Combination therapy in hypertension

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Abstract

Hypertension is one of the most important risk factors for death, heart failure, ischaemic heart disease, stroke and chronic kidney disease. Treatment of hypertension to particularly to goal blood pressure (BP) prevents these complications. In South Africa the reported control rates for treated hypertensives using a goal BP <140/90 mm Hg is about 40%. Control of hypertension remains an elusive goal. The reasons for this are complex, but doctor inertia is emerging as an important barrier to better control rates.

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Introduction:
Hypertension is one of the most important risk factors for death, heart failure, ischaemic heart disease, stroke and chronic kidney disease. Treatment of hypertension, particularly to goal blood pressure (BP), prevents these complications. Despite a range of effective treatments for hypertension, goal BP is achieved in 19-54% of patients worldwide. In South Africa, the reported control rates for treated hypertensives, using a goal BP <140/90 mmHg, is about 40%. This is an overestimate as it does not take into account the lower goal of <130/80 mmHg for diabetics and other high risk patients. Control of hypertension remains an elusive goal. The reasons for this are complex, but doctor inertia is emerging as an important barrier to better control rates.

Doctor inertia – a major stumbling block in the control of hypertension
Paradoxically, despite poor control rates, the majority of doctors are well aware of the importance of hypertension as a major cardiovascular risk factor, are cognisant of local and international guidelines for management of hypertension, and the need to control BP to target. However, in reality there is a gap between theory and practice. Several studies have shown that doctors generally underestimate a patient's cardiovascular risk, overestimate BP control, bias BP measurements to lower levels and tend to blame patients for failure to reach target. There is a reluctance to escalate antihypertensive treatment from monotherapy to combination therapy even when the BP is clearly above target. The main reason cited for failure to do this is that the patient's BP is at an acceptable level. Perhaps subconsciously, there is a fear that low BP is harmful to a hypertensive patient, especially in older persons with isolated systolic hypertension (despite the overwhelming evidence to the contrary).

What is the rationale for combination therapy?
Many studies have shown that target BP is only reached in 30% of patients with hypertension using monotherapy, and therefore it is inevitable that most patients will require combination therapy. This is even more apparent when lower targets are required for diabetics and other high risk patients. Most patients will then require at least 2-3 antihypertensive drugs. For this reason combination therapy is recommended by all major hypertension guidelines. Fixed combinations are preferable as they allow simplicity of dosing and improved adherence.

Besides the need to reach target BP, combination therapy offers additional advantages. Given the multi-factorial nature of essential hypertension it is important to have drugs that act in different mechanisms and potentially interfere with pathophysiology of essential hypertension and its complications; like the activation of renin-angiotensin-aldosterone system (RAAS) and sodium retention. Furthermore, a diuretic stimulates the RAAS and sympathetic activity and an ACE inhibitor blocks the angiotensin cascade and inhibits the sympathetic activity, thereby enhancing the efficacy of each individual agent. Combination therapy may enhance tolerability due to lower doses of each individual agent and block potential harmful metabolic effects of the individual drugs.

Which combinations and why?
Firstly, combination or fixed combination therapy should generally be part of the recommended first line therapies (thiazide or thiazide-like diuretics, ACE inhibitors, calcium channel blockers (CCBs) or angiotensin receptor antagonists (ARBs)) that have shown efficacy in controlled clinical trials.
The principle of combination therapy is to combine two antihypertensive agents that have different mechanisms of action and the combination should enhance the efficacy of the individual agents. In this way, smaller doses of each agent may be used and tolerability is improved. The classical example is the combination of thiazide or thiazide-like diuretic with an ACE inhibitor or ARB, which has led to a plethora of fixed combinations in this class. Diuretics stimulate the RAAS whilst ACE inhibitors and ARBs inhibit it, thus leading to efficacy beyond the individual effects of each drug used as monotherapy. This is particularly pertinent to South Africa because low renin hypertension is common in black hypertensives and ACE inhibitors, as monotherapy, are not particularly effective unless combined with a diuretic. Another important advantage of this combination is that certain adverse effects of diuretics may be minimised e.g. hypokalaemia or possibly predisposition to diabetes.

