Treating hypertension – the race against time

**KEY MESSAGES**

- Treating hypertension with medication saves lives.
- General practitioners need to take a more active role in managing hypertension in South Africa.
- There is a great need for a simplified approach to treating hypertension in South Africa.
- Antihypertensive medication is the most effective and cost-effective way of controlling blood pressure.
- In the stable, hypertensive adult patient (younger than 80 years) with blood pressure >160/100mmHg, therapy should start with two drugs given as a single pill, as stepped care takes too long and is associated with poorer adherence.
- One of the foremost advantages of a single-pill combination is that it minimises the risk of patients interfering with their medication and favouring/eliminating a drug they associate with a particular side-effect.
- Clinicians should choose combinations that have different but synergistic physiological effects.
- Single-pill combinations simplify therapy and help patients to reach target blood pressure quickly.14

Cardiovascular mortality risk doubles with each 20/10mmHg increment in systolic/diastolic blood pressure in adults (40-69 years).1 South Africa has a three-fold higher hypertension-associated mortality rate than the United States. This is primarily due to the dramatic increase in hypertension prevalence, particularly among young adults under 24 years of age, which has almost trebled over the past 10 years (Figure 1).2

Hypertension in this youthful setting is often related to obesity. “The treatment of these young hypertensive patients who do not yet have complicating cardiovascular or other disease needs a unique strategy of intervention, including lifestyle modification and medication protocols,” Professor Rayner pointed out.

![Figure 1. Trends in the prevalence of hypertension in South African men](image-url)

“In the face of this epidemic, the management of hypertension must be simplified, with the use of single-pill combinations of antihypertensive medications being a cornerstone of therapy.”
“Death from hypertension in South Africa occurs predominantly in the economically active population, which highlights the need for doctors to adopt a much more aggressive approach to hypertension detection and management,” he said.

“Already in my practice, 20% of hypertensive patients are also HIV-infected and the epidemics of HIV and hypertension are on a collision course in South Africa. This represents a truly frightening paradigm for health care in the country,” Professor Rayner noted.

The state of hypertension care in South Africa

The screening, detection and management of hypertension are characterised globally by the Rule of 50; 50% of patients do not realise they are hypertensive and do not seek treatment; 50% of patients who know they are hypertensive are either not on treatment or do not take their medication.

Real-life research into patients being treated for hypertension in South Africa has shown that 60% of hypertensive patients are not well controlled and do not reach their target blood pressure. Of those patients not at target, some 40% were only advised to undertake lifestyle changes and, for a further 20%, there was no treatment plan in place to get them to target. This inertia in efforts to get patients to appropriate targets underscores the need for a more intensive approach. This research included patients being treated by primary care practitioners in both the private and the public sector in South Africa. ³

“There is certainly no room for complacency about hypertension care in South Africa,” Professor Rayner noted, “particularly as the PURE study showed that many black South African patients with a normal blood pressure at their first clinical visit in the study progressed to hypertension within a five-year period.” ⁴

Globally, there is a huge variation in the efficacy of hypertensive care and South Africa ranks with countries like China among those with the lowest efficacy. The USA ranks among the best in the world.⁵ “The Americans achieved excellent results because they have a very cohesive policy in place with a unified message about the detrimental effects of high blood pressure (Table 1).” ⁶

Lifestyle is important in hypertension management but once an individual has established hypertension, lifestyle changes are much harder to introduce. Lifestyle efforts should be focused on the young hypertensive. “While reducing sodium intake is also vital at an individual and population level, what is not fully realised across the health care system in South Africa is that antihypertensive medication is the most cost-effective way of controlling hypertension and preventing future disease,” Professor Rayner said.

