Hypertension

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Background

Approximately one in four adults has hypertension, a prevalence that increases with age and may reach to two out of three adults older than 70 years of age. In the Framingham Heart Study 65-75% of hypertension in the elderly is of the isolated systolic hypertension variety. Hypertension causes a two- to threefold increased risk of atherosclerotic cardiovascular events. Hypertension clusters with dyslipidaemia, insulin resistance, glucose intolerance and obesity in more than 80% of cases.[1] The great majority of hypertensives thus have additional cardiovascular risk factors. The global cardiovascular risk, of which hypertension is but one component, is best appreciated by the use of risk charts such as the Framingham Risk Score.

When to start treatment

Major guidelines on the management of hypertension recommend initiating antihypertensive drugs in all patients with a systolic blood pressure (SBP) of 140 mmHg or more and/or a diastolic blood pressure (DBP) of 90 mmHg or more, even in the elderly. The target blood pressure should be under 140/90 mmHg in uncomplicated hypertension. A further recommendation is to start treatment at a lower blood pressure range, that is, an SBP of between 130 mmHg to 139 mmHg and DBP between 85 and 89 mmHg in patients with diabetes or a history of cardiovascular or renal disease. The target blood pressure should be under 130/80 mmHg in these complicated hypertensive patients. The general concept is, the higher the global risk of the patient, the lower the blood pressure where drug treatment will be initiated.[2]

Choice of antihypertensive drugs

The main benefit of antihypertensive treatment is the result of blood pressure lowering per se and is largely independent of the type of drug used.

There are five major classes of drugs that are currently used to treat hypertension; they all lower blood pressure adequately and they all lower the risk of cardiovascular events. The issue of equivalence of the various classes of antihypertensive agents, and of various agents within the same class, has been long debated and has not been resolved. If there are differences, they are of small magnitude.

Diuretics

Thiazide diuretics

Thiazides are currently used in low doses, i.e. 12.5 mg to 25 mg per day (or the equivalent dose of other thiazides). Approximately 50% of patients will respond to this low dose given as monotherapy. Thiazides compared to placebo significantly reduce total mortality (by approximately 13%) coronary artery disease (by approximately 10%), stroke (by approximately 40%) and heart failure (by approximately 49%).[3] Thiazide diuretics increase the risk of diabetes mellitus and have the lowest compliance rate of the antihypertensive drugs owing to side-effects (e.g. gout, impotence). Thiazides combined with beta blockers (especially the older type, such as atenolol), particularly in high doses, are currently regarded as unsuitable for first-line treatment of hypertension, as they potentially increase the risk of diabetes mellitus. On the other hand, thiazide diuretics, as well as calcium-channel blockers (CCBs), are still very effective in older patients (over 55 years of age) and people with hypertension (the low renin groups). Diuretics are the most effective class of drugs in preventing heart failure secondary to hypertension, followed by inhibitors of the renin-angiotensin system. This fact supports the use of diuretics with or without inhibitors of the renin-angiotensin system in older patients with hypertension, who are most at risk of developing heart failure.[3]

Thiazide-like drugs

Chlorthalidone is a thiazide-like drug used in the USA and was the diuretic used in the very large Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) in which the diuretic, angiotensin-converting enzyme (ACE) inhibitor and CCB were equal in their reduction of cardiovascular events.

Indapamide has been used together with ACE inhibitors in a number of trials including the very old (over 80 years of age), and is associated with reductions in cardiovascular events.

Loop diuretics

These agents (e.g. furosemide and others) are most appropriate for the treatment of hypertension when there is reduced glomerular filtration rate (less than 30 ml/minute/1.73m^2), i.e. in renal insufficiency.

Aldosterone antagonists

Spironolactone and eplerenone are very useful in the treatment of resistant hypertension. Eplerenone is associated with less gynaecomastia and breast tenderness than spironolactone.

Beta blockers

Some guidelines have downgraded the role of beta blockers in the management of hypertension unless there is a compelling indication such as a prior myocardial infarction. It is commonly believed that the older beta blockers, such as atenolol, do not offer the same stroke protection as other drugs. A recent meta-analysis of 147 randomised trials showed that beta blockers reduced stroke by 17% vs. 29% reduction with other antihypertensive drugs, but have the same effects as other drugs, preventing coronary events and heart failure, and have higher efficacy in patients with a recent coronary event.[4]

Inhibitors of the renin-angiotensin system

A recent meta-analysis concludes that ACE inhibitors and angiotensin-receptor blockers (ARBs) have the same preventive effects on cardiovascular outcomes.[5] These drugs have been tested in numerous trials. They are also considered the drugs of choice in younger hypertensives and in high cardiovascular risk hypertensive patients, for example those with left ventricular hypertrophy, heart failure, left ventricular dysfunction after myocardial infarction, and atherosclerotic heart disease.

