Combination treatment for hypertension

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On average, one in four adults has hypertension.[1] This figure is higher in certain regions of the world, and in certain areas within countries. Worldwide, however, the prevalence of hypertension is on the rise. The relationship between level of blood pressure and risk for cardiovascular events is linear and continuous.

Nearly 75% of adults with other cardiovascular disease have hypertension as a comorbidity. Hypertension is associated with shorter overall life expectancy, as well as a shorter life expectancy free of cardiovascular disease.

Hypertension can be said to be controlled or at goal if blood pressure is less than 140/90 mmHg, or less than 130/80 mmHg for those with diabetes, kidney disease or a previous vascular event (e.g. myocardial infarction, stroke, etc).

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Blood pressure control

Not achieving optimal blood pressure control is one of the most common attributable risks for death worldwide. Despite the proven benefits of hypertension treatment in improving mortality and morbidity, the treatment and control of hypertension remain less than optimal. In many clinical trials, the message and concept became clear: reduction of blood pressure is the key driver of benefit in hypertension management.

All five major antihypertension classes of drugs, diuretics, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and beta-blockers (maybe not to be used as single first-line agents) are of benefit by reducing events, and do not differ significantly in their overall ability to reduce blood pressure in hypertension.

In numerous clinical trials, the control of blood pressure is achieved in only about half the time with monotherapy, even under strict trial conditions.

Concept of combination therapy

Combination therapy with two or more drugs will be necessary in the majority of hypertensive patients to achieve target blood pressure. Combination therapy will even be more frequently needed in diabetics and other high risk patients to reach the stricter goal blood pressure in these patients. Different classes of antihypertensive agents, when combined, often have greater antihypertensive effect than each on its own (synergistic effect) and may have better tolerability (two components minimising each other's side effects).

Despite this, the majority of trials of blood pressure lowering have focused on initial treatment with monotherapy.

Combination therapy: when to initiate?

Guidelines on hypertension, recommend that **combination treatment be initiated as first-line therapy** when there is a high cardiovascular risk: when the initial blood pressure is more than 20 mmHg systolic and 10 mmHg diastolic above the target (goal) blood pressure, when there is subclinical organ damage (diabetes, renal, cardiovascular disease).[2] The choice between initiating monotherapy or combination therapy is often based more on wisdom and experience than trial evidence. Combination therapy will also be initiated when monotherapy fails.

Preferred drug combinations[3]

An ACE-inhibitor plus a calcium channel blocker was the most widely used combination in Syst-Eur, Syst-China, the HOT study, Invest (nondihydropyridine), and the ASCOT trial. In ACCOMPLISH, the combination of an ACE-inhibitor and a dihydropyridine calcium channel blocker outperformed the combination of the same ACE-inhibitor and a diuretic (thiazide) in reducing events. Whether this combination will always, under all circumstances be the best, remains to be seen in trials.

An ACE-inhibitor plus a diuretic have been used for many years. An ACE-inhibitor plus indapamide was highly successful in PROGRESS (previous stroke), ADVANCE (diabetes) and HYVET (elderly).

An ARB with a diuretic or calcium channel blocker has been used in the LIFE and SCOPE trials and demonstrated a protective effect.

More than one line of evidence is emerging that an ARB plus a calcium channel blocker or diuretic provides effective blood pressure reduction, a high rate of blood pressure control with a better tolerability profile.

Calcium channel blockers with a diuretic or beta-blocker have been used in the FEVER, ELSA and VALUE trials, with great benefit.

The addition of an aldosterone antagonist (in low dose: 25 mg to 50 mg daily) to a drug regimen in resistant hypertension is often effective.

It is important to realise that there is no single optimal treatment for everyone with hypertension. When combinations of drugs are necessary to control blood pressure, physicians need to have choices.

Fixed dose (single pill) combinations

It was shown that a fixed combination pill, by reducing the number of pills to be taken, improves compliance significantly.[4] The availability of different fixed dose combinations of the same two drugs facilitates better titration. Fixed low-dose combinations are available (e.g. low-dose thiazide plus a low-dose "newer" beta-blocker) and are increasingly released on the market, which contributes to simplicity of administration and reduced side effects. However, much more data are needed on fixed-dose combinations as preferred agents.

Which combination is potentially unwise?

It is prudent not to use a nondihydropyridine plus a beta-blocker, due to excessive heart rate reduction.

