Strategies to improve blood pressure control and cardiovascular outcomes in hypertensive patients

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Abstract
Hypertension is a major contributor to cardiovascular morbidity and mortality. However, blood pressure control in clinical practice still falls short of treatment recommendations. The reasons for this are manifold and patient noncompliance with medication has been identified as one important factor.

In this article we discuss the various reasons for patient noncompliance and look at strategies to improve adherence, for example simplifying the medication regimen and reducing side effects in an asymptomatic disease such as hypertension. In this regard, combination treatment, and specifically fixed-dose combinations, has come a long way in enhancing tolerability, reducing counter-regulatory drug mechanisms and bringing blood pressure closer to target.

Furthermore, we investigate the possibility of some combinations having clinical benefits beyond blood pressure control, as this may improve long-term cardiovascular outcomes. On the other hand, certain combinations may only have positive clinical outcomes in carefully selected patient groups and are not recommended for routine management of hypertension.

Lastly, issues such as escape mechanisms in the renin angiotensin aldosterone system (RAAS) are discussed – these mechanisms play a role in treatment failure and may require the use of new antihypertensive drug classes, such as direct renin inhibitors.

Background
Twelve years ago, it was estimated that at least 25% of the adult population in South Africa are hypertensive according to the World Health Organization’s definition of hypertension (blood pressure equal or above 140/90 mmHg).1 Diagnosis and management of high blood pressure is generally poor, and is particularly poor in rural areas.1,2 There is a clear upward trend in prevalence of hypertension, both locally and internationally.2,3,4 By 2025 it is projected that 29% of adults worldwide will be hypertensive, with developed countries extrapolated to be at 42%.2,4

Blood pressure (BP) is a continuous variable with normal distribution in the population.5 With every increase of systolic blood pressure (SBP) of 20 mmHg or in diastolic blood pressure (DBP) of 10 mmHg, over the range from 115/75 mmHg there is a 2-fold increase in mortality related to stroke or coronary artery disease (CAD). This makes hypertension an important risk factor for cardiovascular disease (CVD).5,6 SBP, especially, is a powerful predictor of CAD and adverse renal outcomes.5

Pharmacological treatment of hypertension has been proven effective in protecting against cardiovascular complications such as stroke, myocardial infarct (MI), heart failure and deterioration of renal function.5,7,8,9,10 Effective medical therapies for hypertension have been available for almost 50 years.11 Yet, worldwide only about 50% of patients achieve adequate BP reduction.5,12 In South Africa only 40% of patients achieve the conservative goal of BP < 140/90 mmHg.12

Socio-economic conditions, noncompliance with treatment and inadequate prevention strategies have been shown to be barriers to effective blood pressure control.5,11 In addition, increased life expectancy, reduced physical activity and higher obesity rates are factors that result in antihypertensive treatment resistance.5

Patient adherence
Patient adherence refers to the ability and willingness of a patient to follow health-related advice, take medication as it was prescribed, attend all follow-up consultations and complete the recommended tests.5

It has been shown that about half of patients discontinue their antihypertensive therapy within the first 6–12 months of therapy.5,13 Nonadherence leads to poor BP control, which
increased dosing frequency negatively affect adherence. On the patient from a twice daily dose to a once daily dose. The other hand, by changing the dosage regimen from a 3-times daily dose to a once daily dose, adherence may be increased by the patient may experience from his/her antihypertensive medicine may be deemed as unacceptable in an otherwise asymptomatic disease. Unfortunately, increasing the dose of a medicine in an attempt to improve BP control and at the same time avoid the addition of a second drug, usually results in dose-dependent side effects. This problem can somewhat be overcome by using combination therapy, as medicines can be given at a lower dose than either drug in monotherapy.

Possible reasons for nonadherence are:
- The complexity of the medication regimen
- Misunderstandings regarding the regimen
- Asymptomatic nature of hypertension, therefore the patient does not feel ill and hence may not see the need to take the medication
- The view that medicines are unnatural and hence unsafe
- The patient might feel that chronic medicine use denotes ill health
- Adverse effects, which may be unacceptable to the patient when treating an asymptomatic disease
- A suboptimal patient-physician relationship

Strategies that could improve patient adherence to medication:
- Simplifying the medication regimen
- Drug selection according to the patient’s lifestyle or characteristics
- Electronic medication monitors
- Enhanced patient-physician communication
- More in-depth patient education
- Behavioural changes for the patient e.g. BP diary, self monitoring of BP
- Continuous monitoring of patient adherence done by the physician
- Social support of family and healthcare workers

Simplifying the medication regimen
Since adequate BP control is only experienced by 30–47% of patients on monotherapy, at least half of patients may be on an intricate regimen. One should also not forget that hypertension often occurs together with other chronic conditions, such as dyslipidaemia or diabetes, each requiring its own pharmacological intervention and thus further adding to the patient’s pill burden.