Calcium-channel blockers

Numerous trials have established CCBs as effective, safe antihypertensive agents that also reduce cardiovascular events. In fact, recent data suggest that CCBs may have some additional advantage in preventing stroke. It is still unclear if the stroke protection is due to slightly better blood pressure control or a specific protective effect. CCBs are also preferred in patients in whom low renin hypertension is more common, such as in people of African origin and the elderly. It is unclear whether CCBs have an adequate protective effect in preventing heart failure. Recently CCBs have also emerged as an excellent combination with ACE inhibitors and ARBs.

General principles of drug treatment

Because of the linear relationship between cardiovascular risk and increasing blood pressure, any reduction in blood pressure, however small, will have the same proportional risk reduction, regardless of the starting (baseline) blood pressure. This proportional (relative) risk varies between approximately 20% and 30%.

The absolute risk reduction will depend on:

- The pre-treatment (baseline) blood pressure level: The higher the starting blood pressure, the more absolute benefit.
- The global cardiovascular risk of the patient: The higher the absolute risk, the more absolute benefit will be derived from blood pressure lowering.

Blood pressure reduction is the key driver of benefit and this applies to the five major classes of antihypertensive drugs: ACE inhibitors, ARBs, CCBs, diuretics and beta blockers. Some cause-specific outcomes may differ between drug classes, for example CCBs may reduce strokes slightly better. Each of these major classes appears as a reasonable first-line therapy.[6]

The primary aim is to reach a target blood pressure of under 140/90 mmHg for all uncomplicated hypertensives, and under 130/80 mmHg for all diabetics and complicated hypertensives. To reach this goal, multiple drugs may be necessary.

In all age groups (below and above 65 years of age) the benefits of blood pressure lowering are the same, with no differences between the effects of the drug classes on major cardiovascular events.[7]

Preferred (compelling) indications for antihypertensive drugs

- Previous stroke: any blood pressure lowering drug
- Postmyocardial infarction: ACE inhibitor, beta blocker, ARB
- Angina: ACE inhibitor, ARB, beta blocker, CCB
- Chronic renal disease: ACE inhibitor, ARB, loop diuretic
- Diabetes mellitus: ACE inhibitor, ARB
- High coronary heart disease risk: ACE inhibitor, ARB, beta blocker, CCB
- Co-existing migraine: CCB, beta blocker. [8]

Ranking order of antihypertensive drugs

The question is whether there are drugs that should be considered as general overall first choice. However, any all-purpose ranking of drugs for general usage as antihypertensive is unnecessary and probably deceiving.[9]

Combination therapy

Combination drug therapy is traditionally used when monotherapy fails.

Initiation of therapy with a combination of drugs is recommended in the following scenarios:

- If the patient's initial blood pressure is more than 20/10 mmHg above target.
- In a high risk patient, as the aim is to:
  - Reduce blood pressure effectively and rapidly
  - Protect organs (heart, brain, kidney)
  - Have a predictable effect.
- Better initial control of blood pressure is required in order to improve compliance with therapy; the patient has more faith in the treatment.
- A reduction of SBP by 20 mmHg can halve cardiovascular risk.

The following combinations are to be avoided:[10]

- ACE inhibitor and ARB
- Beta blocker and hydrochlorothiazides, especially in high doses.

Preferred combinations include:

- ACE inhibitor and diuretic
- ARB and diuretic
- ACE inhibitor and CCB, e.g. nifedipine, amlodipine, verapamil, felodipine
- ARB and CCB.

New antihypertensive drugs

Aliskiren is a direct inhibitor of renin at the site of its activation. Aliskiren may effectively lower blood pressure given as monotherapy or in combination with thiazide diuretics, CCBs, ACE inhibitors and ARBs. Aliskiren has also been shown to protect against subclinical organ damage when combined with an ARB.

Drugs under investigation, still far from use in the clinical setting, include nitric oxide donors, vasopressin antagonists, neural endopeptidase inhibitors, angiotensin 2 receptor antagonists and endothelin receptor antagonists.

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