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

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Keywords: blood pressure control, cardiovascular outcomes, hypertensive patients, renin angiotensin aldosterone system, RAAS, direct renin inhibitors

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 non-compliance with medication has been identified as one important factor. In this article, we discuss the various reasons for patient non-compliance 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, have come a long way in enhancing tolerability, reducing counter-regulatory drug mechanisms and bringing blood pressure closer to target. 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 the 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.

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Introduction

In 1998, it was estimated that at least 25% of the adult population in South Africa was hypertensive, according to the World Health Organization definition of hypertension (blood pressure equal to or above 140/90 mmHg).[1] Diagnosis and management of high blood pressure is generally poor, and is particularly inadequate in rural areas.[1,2] There is a clear upward trend in the 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%.[3,4]

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 twofold 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 proven to be effective in protecting against cardiovascular complications such as stroke, myocardial infarction (MI), heart failure and deterioration of renal function.[3,7-10] Effective medical therapies for hypertension have been available for almost 50 years.[11] Yet, worldwide only about 50% of patients achieve adequate BP reduction.[3,12] In South Africa, only 40% of patients achieve the conservative goal of BP < 140/90 mmHg.[12]

Socio-economic conditions, non-compliance with treatment, and inadequate prevention strategies have been shown to be barriers to effective blood pressure control.[7,11] In addition, increased life expectancy, reduced physical activity and higher obesity rates are factors that result in antihypertensive treatment resistance.[6]

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.[6] It has been shown that about half of patients discontinue their antihypertensive therapy within the first six to 12 months of therapy.[3,13] Non-adherence leads to poor BP control, which relates to higher costs in physician visits, hospital stays and loss of productivity from missed work days.[4,6,14] It also contributes to the practice-outcome gap, where the clinical guidelines

are implemented, but the expected benefits are not achieved.[6]

Possible reasons for non-adherence are:[4,6,13,15]

- The complexity of the medication regimen.
- Misunderstandings regarding the regimen.
- The asymptomatic nature of hypertension. The patient does not feel ill and may not see the need to take the medication.
- The view that medicines are unnatural and 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 include:[15]

- Simplifying the medication regimen.
- Selecting drugs according to the patient's lifestyle or characteristics.
- Using electronic medication monitors.
- Enhancing patient-physician communication.
- Educating patients in-depth.
- Suggesting behavioural changes for the patient, e.g. keeping a BP diary, self-monitoring of BP.
- Continuous monitoring of patient adherence, carried out by the physician.
- Providing social support in the form of family and health-care 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.[11,12] 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 further adding to the patient's pill burden.[16]

There is an inverse relationship between the complexity of the dosage regimen and patient compliance.[5,6] Treatments that relate to an increased dosing frequency negatively affect adherence.[6,16] On the other hand, by changing the dosage regimen from a three-times daily dose to a once-daily dose, adherence may be increased by as much as 25%.[15] Adherence is similarly improved by changing the patient from a twice-daily to a once-daily dose.[6]

Reducing side-effects and counter-regulatory mechanisms

As stated earlier, one reason for non-compliance is that the side-effects that the patient may experience from his/her antihypertensive medicine may be deemed as unacceptable in an otherwise asymptomatic disease.[15] 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.[6,8] This problem can be overcome somewhat by using combination therapy, as medicines can be given at a lower dose than that required for either drug as monotherapy.[9,11,12]

Appropriate combination therapy can improve tolerability if one component can neutralise unpleasant side-effects, e.g. thiazides have a tendency to cause hypokalaemia, which is blunted by the addition of a potassium-sparing diuretic, or the addition of an angiotensin-receptor blocker (ARB) or angiotensin-converting enzyme (ACE) inhibitor. An ARB or ACE inhibitor, in combination with amlodipine, can reduce the peripheral oedema associated with amlodipine.[6,10,12]