The older type of beta-blocker/diuretic combination in high doses favours the development of diabetes and should be avoided (especially in the young and obese individuals).

The combination of an ACE-inhibitor with an ARB has no proven benefit and could lead to more side effects.

Conclusion

New and old evidence strongly supports combination treatment as the most effective way to control blood pressure.

There are a number of likely combinations of drug therapy for hypertension from which the physician can choose. Currently, renin-angiotensin system blockade combined with a calcium channel blocker or a diuretic are commonly used.

Trial		Reference citation	Study rationale and design	Conclusion
Syst-Eur	Systolic Hypertension in Europe	Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Lancet. 1997;350:757-64.	Designed to investigate whether active treatment of isolated systolic hypertension, which occurs in 15% of people 60 years or older, could reduce cardiovascular complications. All patients were initially administered placebo. After stratification, 4 695 patients were randomly assigned to nitrendipine 10-40 mg daily, with possible enalapril 5-20 mg and hydrochlorothiazide 12.5-25 mg, or placebo. Patients withdrawing from treatment were followed up.	Antihypertensive drug treatment, starting with nitrendipine, reduces the rate of cardiovascular complications among elderly patients with isolated systolic hypertension.
Syst-China	Systolic Hypertension in China	Wang JG, Staessen JA, Gong L, Liu L. Chinese trial on isolated systolic hypertension in the elderly. Systolic Hypertension in China (Syst-China) Collaborative Group. Arch Intern Med. 2000;160:211-20.	Designed to explore how the benefits of active treatment of isolated systolic hypertension were distributed across patient groups according to gender and previous cardiovascular complications, and whether the morbidity and mortality results were influenced by age, level of systolic or diastolic blood pressure, smoking or drinking habits, or diabetes mellitus. Patients 60 years or older (systolic BP 160-219 mm Hg, diastolic BP < 95 mm Hg were enrolled. 1 253 patients were assigned to active treatment (initial nitrendipine, 10-40 mg, with possible captopril, 12.5-50 mg, and/or hydrochlorothiazide, 12.5-50 mg). 1 141 control patients received placebo.	In elderly Chinese patients with isolated systolic hypertension, stepwise antihypertensive drug treatment improved prognosis. The benefit was particularly evident in diabetic patients and, for cardiac end points, non-smokers.
HOT	Hypertension Optimal Treatment	Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet. 1998;351:1755-1762.	There is often a higher incidence of cardiovascular complications in hypertensive patients on treatment than in normotensive individuals, possibly as a result of inadequate reduction of blood pressure. The investigators aimed to assess the optimum target diastolic blood pressure, and the potential benefit of a low dose of aspirin in the treatment of hypertension. 18 790 patients, aged 50-80 years with hypertension and diastolic blood pressure of 100-115 mmHg (mean 105 mmHg) were randomly assigned a target diastolic blood pressure. 6264 patients were allocated the target of < 90 mmHg, 6 264 < 85 mmHg, and 6 262 < 80 mmHg. Felodipine was given as baseline therapy with the addition of other agents, according to a five-step regimen. In addition, 9 399 patients were randomly assigned 75 mg/day aspirin and 9 391 patients were assigned placebo.	Intensive lowering of blood pressure was associated with a low rate of cardiovascular events, with benefits when the diastolic blood pressure was lowered 82.6 mmHg. Aspirin significantly reduced major cardiovascular events, particularly myocardial infarction. There was no effect on the incidence of stroke or fatal bleeds, but non-fatal major bleeds were twice as common.
INVEST	International Verapamil SR/ Trandolapril	Pepine CJ, Handberg EM, Cooper-DeHoff RM, et al. Rationale and design of the International Verapamil SR/Trandolapril Study (INVEST): an internet-based randomized trial in coronary artery disease patients with hypertension. J Am Coll Cardiol. 1998;32:1228-37.	In this randomised, open label, blinded end point study, 22 576 hypertensive patients (> 50 years) with coronary artery disease were randomly assigned to one of two arms, CAS (verapamil sustained release) or NCAS (atenolol). Trandolapril and/or hydrochlorothiazide were administered to achieve blood pressure goals of < 140 mmHg (systolic) and < 90 mmHg (diastolic); and < 130 mmHg (systolic) and < 85 mmHg (diastolic) if diabetes or renal impairment was present. Trandolapril was also recommended for patients with heart failure, diabetes, or renal impairment.	The verapamil-trandolapril-based treatment was as clinically effective as the atenolol-hydrochlorothiazide-based treatment in hypertensive patients with coronary artery disease.
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial	Dahlof B, Sever PS, Poulter NR, et al; ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet. 2005;366:895–906.	The failure to prevent coronary heart disease observed in early hypertension trials has been attributed to the disadvantages associated with the use of diuretics and beta blockers. It was suggested that newer drugs would confer advantages. The aim was to compare the effect, on non-fatal myocardial infarction and fatal coronary heart disease, of atenolol plus a thiazide versus amlodipine plus perindopril. This was a multicentre, prospective, randomised controlled trial in 19 257 hypertensive patients, aged 40-79 years, with at least three other cardiovascular risk factors. Patients were assigned either amlodipine 5-10 mg plus perindopril 4-8 mg as required (n=9 639) or atenolol 50-100 mg plus bendroflumethiazide 1.25-2.5 mg and potassium as required (n=9 618). The primary endpoint was non-fatal myocardial infarction and fatal coronary heart disease.	Amlodipine-based therapy prevented more major cardiovascular events and induced less diabetes than atenolol-based therapy.

