Hg for diabetic patients) at 6 months was analyzed at the practice level. The proportion of patients achieving target was significantly higher in the intervention group (64.7% versus 52.7%; absolute difference: 12.0%; 95% CI: 1.5% to 22.4%; P=0.026). Multivariate analysis of patient-level data showed that assignment to the intervention arm increased the chance of reaching the target by 20% (P=0.028), when adjusted for other covariates. In conclusion, the Simplified Treatment Intervention to Control Hypertension Study indicates that a simplified antihypertensive algorithm using initial low-dose fixed-dose combination therapy is superior to guideline-based practice for the management of hypertension.	Feldman RD, Zou GY, Vandervoort MK, Wong CJ, NelsonSA, FeaganBG. A simplified approach to the treatment of uncomplicated hypertension. A cluster randomized, controlled trial. Hypertension 2009;53:646–53.
OBJECTIVE: To quantify the incremental effect of combining blood pressure-lowering drugs from any 2 classes of thiazides, beta-blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers over 1 drug alone and to compare the effects of combining drugs with doubling dose. METHODS: Meta-analysis of factorial trials in which participants were randomly allocated to 1 drug alone, another drug alone, both drugs together, or a placebo. RESULTS: We identified 42 trials (10,968 participants). With a thiazide used alone, the mean placebo-subtracted reduction in systolic blood pressure was 7.3 mm Hg and 14.6 mm Hg combined with a drug from another class. The corresponding reductions were 9.3 mm Hg and 18.9 mm Hg with a beta-blocker, 6.8 mm Hg and 13.9 mm Hg with an angiotensin-converting enzyme, and 8.4 mm Hg and 14.3 mm Hg with a calcium channel blocker. The expected blood pressure reduction from 2 drugs together, assuming an additive effect, closely predicted the observed blood pressure reductions. The ratios of the observed to expected incremental blood pressure reductions from combining each class of drug with any other over that from 1 drug were, respectively, for thiazides, beta-blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers: 1.04 (95% confidence interval [CI], 0.88-1.20), 1.00 (95% CI, 0.76-1.24), 1.16 (95% CI, 0.93-1.39), and 0.89 (95% CI, 0.69-1.09); the overall average was 1.01 (95% CI, 0.90-1.12). Comparison of our results with those of a published meta-analysis of different doses of the same drug showed that doubling the dose of 1 drug had approximately one fifth of the equivalent incremental effect (0.22 [95% CI, 0.19-0.25]). CONCLUSION: Blood pressure reduction from combining drugs from these 4 classes can be predicted on the basis of additive	Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. Am J Med 2009;122:290–300.

effects. The extra blood pressure reduction from combining drugs from 2 different classes is approximately 5 times greater than doubling the dose of 1 drug.	
METHODS: This analysis pooled patient-level data from nine randomized, double-blind, fixed-dose, placebo-controlled trials (N = 4278) of once-daily valsartan 80 mg, 160 mg, and 320 mg, and valsartan/hydrochlorothiazide (HCTZ) 80/12.5 mg, 160/12.5 mg, 160/25 mg, 320/12.5 mg, and 320/25 mg. Kaplan-Meier methods estimated the cumulative proportion of patients achieving BP <140/90 mm Hg over 8 weeks and the median time to BP goal. The HCTZ 12.5-mg and 25-mg doses were pooled for the time-to-goal analysis in patients receiving combinations with valsartan 160 mg or 320 mg. RESULTS: Overall, the median time-to-goal was 8.1 weeks with valsartan 160 mg, 6.1 weeks with valsartan 320 mg, 2.6 weeks with valsartan 160 mg/HCTZ, and 2.1 weeks with valsartan 320 mg/HCTZ. In patients with stage 2 hypertension, the median time-to-goal was 4.3 weeks with valsartan 160 mg/HCTZ and 2.4 weeks with valsartan 320 mg/HCTZ. Goal rates by Week 4 for valsartan/HCTZ exceeded rates by Week 8 with the same doses of valsartan alone. Overall, the proportion that achieved BP goal by Week 8 was 32.6% with valsartan 80 mg, 48.4% with valsartan 160 mg, 54.2% with valsartan 320 mg, 74.6% with valsartan 160 mg/HCTZ, and 84.8% with valsartan 320 mg/HCTZ, versus 24.2% with placebo. With valsartan 320 mg/HCTZ, 75.8% of stage 2 patients and 94% of stage 1 patients reached BP goal by Week 8. Discontinuation rates due to adverse events were generally low across doses.	Weir M, Levy D, Crikelair N, et al. Time to achieve blood-pressure goal: influence of dose of valsartan monotherapy and valsartan and hydrochlorothiazide combination therapy. Am J Hypertens. 2007;20:807–815.