Furthermore, by combining agents that have different pharmacological profiles, an additive reduction in BP, as well as reduced activation of counter-regulatory mechanisms, can be achieved.[6,8,12] A limitation of the thiazide diuretics is that by reducing sodium and water retention, the renin-aldosterone-angiotensin system (RAAS) is activated, which renders the BP more angiotensin-dependent. The combination of an ARB or ACE inhibitor, together with a thiazide diuretic, is more effective in lowering BP than either agent alone.[6,12,17] ACE inhibitor and calcium-channel blocker combinations also have additive antihypertensive effects.[5,10,18] The natriuretic effect of calcium-channel blockers complements ACE inhibitor treatment in a similar way to the effect that diuretics have, but BP reduction is managed without the use of diuretics. In addition, the ACE inhibitor counteracts the reflex increase in sympathetic nervous system activity that is caused by some of the calcium-channel blockers.[10,18]

Benefits beyond blood pressure reduction?

About 50% of type 2 diabetics are also hypertensive at the time of diagnosis.[18] The aggressive treatment of hypertension in diabetics could slow down the progression to end-stage renal disease. Frequently, a combination of antihypertensives is needed to reach the lower BP target of 130/80 mmHg in these patients.[9,12,19]

Non-dihydropyridine calcium-channel blockers, e.g. verapamil, offer a mild protective effect against proteinuria in diabetic nephropathy, beyond their antihypertensive action.[18] However, whether the combination of an ACE inhibitor and calcium-channel blocker gives better protection against microalbuminuria as compared to monotherapy, is still a matter of debate. Not all studies could confirm this.[9,18,19]

However, the combination of trandolapril and verapamil may have favourable metabolic effects by increasing delivery of glucose to skeletal muscles through increased blood flow

to the muscle, due to the vasodilatory effect of the calcium-channel blocker. Calcium-channel blockers also increase insulin sensitivity at the cellular level. Lastly, combining an ACE inhibitor and a calcium-channel blocker causes stimulation of the production of nitric oxide through kinin-dependent 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 distensability.[18]

Fixed-dose combinations

The use of fixed-dose combination medicines is an alternative approach to multiple drug therapy, and is employed to increase patient adherence.[5,6,10,14] In fact, the risk of non-compliance can be reduced by up to 24% when fixed-dose combinations are given, as compared to free-drug combinations.[6] There are already a few fixed-dose combinations available on the market that combine ARBs or ACE inhibitors with diuretics or calcium-channel blockers. See Table I.

Table I: Examples of currently available fixed-dose combinations in South Africa

Product examples	ARB	ARB inhibitor	Calcium-channel blocker	Diuretic
Adco-Zetomax Co® Lisoretic® Hexal-lisinopril Co® Lisozide® Zestozide® Diace Co® Lisinozide® Zestoretic®		Lisinopril		HCTZ
Accuretic® Quinace Co® Adco-Quinaretic® Quinazide® Accumax Co®		Quinapril		HCTZ
Captoretic® Zapto-Co® Capozide®		Captopril		HCTZ
Inhibace Plus®		Cilazapril		HCTZ
Cibadrex®		Benazepril		HCTZ
Spec-Perindopril Plus® Prexum Plus® Vectoryl Plus® Preterax® Coversyl Plus®		Perindopril		Indapamide
Co-Renitec® Pharmapress Co® Enap-Co®		Enalapril		HCTZ
Zaneril®		Enalapril	Lercanidipine	
Tri-Plen® Tri-Plen Forte®		Ramipril	Felodipine	
Tarka®		Trandolapril	Verapamil	
Co-Diovan® Co-Tareg®	Valsartan			HCTZ
Co-Micardis® Co-Pritor®	Telmisartan			HCTZ
Coaprovel® Co-Irbewin®	Irbesartan			HCTZ
Exforge®	Valsartan		Amlodipine	
Atacand plus®	Candesartan			HCTZ
Netrasol Co® Cozaar Comp® Fortzaar®	Losartan			HCTZ
Teveten Plus®	Eprosartan			HCTZ