There is an inverse relationship of the complexity of the dosage regimen to patient compliance. Treatments related to increased dosing frequency negatively affect adherence. On the other hand, by changing the dosage regimen from a 3-times daily dose to a once daily dose, adherence may be increased by as much as 25%. Adherence is similarly improved by changing the patient from a twice daily dose to a once daily dose.

Reducing side effects and counter-regulatory mechanisms
As stated earlier, one reason for noncompliance is that the side effects the patient may experience from his/her antihypertensive medicine may be deemed as unacceptable in an otherwise asymptomatic disease. However, the combination of trandolapril and verapamil may have favourable metabolic effects by increasing the delivery of glucose to skeletal muscles through increased blood flow to the muscle due to the vasodilatory effect of the CCB. CCBs furthermore increase insulin sensitivity at the cellular level. Lastly, combining an ACEI and CCB causes stimulation in the production of nitric oxide through kinin-dependant mechanisms, thereby decreasing all levels of inflammatory markers. Preclinical evidence suggests that this combined therapy may be effective in the management of cardiac ischaemia and left ventricular hypertrophy by limiting inflammation and restoring the normohormonal balance, fibrinolytic balance and arterial distensibility.
Fixed-dose combinations
The use of fixed-dose combination medicines is an alternative approach to multiple drug therapy in order to increase patient adherence. In fact, the risk of noncompliance can be reduced by up to 24% when fixed-dose combinations are compared to free-drug combinations.

There are already a few fixed-dose combinations, which combine ARBs or ACEIs with diuretics or calcium channel blockers, available in the market. See Table I.

There is a lack of comparative data on these combinations. However, in the ACCOMPLISH trial it was demonstrated that a fixed-dose ACEI/CCB combination significantly reduced the risk of morbidity and mortality relative to ACEI/diuretic therapy, despite similar BP reductions. Furthermore, in hypertensive patients with impaired glucose tolerance, the fixed combination of trandolapril and verapamil reduced the risk of new-onset diabetes, in comparison to an ARB/thiazide combination.

As shown in the discussion above, there is evidence to support the use of fixed-dose combination therapy with one agent acting on RAAS and a CCB in high-risk patients. The combination of an ARB (valsartan) and the CCB amlodipine is therefore an attractive option for hypertensive therapy. In studies where amlodipine and valsartan were used in a fixed-dose combination, it was seen that, overall, there was a significantly greater reduction in blood pressure with the combination therapy than with either agent alone. In particular there were noteworthy decreases in SBP, especially in patients with stage 2 hypertension (SBP ≥ 160 mmHg and/or DBP ≥ 100 mmHg). In view of the powerful link between SBP and CV risk, the introduction of a fixed-dose ARB/CCB combination may be a useful strategy in the management of CV morbidity and mortality.

Whether the fixed-dose combination of ARB and CCB is superior to other combinations in terms of CV and renal outcomes is not clear. In a 6-week study of valsartan/amlodipine vs lisinopril/hydrochlorothiazide (HCTZ), the mean SBP reduction with the valsartan-based treatment was -35.8 mmHg compared to -31.8 mmHg with the lisinopril-based regimen, but the difference was not statistically significant. In addition, both treatments were equally well tolerated.

In elderly patients, an ARB/CCB regimen may be better tolerated than combinations containing HCTZ. In one study conducted in patients aged 75 to 89 years, the combination of valsartan 160 mg/amlodipine 5 mg resulted in significantly less orthostatic hypotension and less profound changes in potassium and uric acid compared to irbesartan 300 mg/HCTZ 12.5 mg.