Table 1. The treatment of hypertension: a remarkable success story in the USA

- 90% of the public is aware of the relationship between high blood pressure, stroke and heart disease.
- Every six months, 75% of the population has their blood pressure measured and virtually every American has had their blood pressure measured at least once.
- Visits to physicians for hypertension have increased 10-fold, a clear indication that patients have heard the message to see their doctor.
- Hypertension is the primary reason adults visit their physicians.
- Most physicians are actively treating patients with less severe degrees of elevated blood pressure.
- Today, 81% of Americans are being treated.
- >50% have their blood pressure controlled at levels <140/90mmHg.
The state of hypertension care in South Africa

“There is, in my view, an unfortunately retrogressive step being advised by the American JNC 8 breakaway committee. It is proposing the initiation of treatment in adults over the age of 60 years only when blood pressure is 150/90mmHg or higher. This will take some six million Americans off their hypertension medication regimen with adverse consequences for the patient and the health care system. This has introduced an element of disagreement into the generally accepted view of when hypertension should be treated.1

“In South Africa, we are likely to retain the approach of treating hypertension from levels of 140/90mmHg and higher,” Professor Rayner said. “It is also vital that as clinicians we develop and maintain a unified approach to determining and treating hypertension across the country and not be diverted by this recent development.”

Targets – and how to get there

The JNC 8 Breakaway Committee recommends starting hypertension treatment with low-dose monotherapy for the average stable hypertensive patient with moderately increased blood pressure and adding a second drug in a stepwise approach, until the desired target blood pressure is achieved.

In patients who are not elderly but have more severe hypertension (blood pressure levels of 160/100mmHg and higher), initiation of two-drug therapy is recommended, preferably given as a single pill. This approach is also advocated by the ESH/ESC, the American Hypertension Society and the International Society for Hypertension.8

“The problem with the stepped care approach for the average stable patient, also currently the approach of the South African hypertension guidelines, is that it takes too long to implement, increases the incidence of side-effects and leads to patient loss of confidence in their ability to control their blood pressure, thereby reducing compliance,” Professor Rayner noted (Figure 2).

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FDC – Fixed-dose combinations; RAS – Renin angiotensin system; CCB – Calcium channel blocker

Figure 2. Fixed-dose combinations from the outset versus stepped care

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Stepped care versus initiating fixed-combination therapy

Side-effects
In the stepped-care approach, which starts with monotherapy using a single drug of the physician’s choice and then increasing the dose of the agent before adding another medication, the incidence of side-effects is increased, while less blood pressure lowering is achieved with each increase in dose. This increase in side-effects occurs with all antihypertensive medications except ACE-inhibitors/ARBs, according to an extensive meta-analysis of 354 randomised trials, involving 56,000 patients (40,000 on treatment, 16,000 on placebo).

Figure 3. Dose versus toxicity in different drug classes

Figure 4. Working in synergy – CCBs and ACE-inhibitors
TREATING HYPERTENSION

Table 2. Tolerability of perindopril and amlodipine in fixed-dose *Combination over the 60 days of the STRONG study*

<table>
<thead>
<tr>
<th>Treatment-related adverse event</th>
<th>Patient [n (%)]</th>
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<tbody>
<tr>
<td>Resulting in study withdrawal</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>5 (0.4)</td>
</tr>
<tr>
<td>Ankle oedema</td>
<td>3 (0.2)</td>
</tr>
<tr>
<td>Cerebral haemorrhage</td>
<td>1 (0.08)</td>
</tr>
<tr>
<td>Not resulting in study withdrawal</td>
<td></td>
</tr>
<tr>
<td>Mild cough</td>
<td>14 (1.1)</td>
</tr>
<tr>
<td>Ankle oedema</td>
<td>6 (0.5)</td>
</tr>
<tr>
<td>Headache with dizziness</td>
<td>4 (0.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (0.2)</td>
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*Perindopril 5mg/Amlodipine 5mg

Adherence to therapy

Adherence to hypertension therapy is generally poor. A recent study showed that within one year about 50% of patients had stopped taking their medication. Among treated with the five main categories of blood-pressure lowering drug in single dosage and in combination (Figure 3).^9

When combinations are used from the outset, efficacy is increased and adverse effects are fewer.^9 For example, reductions in potassium levels are less dramatic when low-dose thiazides are used in combination with other agents, such as ACE-inhibitors, than when used alone. Ankle oedema is less frequent when a CCB is used in combination with an ACE-inhibitor. This was shown in the STRONG trial, which used a single-pill combination of perindopril and amlodipine in daily clinical practice (Table 2).^10

The beneficial result from using this particular combination of two drugs is because of their different but complementary physiological actions, which tend to offset this often painful and distressing oedema (Figure 4).