There is a lack of comparative data on these combinations. However, in the Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial, it was demonstrated that a fixed-dose ACE inhibitor/calcium-channel blocker combination significantly reduced the risk of morbidity and mortality relative to ACE inhibitor/diuretic therapy, despite similar BP reductions.[5,10] 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.[18]

As shown in the discussion above, there is evidence to support the use of fixed-dose combination therapy with one agent acting on the RAAS and a calcium-channel blocker in high-risk patients.[5] The combination of an ARB (valsartan) and calcium-channel blocker (amlodipine) is therefore an attractive option for hypertensive therapy. In studies where amlodipine and valsartan were used in a fixed-dose combination, it was noted that, overall, there was a significantly greater reduction in BP with the combination therapy than with either agent alone.[5,10] 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 cardiovascular risk, the introduction of a fixed-dose ARB/calcium-channel blocker combination may be a useful strategy in the management of cardiovascular morbidity and mortality.[5]

Whether the fixed-dose combination of ARB and calcium-channel blocker is superior to other combinations, in terms of cardiovascular and renal outcomes is not clear. In a six-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.[5,10]

In elderly patients, an ARB/calcium-channel blocker 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 and amlodipine 5 mg resulted in significantly less orthostatic hypotension and less profound changes in potassium and uric acid, compared to irbesartan 300 mg and HCTZ 12.5 mg. 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 adherence, and 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.[16]
- *Convenience and safety:* It is more convenient for the patient to take one tablet. The lower doses used in combination therapy result in better 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

Only a few unusual combinations of antihypertensive medicines are found in fixed-dose combination tablets, but these may be beneficial in selected patient groups. CVD usually starts with risk factors like hypertension, which advances to atherosclerosis, target organ damage and ultimately heart failure, MI, stroke or death. ACE inhibitors and ARBs are each effective in the management of all stages of CVD, as both 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 cardiovascular events.[22-24] For example, the ONTARGET (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) study in > 25 000 patients with vascular disease or high-risk diabetes found that the combination of an ARB with an ACE inhibitor was associated with more adverse events, without an increase in clinical benefit.[23,24] In this population, the primary composite end-point (doubling of serum creatinine, dialysis or death) occurred more often in patients receiving the combination of ramipril and telmisartan than either agent alone, despite additive reductions in BP that were experienced with the combination. It is postulated that the excessive hypotension could have caused acute worsening of renal function. In addition, acute hypotension may increase the risk of myocardial ischaemia in patients with stenosed coronary arteries.[23]

From these results, it can be concluded that it is not advisable to use an ARB/ACE inhibitor combination routinely in the treatment of hypertension.[24] However, dual RAAS blockade using an ARB plus an ACE inhibitor may be considered in selected patients with proteinuria, such as diabetic patients without other diseases.[23-25] 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.[22,26,27] Where indicated, the ARB/ACE inhibitor combination should be used with caution. Close monitoring of potassium levels and kidney function should always be carried out.[22,24]

Novel antihypertensive drugs

Current antihypertensive therapy may prove suboptimal as a result of "escape mechanisms". As discussed, thiazide diuretics have a counteracting feedback on the RAAS. While ACE inhibitors block the conversion of angiotensin I to angiotensin II, non-ACE pathways stimulate the production of angiotensin II, and these pathways become more pronounced under the conditions of ACE inhibition.[11] Furthermore, inhibition of RAAS, either by an ACE inhibitor or ARB, increases renin release by reducing the negative feedback effect of angiotensin II.[11,28] The increased renin eventually restores angiotensin II levels.[11] The rate-limiting step in RAAS is the conversion from angiotensinogen to angiotensin I under the influence of renin, which has 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 help uncontrolled hypertensive patients, as animal studies have shown an elevation in BP in rats that had increased copies of the