<table>
<thead>
<tr>
<th>ARB</th>
<th>ACEI</th>
<th>CCB</th>
<th>Diuretic</th>
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<tr>
<td>Adco-Zetomax co®</td>
<td>Lisinopril</td>
<td>Lisinopril co®</td>
<td>HCTZ</td>
</tr>
<tr>
<td>Accuretic®</td>
<td>Quinapril</td>
<td>Quincace Co®</td>
<td>HCTZ</td>
</tr>
<tr>
<td>Co-Renitec®</td>
<td>Enalapril</td>
<td>Enap-Co®</td>
<td>HCTZ</td>
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<tr>
<td>Zaneril®</td>
<td>Enalapril</td>
<td>Lercanidipine</td>
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<tr>
<td>Tri-Plen®</td>
<td>Ramipril</td>
<td>Telmisartan</td>
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<tr>
<td>Tanka®</td>
<td>Trandolapril</td>
<td>Verapamil</td>
<td></td>
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<tr>
<td>Co-Diovan®</td>
<td>Valsartan</td>
<td>HCTZ</td>
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<tr>
<td>Co-Micardis®</td>
<td>Telmisartan</td>
<td>HCTZ</td>
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<tr>
<td>Co-Irbewin®</td>
<td>Irbesartan</td>
<td>HCTZ</td>
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<td>Coaprol®</td>
<td>Valsartan</td>
<td>Amlodipine</td>
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<td>Atacand plus®</td>
<td>Candesartan</td>
<td>HCTZ</td>
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<tr>
<td>Cozaar Comp®</td>
<td>Losartan</td>
<td>HCTZ</td>
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<td>Teveten Plus®</td>
<td>Eprosartan</td>
<td>HCTZ</td>
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ARB – Angiotensin receptor blocker; CCB – Calcium channel blocker; ACE I – Angiotensin converting enzyme inhibitor; HCTZ – Hydrochlorothiazide
The mean reduction in ambulatory BP was similar in the two treatment groups.20

Based on the efficacy and tolerability profile of the amlodipine plus valsartan regimen, fixed-dose combinations of these drugs are becoming increasingly appealing.10

There are other advantages of fixed-dose combination medicines, which include:

• **Cost:** Although the immediate or direct medication cost may be higher compared to individual generic combinations, fixed-dose combinations may offer downstream cost savings by increasing the adherence and thus decreasing health complications and hospital visits.14,16,21
• **Wellness:** There is a psychological aspect, because of an association between the number of pills taken by patients and their perceived health. By decreasing the pill burden, one can improve the patient’s mental as well as physical health without changing the actual drugs.13
• **Convenience and safety:** It is more convenient for the patient to take one tablet. The lower doses used in combination therapy result in increased safety profiles. A single fixed-dose combination may help to alleviate confusion in the elderly and may stop them from skipping a dose or doubling up on a dose.16

**Unconventional combinations in high-risk patients**

A few unusual combinations of antihypertensive medicines are not as yet found in fixed-dose combination tablets, but may be beneficial in selected patient groups.

CVD usually starts with risk factors like hypertension, which advances to conditions like atherosclerosis, target organ damage and ultimately heart failure, MI, stroke or death. ACEIs and ARBs are each effective in the management of all stages of CVD, as both medicines can reverse or prevent endothelial dysfunction and atherosclerosis and have both been shown to decrease target organ damage in the brain, kidney and heart.22 More specifically, each drug has been shown to have renoprotective effects that are partially independent on BP reduction.23

However, dual RAAS blockade may not further reduce CV events.25,23,24 For example, the ONTARGET study in > 25 000 patients with vascular disease or high-risk diabetes, found that the combination of an ARB with an ACEI was associated with more adverse events without an increase in clinical benefit.25,24

In this population, the primary composite endpoint (doubling of serum creatinine, dialysis or death) occurred more commonly in patients receiving the combination of ramipril and telmisartan than patients with vascular disease or high-risk diabetes, found that the combination of an ARB with an ACEI was associated with more adverse events without an increase in clinical benefit.25,24

From these results it can be concluded that it is not advisable to use an ARB/ACEI combination routinely in the treatment of hypertension.24 Dual RAAS blockade using an ARB plus ACEI may however be considered in selected patients with proteinuria, such as diabetic patients without other diseases.23,24,25 Dual RAAS blockade has also been shown to be beneficial in chronic heart failure (CHF) patients with low ventricular ejection fraction (≤ 40%), but not in all CHF patients.13,26,27 Where indicated, the ARB/ACEI combination should be used with caution; close monitoring of potassium levels and kidney function should always be done.22,24

**Novel antihypertensive drugs**

Current antihypertensive therapy may prove suboptimal due to “escape mechanisms”. As discussed above, thiazide diuretics have a counteracting feedback on the RAAS. While ACEIs block the conversion of angiotensin I (Ang I) to angiotensin II (Ang II), there are non-ACE pathways which stimulate the production of Ang II and these pathways become more pronounced under the conditions of ACE inhibition.11 Furthermore, inhibition of RAAS, either by ACEI or ARB, increases renin release by reducing the negative feedback effect of Ang II.11,28 The increased renin eventually restores Ang II levels.13 The rate-limiting step in RAAS is the conversion from angiotensinogen to Ang I under the influence of renin, which always made renin inhibition an attractive option for RAAS blockade.11,25,28 Please refer to Figure 1 for a simplified schematic representation of the RAAS.