METHODS: 15?245 patients, aged 50 years or older with treated or untreated hypertension and high risk of cardiac events participated in a randomised, double-blind, parallel-group comparison of therapy based on valsartan or amlodipine. Duration of treatment was event-driven and the trial lasted until at least 1450 patients had reached a primary endpoint, defined as a composite of cardiac mortality and morbidity. Patients from 31 countries were followed up for a mean of 4.2 years. FINDINGS: Blood pressure was reduced by both treatments, but the effects of the amlodipine-based regimen were more pronounced, especially in the early period (blood pressure 4.0/2.1 mm Hg lower in amlodipine than valsartan group after 1 month; 1.5/1.3 mm Hg after 1 year; p<0.001 between groups). The primary composite endpoint occurred in 810 patients in the valsartan group (10.6%, 25.5 per 1000 patient-years) and 789 in the amlodipine group (10.4%, 24.7 per 1000 patient-years; hazard ratio 1.04, 95% CI 0.94-1.15, p=0.49).	Julius S, Kjeldsen SE, Weber M, et al. : Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 2004, 363: 2022– 2031.
METHODS: The Syst-Eur trial included 4695 randomized patients with minimum age of 60 years and an untreated blood pressure of 160-219 mmHg systolic and below 95 mmHg diastolic. The double-blind trial ended after a median follow-up of 2.0 years (range 1-97 months). Of 4409 patients still alive, 3517 received open-label treatment consisting of nitrendipine (10-40 mg daily) with the possible addition of enalapril (5-20 mg daily), hydrochlorothiazide (12.5-25 mg daily), or both add-on drugs. Non-participants (n = 892) were also followed up. RESULTS: Median follow-up increased to 6.1 years. Systolic pressure decreased to below 150 mmHg (target level) in 2628 participants (75.0%). During the 4-year open-label follow-up, stroke and cardiovascular complications occurred at similar frequencies in patients formerly randomized to placebo and those continuing active treatment. These rates were similar to those	Staessen JA, Thijisq L, Fagard R, et al. : Effects of immediate versus delayed antihypertensive therapy on outcome in the Systolic Hypertension in Europe Trial. *J Hypertens* 2004, 22: 847– 857.

previously observed in the active-treatment group during the double-blind trial. Considering the total follow-up of 4695 randomized patients, immediate compared with delayed antihypertensive treatment reduced the occurrence of stroke and cardiovascular complications by 28% (P = 0.01) and 15% (P = 0.03), respectively, with a similar tendency for total mortality (13%, P = 0.09). In 492 diabetic patients, the corresponding estimates of long-term benefit (P < 0.02) were 60, 51 and 38%, respectively.	
METHODS: For the Pittsburgh SHEP cohort, 11- to 14-year death or cardiovascular event rates were compared for active (n = 135) and placebo (n = 133) arms plus normotensive controls (n = 187). Carotid ultrasound and ankle blood pressures were used to identify subclinical atherosclerosis at baseline. RESULTS: Fourteen-year Kaplan-Meier event rate estimates were 58% vs 79% for the active vs placebo groups (P =.001). Eleven-year event rates for the control, active, and placebo groups were 35%, 47%, and 65%, respectively. Compared with controls, the relative risk of an event was 1.6 (95% confidence interval, 1.1-2.4) for the active treatment group and 3.0 (95% confidence interval, 2.1-4.4) for the placebo group. Baseline history of cardiovascular disease was present in 19% of SHEP participants vs 15% of controls (P =.32), and subclinical disease (carotid stenosis or low ankle blood pressure) was detected in 33% of SHEP participants vs 10% of controls (P<.001). Among those with no clinical or subclinical disease at baseline, the ISH group assigned to active treatment had 10-year event rates similar to those of the control group (29% vs 27%), whereas the placebo rates were much higher (69%).	Sutton Tyrrell K, Wildman R, Newman A, Kuller LH: Extent of cardiovascular risk reduction associated with treatment of isolated systolic hypertension. *Arch Intern Med* 2003, 163: 2728– 2731.