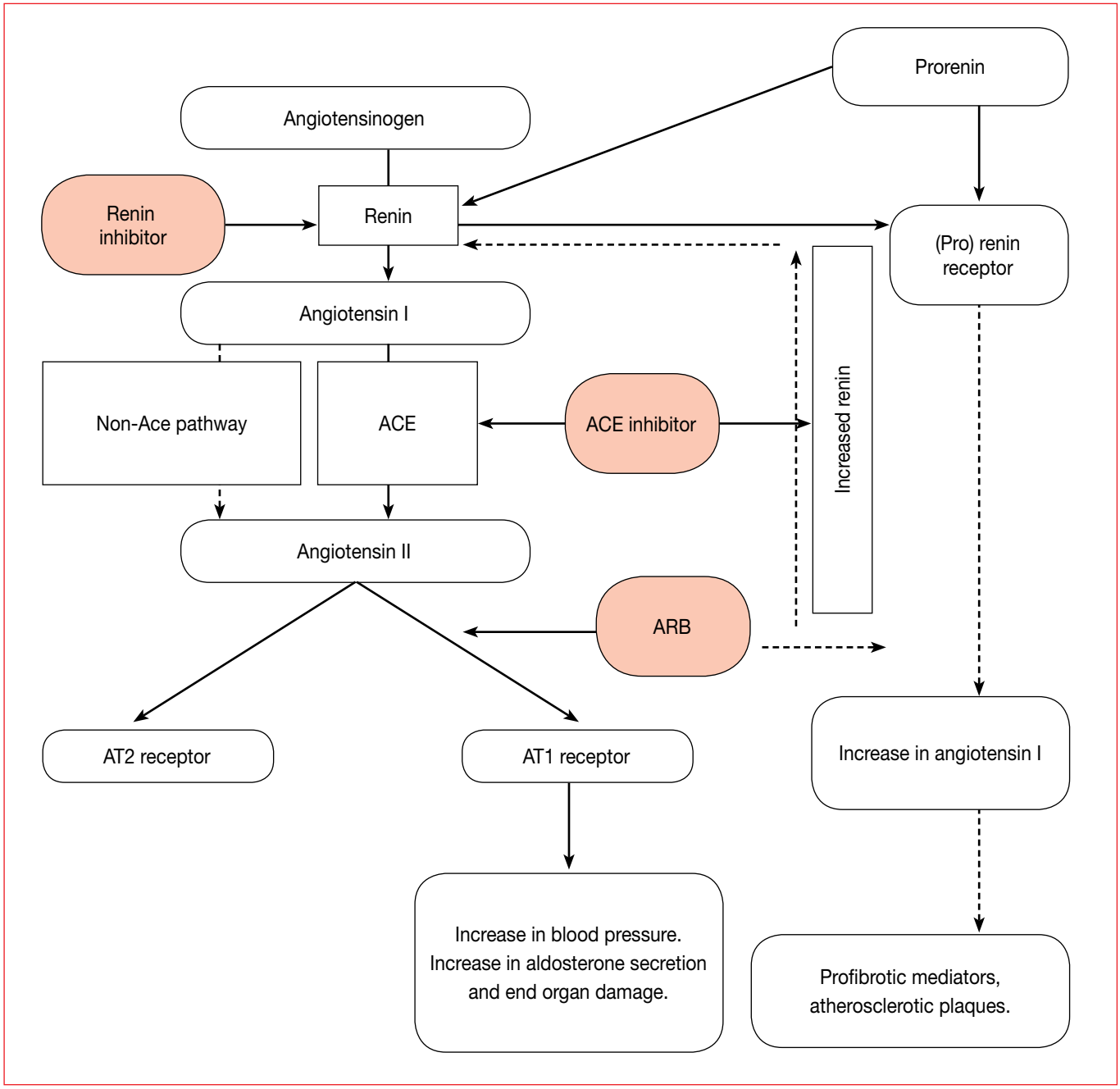

Figure 1: Schematic representation of the renin aldosterone angiotensin system (RAAS)[11,28,29]

angiotensinogen gene, but not in rats with increased 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.[11,28,30] Aliskiren has a long half-life, which makes it suitable for a once-daily regimen.[11,28] It has proven to be effective in doses between 75-300 mg/day. Doses below 75 mg/day had no BP lowering effect, and doses above 300 mg showed a 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. The antihypertensive effects are comparable to those of losartan, valsartan, irbesartan, lisinopril, ramipril and HCTZ.[11,28,30]

The major side-effects of aliskiren are listed below:[11,31]

- Diarrhoea
- Rash (1%)
- Increased creatine kinase level
- Cough (1%)
- Excessive hypotension (0.1%)
- Acute renal failure
- Angioedema (0.06%).