A new antihypertensive class that directly inhibits renin is an important strategy to achieve optimal hypertensive control.28 Such a drug has recently become available in other countries and presumably will be making its way to South Africa soon. This new class may indeed help uncontrolled hypertensive patients, as animal studies have shown an elevation in blood pressure in rats that had increased copies of the angiotensinogen gene, but not in rats with an increase in copies of the ACE gene.11

The only agent currently available in this class is aliskiren, as other investigational renin inhibitors (remikiren, enalkiren, ditekiren and zanikiren) were limited by their short half-life, poor oral bioavailability and high cost.11,29,30 Aliskiren has a long half-life, which makes it suitable for a once daily regimen.11,28 It has been proven effective in doses between 75 and 300 mg/day; doses below 75 mg/day had no BP lowering effect and doses above 300 mg showed marked increase in the side effects, without any additional BP reduction.11,28 The antihypertensive effect of aliskiren is comparable in men, women and in patients of different ages.28 Monotherapy of aliskiren is well tolerated with the antihypertensive effects comparable to losartan, valsartan, irbesartan, lisinopril, ramipril and HCTZ.11,28,30

The major side effects of aliskiren are listed below11,31:

• **Diarrhoea**
• **Rash 1%**
• **Increased creatine kinase level**
• **Cough 1%**
• **Excessive hypotension 0.1%**
• **Acute renal failure**
• **Angioedema 0.06%**

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Similar to ARBs, ACEIs and HCTZ, aliskiren does cause an increase in plasma renin concentration (PRC) by reducing the levels of Ang II. However, unlike ACEIs and ARBs, aliskiren decreases the plasma renin activity (PRA) when used in monotherapy or when combined with HCTZ.\(^{11,28,30}\) It will become important to clarify whether the high levels of PRC seen with the use of aliskiren will translate into biological effects through the stimulation of (pro)renin receptors.\(^{28,30}\)

As monotherapy, aliskiren should be reserved for patients who cannot tolerate ARBs or ACEIs, or for patients where ARB or ACEI therapy has proven ineffective.\(^{25,28}\) Aliskiren plays an important role in combination therapy: its antihypertensive effect is improved by drugs that elicit an increase in PRA e.g. ACEIs, ARBs and diuretics.\(^{28,30}\) See Table II for results of studies investigating combination therapy. These combinations are well tolerated, however when implementing strategies involving dual blockade of RAAS, one should be cautious of hyperkalaemia, especially in patients with renal dysfunction.\(^{11}\)

Optimal RAAS suppression is an important goal in anti-hypertensive therapy. Currently, when combining an ARB and an ACEI, optimal RAAS suppression is not achieved due to the compensatory feedback mechanisms in renin release and increased PRA. Renin inhibitors however neutralise any increase in PRA and prevent the formation of Ang I and II, thereby effectively blocking the compensatory feedback mechanism.\(^{11,28,30}\)

Although combination therapy with aliskiren lowers BP more effectively than monotherapy, it still remains to be seen whether these treatment combinations will translate into clinical outcomes such as reduced morbidity and mortality.\(^{25,30}\) In the AVOID study, which recruited patients with type 2 diabetes mellitus and proteinuria, subjects were given 300 mg of aliskiren in addition to losartan 100 mg per day. The study showed a 20% reduction in proteinuria independent of BP control. However, this did not transpire into a significant change in renal function.\(^{11,25}\)

**Conclusion**

In conclusion, it can be seen that the reasons for suboptimal BP control are many and varied. Nonadherence to medicine is one of these reasons and can be addressed somewhat by changing a
patient to a fixed-dose combination, as this reduces the patient’s pill burden and may reduce side effects. The high interpatient variability seen with antihypertensive treatment can account for patients whose BP remains uncontrolled despite compliance with therapy. One way of addressing this is by using combinations of hypertensive medicines with complementary mechanisms of actions, thereby increasing the reduction of BP.