Another important emerging combination therapy is an ACE inhibitor (or ARB) and CCB. This combination is effective

because each individual agent acts by different mechanism, and thereby, complementing each other's antihypertensive activity. CCBs, in addition to their vasodilating activity, stimulate sympathetic activity and the RAAS, which is inhibited by the ACE inhibitor. However, overriding all these considerations is that in the ASCOT Blood Pressure-Lowering Trial, the combination of amlodipine with perindopril was shown to significantly reduce a range of cardiovascular and stroke endpoints compared to an atenolol/thiazide combination.

Combination of a CCB with a diuretic can be used in certain circumstances, but makes little physiological sense. No fixed combination of a diuretic or CCB is available commercially. Alpha- and β-blockers, and β-blockers and dihydropyridine CCBs, may be used in combination but there is little outcome data to support their use in hypertension. However, carvedilol, a β-blocker with α-blocking properties, has proven benefits in heart failure.

The recommended fixed combinations are summarised in table 1.

Table 1: Recommendations for fixed combination antihypertensive therapy.

1. Recommended combinations
   a. ACE inhibitor (ARB) plus low dose diuretic
   b. CCB plus ACE inhibitor (ARB)
2. Fixed combinations of equivocal benefit
   a. CCB plus low dose diuretic
   b. CCB plus β-blocker
   c. α-blocker plus β-blocker
3 Fixed combinations not generally recommended
   a. β-blocker plus diuretic
   b. β-blocker plus non-dihydropyridine CCB
c. CCB plus α-blocker or direct vasodilator
4. Recommended in special circumstances
   a. ACE inhibitor plus ARB

Which combinations should be avoided?

There are two reasons that certain combinations should be avoided. Firstly, a combination may be effective in lowering BP but in the long term there are adverse effects. A classical example is the β-blocker (especially atenolol)/diuretic combination, which in the long term may predispose to new onset diabetes. Another example is the combination of a β-blocker and a non-dihydropyridine CCB, which could lead to significant bradycardia and heart block.

Secondly, combinations may be ineffective because they have similar mechanisms of actions and little enhancement of BP response. A good example of this would be the combination of vasodilating drugs like a dihydropyridine CCB and α-blockers or hydralazine, or a β-blocker and an ACE inhibitor.

However, there is an emerging concept that in certain circumstances a more complete inhibition of the RAAS is required to control target organ damage. This is best achieved by the combination of an ACE inhibitor and ARB. For instance in patients with renal disease where proteinuria is not sufficiently reduced by either agent, the other may be added.

When to use combination therapy *ab initio*?

In general terms, any patient presenting with a sustained BP > 180/110 mm Hg (Grade 3 hypertension) requires immediate initiation of combination therapy unless there are compelling reasons not to do so. It is extremely unlikely that this patient will achieve target BP with monotherapy. Another category of patient requiring initial combination therapy is a high risk patient, e.g. diabetic, who has a BP > 160/100 mmHg. Again, because of the lower target BP (<130/80 mmHg), this patient is unlikely to reach goal on monotherapy. This approach shortens the time period for uncontrolled BP and increases the confidence of the patient, who is unlikely to feel let down because BP will be at, or close to, target at follow-up.

Is their a place for a polypill?

It is increasingly recognised that patients with hypertension often have co-existent hyperlipidaemia and other cardiovascular risks. The ASCOT Lipid-lowering Study clearly showed the addition of atorvastatin 10mg daily was clearly beneficial to hypertensive patients almost regardless of starting cholesterol. This has led to the concept of the polypill where multiple drugs are combined to address different cardiovascular risks. The antihypertensive plus statin combination (e.g. Caduet®) is the most likely to succeed because of proven efficacy and safety of the individual components. It is anticipated that more fixed combinations in this class will be developed. However, an aspirin/statin/antihypertensive fixed combination is not advised because of the potential dangers of aspirin in individual patients. For instance, if the BP is not controlled there is the risk of haemorrhagic stroke, aspirin allergy is not uncommon and certain patients may be at risk for gastrointestinal haemorrhage.

Conclusion

Twenty five years ago fixed combination antihypertensive therapy was frowned on by academics possibly because only high dose combinations were available, leading to increased risk of adverse events. However, today fixed combinations are to be encouraged because they offer better dosing ranges, simplicity of dosing, better adherence, less side effects and, most importantly, better BP control.

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This article has been peer reviewed

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