ACCOMPLISH	Avoiding cardiovascular events through combination therapy in patients living with systolic hypertension	Jamerson K, Weber MA, Bakris GL, et al. or Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med. 2008;359:2417-2428.	The investigators hypothesised that treatment with an ACE inhibitor combined with a dihydropyridine calcium channel blocker would reduce the rate of cardiovascular events more effectively than treatment with an ACE inhibitor plus a thiazide diuretic. 11 506 hypertensive patients at high risk for cardiovascular events were randomised to receive benazepril plus amlodipine, or benazepril plus hydrochlorothiazide. The primary end point was the composite of death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, hospitalisation for angina, resuscitation after sudden cardiac arrest, and coronary revascularisation.	Benazepril-amlodipine was superior to benazepril-hydrochlorothiazide in reducing cardiovascular events in patients who were at high risk for such events.
PROGRESS	Perindopril protection against recurrent stroke study	PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet. 2001;358:1033-1041.	This study was designed to determine the effects of a blood pressure-lowering regimen in hypertensive and non-hypertensive patients with a history of stroke or transient ischaemic attack. 6 105 individuals were randomly assigned active treatment (3 051) or placebo (3 054). Active treatment consisted of a regimen based on perindopril (4 mg), with the addition of the diuretic indapamide at the discretion of treating physicians. The primary outcome was total stroke (fatal or non-fatal).	The regimen reduced the risk of stroke among both hypertensive and non-hypertensive individuals with a history of stroke or transient ischaemic attack. Combination therapy with perindopril and indapamide produced larger blood pressure and risk reductions.
ADVANCE	Action in Diabetes and Vascular disease: preterAx and diamicroN MR Controlled Evaluation	ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet. 2007;370:829-840.	This trial assessed the effects of the routine administration of an ACE inhibitor-diuretic combination on serious vascular events in patients with diabetes, irrespective of initial blood pressure levels or the use of other antihypertensives. 11 140 patients with type 2 diabetes received either a combination of perindopril and indapamide or placebo, in addition to current therapy. The primary end points were composites of major macrovascular and microvascular events, defined as death from cardiovascular disease, non-fatal stroke or non-fatal myocardial infarction, and new or worsening renal or diabetic eye disease.	Routine administration of perindopril and indapamide to patients with type 2 diabetes was well tolerated and reduced the risks of major vascular events, including death.
HYVET	Hypertension in the Very Elderly Trial	Beckett NS, Peters R, Fletcher AE; HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. N Engl J Med. 2008;358:1887-1898.	It was unclear whether there is any benefit in the treatment of patients with hypertension who are 80 years or older; antihypertensive therapy may reduce the risk of stroke, but could possibly increase the risk of death. 3 845 hypertensive patients, 80 years or older, were randomised to receive either indapamide (sustained release, 1.5 mg) or placebo. Perindopril (2 or 4 mg), or placebo, was added if necessary to achieve the target blood pressure of 150/80 mmHg. The primary end point was fatal or non-fatal stroke.	Antihypertensive treatment with indapamide (sustained release), with or without perindopril, in persons 80 years of age or older, is beneficial.
LIFE	Losartan Intervention For Endpoint reduction in hypertension study	Dahlöf B, Devereux RB, Kjeldsen SE, et al; LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet. 2002;359:995-1003.	Left ventricular hypertrophy is a good indicator of risk of cardiovascular morbidity and death. The investigators wanted to establish whether selective blocking of angiotensin II improves hypertrophy beyond reducing blood pressure, and if this reduces cardiovascular morbidity and death. 9 193 hypertensive participants, with left ventricular hypertrophy were assigned losartan-based or atenolol-based treatment for at least four years, until 1 040 patients had a primary cardiovascular event (death, myocardial infarction, stroke).	Losartan prevents more cardiovascular morbidity and death than atenolol for a similar reduction in blood pressure, is better tolerated, and seems to confer benefits beyond reduction in blood pressure.