Unconventional antihypertensive combinations e.g. dual RAAS blockade using an ARB plus ACEI seem to only be beneficial in specific patients like CHF patients with a low ventricular ejection fraction (≤ 40%) and possibly diabetics with proteinuria but without any comorbidities. Patients on dual RAAS blockade must have close monitoring of their potassium levels and kidney function. Novel antihypertensives like aliskiren should be reserved for the treatment of hypertension where other RAAS inhibitors, in combination with other antihypertensive drug classes have been tried and are poorly tolerated or ineffective.

However, patient monitoring by pharmacists and doctors remains imperative in the fight to lower BP. Without constant counselling and feedback between healthcare professionals and the patient, an uncontrolled patient may remain just that.

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**Table II: Combination therapy with aliskiren**

<table>
<thead>
<tr>
<th>Combination</th>
<th>Study design</th>
<th>BP reduction</th>
<th>Effect on PRA and PRC</th>
<th>Other effects</th>
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<tbody>
<tr>
<td>Aliskiren 150–300 mg and HCTZ</td>
<td>Double-blind RCT; 490 obese, hypertensive patients not responding to 25 mg HCTZ; low dose aliskiren, irbesartan, amlodipine or placebo added to HCTZ for 4 weeks, then higher doses of add-on drugs for 4 weeks</td>
<td>BP reduction with aliskiren/HCTZ combination superior to HCTZ monotherapy, but similar to BP reductions with irbesartan/HCTZ and amlodipine/HCTZ at 8 weeks</td>
<td>Reduction in PRA when used in combination, compared to an increase in PRA seen with HCTZ alone</td>
<td>Aliskiren has potassium-sparing effects and may mitigate the hypokalaemia caused by HCTZ</td>
</tr>
<tr>
<td>Aliskiren 150 mg and CCB</td>
<td>Double-blind RCT; 545 patients uncontrolled on amlodipine 5 mg divided into 3 groups for 6 weeks: continue amlodipine 5 mg, increase dose to 10 mg or add aliskiren 150 mg to amlodipine 5 mg</td>
<td>Combination of aliskiren with amlodipine 5 mg showed a greater reduction in BP than amlodipine 5 mg alone, but a similar reduction to amlodipine 10 mg therapy</td>
<td>Reduction in PRA of 9.9% with amlodipine 5 mg and a 74.4% reduction with aliskiren 150 mg/amlodipine 5 mg combination; amlodipine 10 mg caused an increase in PRA of 58%</td>
<td>Peripheral oedema was less frequent when using amlodipine 5 mg/ aliskiren combination than amlodipine 10 mg alone</td>
</tr>
<tr>
<td>Aliskiren 150–300 mg and ARB</td>
<td>Double-blind RCT; 1797 patients with hypertension divided into 4 groups: aliskiren 150 mg, valsartan 160 mg, combination of these or placebo for 4 weeks, then double doses for 4 weeks</td>
<td>Aliskiren in combination with valsartan resulted in an additional reduction in ambulatory BP of about 4.5/3.2 mmHg over either monotherapy at 8 weeks</td>
<td>PRC increased in all 3 groups; valsartan increased PRA by 160%; aliskiren and the combination reduced PRA by 73% and 44%, respectively</td>
<td>When using an aliskiren/valsartan combination, 4% of patients experienced hyperkalaemia in comparison to 2% in patients on monotherapy</td>
</tr>
<tr>
<td>Aliskiren 150–300 mg and ACEI</td>
<td>Double-blind RCT; 837 patients with hypertension and diabetes divided into 3 groups: aliskiren 150 mg, ramipril 5 mg or combination for 4 weeks, then double doses for 4 weeks</td>
<td>Addition of aliskiren to ramipril resulted in an additional reduction in mean BP of 4.6/2.1 mmHg at 8 weeks, but no significant difference in SBP vs. ramipril monotherapy</td>
<td>Increase in PRA with ramipril; a 66% reduction in PRA with aliskiren and a 48% reduction in the combination group, but an increase in PRC in all groups</td>
<td>Aliskiren/ramipril combination showed a two-fold increase in hyperkalaemia when compared to monotherapy</td>
</tr>
</tbody>
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**Notes:** ARB – Angiotensin receptor blocker; CCB – Calcium channel blocker; ACEI – Angiotensin converting enzyme inhibitor; HCTZ – Hydrochlorothiazide; RCT – randomised controlled trial; PRA – plasma renin activity; PRC – plasma renin concentration

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