In a similar way to ARBs, ACE inhibitors and HCTZ, aliskiren causes an increase in plasma renin concentration (PRC) by reducing the levels of angiotensin II. However, unlike ACE inhibitors and ARBs, aliskiren decreases the plasma renin activity (PRA) when used in monotherapy, or when combined with HCTZ.[11,28,30] It is important to clarify whether the high levels of PRC, seen with the use of aliskiren, 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 ACE inhibitors, or for patients in whom ARB or ACE inhibitor therapy has proven to be 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. ACE inhibitors, 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, caution should be exercised regarding hyperkalaemia, especially in patients with renal dysfunction.[11]

Optimal RAAS suppression is an important goal in antihypertensive therapy. Currently, when combining an ARB and an ACE inhibitor, optimal RAAS suppression is not achieved, as a result of the compensatory feedback mechanisms in renin release and increased PRA. However, renin inhibitors neutralise any increase in PRA and prevent the formation of angiotensin I and angiotensin 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 result in a significant change in renal function.[11,25]

Conclusion

It can be seen that the reasons for suboptimal BP control are many and varied. Non-adherence to medicine is one of these reasons, and can be addressed by changing a patient to a fixed-dose combination, as this reduces the patient's pill burden and may reduce side-effects.[5,10-12] The high interpatient variability seen with antihypertensive treatment can account for patients whose BP remains uncontrolled,

Table II: Combination therapy with aliskiren[11,25]

Combination	Study design	BP reduction	Effect on PRA and PRC	Other effects
Aliskiren 150-300 mg and HCTZ	Double-blind trial ᵉRCT: 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.	BP reduction with aliskiren/HCTZ combination superior to HCTZ monotherapy, but similar to BP reductions with irbesartan/HCTZ and amlodipine/HCTZ at 8 weeks.	Reduction in PRA when used in combination, compared to an increase in PRA seen with HCTZ alone.	Aliskiren has potassium-sparing effects and may mitigate the hypokalaemia caused by HCTZ.
Aliskiren 150 mg and calcium-channel blocker	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.	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.	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%.	Peripheral oedema was less frequent when using amlodipine 5 mg/aliskiren combination, than amlodipine 10 mg alone.
Aliskiren 150 – 300 mg and ARB	Double-blind RCT: 1 797 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.	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.	PRC increased in all 3 groups. Valsartan increased PRA by 160%, aliskiren and the combination reduced PRA by 73% and 44%, respectively.	When using an aliskiren/valsartan combination, 4% of patients experienced hyperkalaemia in comparison to 2% in patients on monotherapy.
Aliskiren 150-300 mg and ACE inhibitor	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.	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 systolic blood pressure vs. ramipril monotherapy.	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.	Aliskiren/ramipril combination showed a two fold increase in hyperkalaemia, when compared to monotherapy.

despite compliance with therapy.[32] One way of addressing this is by using combinations of hypertensive medicines with complementary mechanisms of actions, thereby increasing the reduction of BP.[6,12,17,18]

Unconventional antihypertensive combinations, e.g. dual RAAS blockade using an ARB plus an ACE inhibitor, seem to only be beneficial in specific patients; for example, CHF patients with a low ventricular ejection fraction (≤ 40%), and possibly diabetics with proteinuria, but without any co-morbidities. Patients on dual RAAS blockade must have their potassium levels and kidney function closely monitored.[22,24,25] 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.[25,28]

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.[3,15,33]

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