SCOPE	Study on Cognition and Prognosis in the Elderly	Lithell H, Hansson L, Skoog I, et al: SCOPE Study Group. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. J Hypertens. 2003;21(5):875-886.	The objective was to assess whether candesartan-based antihypertensive treatment in elderly patients, with mild to moderate hypertension, causes a reduction in cardiovascular events, cognitive decline and dementia. 4 964 patients, aged 70-89 years, were assigned randomly to receive candesartan or placebo, with open-label antihypertensive therapy added on if needed. The primary outcome measure was a composite of cardiovascular death, non-fatal stroke and non-fatal myocardial infarction, and secondary outcome measures included cardiovascular death, stroke and myocardial infarction, cognitive function and dementia.	A slightly more effective blood pressure reduction with candesartan-based therapy was associated with a statistically non-significant reduction in major cardiovascular events and with a marked reduction in non-fatal stroke. Cognitive function was well maintained in both treatment groups. Both treatment regimens were generally well tolerated.
FEVER	Felodipine Event Reduction	Liu L, Zhang Y, Liu G, et al; FEVER Study Group. The Felodipine Event Reduction (FEVER) Study: a randomized long-term placebo-controlled trial in Chinese hypertensive patients. J Hypertens. 2005;23(12):2157-2172.	The study was designed to compare the incidence of stroke and other cardiovascular events in patients receiving a low-dose diuretic and a low-dose calcium antagonist combination, with those on low-dose diuretic monotherapy, and assess the effects of a small blood pressure difference at levels lower than those achieved in previous trials. 9 800 Chinese hypertension patients, with additional cardiovascular risk factors/disease, were enrolled. Six weeks after switching to low-dose (12.5 mg) hydrochlorothiazide, if their blood pressure was in the range 140-180 mmHg (systolic) or 90-100 mmHg (diastolic), they were assigned to low-dose felodipine extended release or placebo, and followed up for 40 months.	In these moderately complicated patients, a difference in SBP/DBP as small as 4/2 mmHg is associated with substantial reductions in the incidence of most cardiovascular events.
ELSA	European Lacidipine Study on Atherosclerosis	Zanchetti A, Bond MG, Hennig M, et al; European Lacidipine Study on Atherosclerosis investigators. Calcium antagonist lacidipine slows down progression of asymptomatic carotid atherosclerosis: principal results of the European Lacidipine Study on Atherosclerosis (ELSA), a randomized, double-blind, long-term trial. Circulation. 2002;106:2422-2427.	Usually, the cardiovascular complications of hypertension arise as a result of atherosclerosis. Some antihypertensive agents influence atherosclerosis independently of blood pressure lowering. This trial in 2 334 patients with hypertension compared the effects of four-year treatment with either lacidipine or atenolol on an index of carotid atherosclerosis, the mean of the maximum intima media thicknesses. This index has been shown by epidemiological studies to be predictive of cardiovascular events.	The greater efficacy of lacidipine on carotid intima media thickness progression and number of plaques per patient, despite a smaller ambulatory blood pressure reduction, indicates an antiatherosclerotic action independent of antihypertensive action.
VALUE	Valsartan Antihypertensive Long-term Use Evaluation	Julius S, Kjeldsen SE, Weber M, et al; VALUE trial group. 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.	The trial was designed to test the hypothesis that, for the same blood pressure control, valsartan would reduce cardiac morbidity and mortality more than amlodipine in hypertensive patients at high cardiovascular risk. 15 245 patients, 50 years and older, with hypertension and high risk of cardiac events participated in a comparison of therapy based on valsartan or amlodipine. The trial lasted until at least 1 450 patients had reached a primary endpoint, a composite of cardiac mortality and morbidity. Patients were followed up for 4.2 years.	The main outcome of cardiac disease did not differ between the treatment groups. Unequal reductions in blood pressure might account for differences between the groups.

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