Combination treatment for hypertension

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).

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 combinations³

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 worse?**

It is prudent not to use a nonidipryridine 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.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference citation</th>
<th>Study rationale and design</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syst-Eur</td>
<td>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;330:57-64.</td>
<td>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 bendroflumethiazide 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.</td>
<td>Antihypertensive drug treatment, starting with nitrendipine, reduces the rate of cardiovascular complications among elderly patients with isolated systolic hypertension.</td>
</tr>
<tr>
<td>Syst-China</td>
<td>Wang JL, 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.</td>
<td>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 50 years or older (systolic BP 160-219 mm Hg, diastolic BP &lt; 90 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.</td>
<td>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.</td>
</tr>
<tr>
<td>HOT</td>
<td>Harrison L, Zanchetti A, Carnethons 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.</td>
<td>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 to target diastolic blood pressure, 8264 patients were allocated the target of &lt; 90 mmHg, 6,264 &lt; 85 mmHg, and 6,262 &lt; 80 mmHg. Felodipine was given as baseline therapy with the addition of other agents, according to a five-step regimen. In addition, 9,989 patients were randomly assigned 75 mg daily aspirin and 9,981 patients were assigned placebo.</td>
<td>Intensive lowering of blood pressure was associated with a lower rate of cardiovascular events, with benefits when the diastolic blood pressure was lowered 82.5 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.</td>
</tr>
<tr>
<td>INVEST</td>
<td>Pepine CJ, Handsberg EM, Cooper-Deftiof FM, 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. 1998:32:1207-28.</td>
<td>This randomised, open label, blinded end point study, 22,576 hypertensive patients (&gt;50 years) with coronary artery disease were randomly assigned to one of two arms, (C) verapamil sustained release or (N) placebo. Trandolapril and/or hydrochlorothiazide were administered to achieve blood pressure goals of &lt;140 mmHg (systolic) and &lt;90 mmHg (diastolic) and &lt;130 mmHg (systolic) and &lt;85 mmHg (diastolic) if diabetes or renal impairment was present. Trandolapril was also recommended for patients with heart failure, diabetes, or renal impairment.</td>
<td>The verapamil-trandolapril-based treatment was as clinically effective as the atenolol-hydrochlorothiazide-based treatment in hypertensive patients with coronary artery disease.</td>
</tr>
<tr>
<td>ASCOT</td>
<td>Dahlöf B, Sever PS, Poulter NR, et al. ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amiodipine adding perindopril as required versus atenolol adding bendrofluamide 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.</td>
<td>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 amiodipine 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 amiodipine 5-10 mg plus perindopril 4-8 mg as required ([N=8 659]) or atenolol 50-100 mg plus bendrofluamide 1.25-2.5 mg and potassium as required ([N=8 618]). The primary endpoint was non-fatal myocardial infarction and fatal coronary heart disease.</td>
<td>Antidiabetic-based therapy prevented more major cardiovascular events and induced less diabetes than atenolol-based therapy.</td>
</tr>
</tbody>
</table>
**References**