“...you get better control earlier with fixed-combination therapy and this translates into benefits and reduced cardiovascular events” Professor Brian Rayner

Figure 5. Time course of adherence/compliance parameters (execution, persistence)^12

Vrijens, B. et al. BMJ 2006;336:1114-1117
Efficacy of fixed-dose combinations

One of the key studies of free versus fixed-dose combinations was ACCOMPLISH. It involved patients at very high risk of cardiovascular events, including diabetics. It showed that initiation of therapy with a fixed-dose of benazapril/amlodipine in a single pill achieved target blood pressure control in 70% of patients as compared to the 30% control achieved with forced titration using the combination of benazapril and hydrochlorothiazide, also initiated as a single pill.¹⁴ (Table 3)

A retrospective evaluation of the outcomes of patients treated from the outset with a fixed-drug combination compared to similar patients treated with monotherapy and later switched to combination therapy provides a real world view of the consequences of these two different approaches (Figure 7).¹⁴ “Although not a prospective randomised

Table 3. Summary of the advantages of early use of a fixed-dose combination

<table>
<thead>
<tr>
<th>Advantage</th>
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<tbody>
<tr>
<td>Achieves better blood pressure control, particularly if synergistic physiological actions are chosen, e.g. low-dose thiazides and RAS blocker; ACE-inhibitor and CCB¹³</td>
</tr>
<tr>
<td>Achieves earlier blood pressure control¹³</td>
</tr>
<tr>
<td>Fewer traditional side-effects¹³</td>
</tr>
<tr>
<td>Fewer withdrawals from medication¹⁴</td>
</tr>
<tr>
<td>Improved patient compliance¹³</td>
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</tbody>
</table>

Footnote: Key summary by Professor Brian Rayner
Which combination therapy?

“In South Africa, thiazide and thiazide-like diuretics still have a place in the management of blood pressure, but low-dose thiazides should generally be used. In addition, we really do need a study of indapamide and chlorthalidone in our black African population,” Professor Rayner noted.

“The ASCOT-BPLA study is a landmark trial that changed clinical practice. It showed the value of a CCB/ACE-inhibitor approach in patients at high risk of cardiovascular events as compared to an atenolol/thiazide combination.

“All-cause mortality risk was reduced (11%) in the ASCOT study and the cardiovascular mortality risk significantly reduced in those receiving the CCB ± ACE-inhibitor combination, despite a small difference in blood pressure in the two treatment arms (2mmHg).” There has been much discussion trial, the results are interesting and show that the initial combination therapy was associated with a significant reduction in the risk of cardiovascular events or death. This was found to be primarily due to the rapid achievement of target blood pressure.”

**PRACTICE TIPS FROM THE EXPERT PANEL – DR RAS THERON, DR NAOMI RAPEPORT AND PROFESSOR BRIAN RAYNER**

- Start with low-dose combinations in young people.
- The use of combination therapy does not crash blood pressure, but the more complex the situation, e.g. in the elderly and patients with comorbidities, be more careful in your approach.
- Getting patients to understand the disease of hypertension is vital; sharing the concept of vascular age from the Framingham Risk Factor tables can help the patient to understand the need to take medication to maintain and even reduce their vascular age. - Dr Naomi Rapeport.
- Professor Brian Rayner advises indapamide as a diuretic in the elderly. Test postural hypertension at every visit by asking vulnerable elderly patients to stand up.
- Cough is an issue with ACE-inhibitors, but should not be a reason for avoiding this therapy.
about the reasons for these significant outcome benefits with amlopidine ± perindopril. We now believe it is likely to be due to better nocturnal blood pressure lowering and less visit-to-visit and within-visit variability, factors which are now known to be associated with improved outcomes,” Professor Rayner concluded.

References:


