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REVIEW

An overview of fixed-dose combinations of antihypertensive drugs in South Africa

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Hypertension is a pressing global health issue, contributing to an increase in cardiovascular risk, as well as being the most common condition seen in South Africa. Lack of compliance with the prescribed therapy is one of the largest obstacles to achieving goal blood pressure in antihypertensive patients. The complexity of the drug therapy is a very important factor that is associated with noncompliance, as most patients require treatment with two or more drugs. The use of fixed-dose combination (FDC) therapy has various advantages, including simplification of the regimen, resulting in improved adherence. However, there are also disadvantages, e.g. the inability to provide individualised dose flexibility. This article provides an overview of available FDC therapy for hypertension in South Africa and the rational use thereof, by taking into account each combination's complementary action, efficacy, safety and tolerability.

Keywords: antihypertensives, fixed-dose combination, hypertension

Introduction

Hypertension is a haemodynamic disorder, associated with a rise in peripheral vascular resistance that, in turn, can lead to myocardial infarction, renal failure, strokes and death, if not identified early and treated properly.[1–3] It is the most common condition seen in South Africa, estimated to have caused 46 888 deaths and 390 860 disability-adjusted life years in 2 000 disability-adjusted lives in the year 2000.[4] Many patients with hypertension do not attain the desired blood pressure (BP) goal of < 140/90 mmHg. A reduction in BP is considered to be the primary determinant of a reduction in cardiovascular risk. The complex relationship of genetic and environmental elements includes factors associated with high BP, and can lead to activation or inhibition of one or more of the processes involved in its control.[1,3,5–7] Dietary factors and physical inactivity contribute to the genetic predisposition, while environmental factors include smoking, drinking, obesity and alcohol. This means that hypertension is a preventable cause of morbidity and mortality. The advantages of leading a healthy lifestyle, including a controlled diet and regular exercise for all populations with hypertension cannot be stressed more. The primary goal of treatment is to abolish the risks associated with hypertension, without reducing a patient's quality of life.[1–4]

The renin-angiotensin-aldosterone system (RAAS), as well as the sympathetic nervous system is involved in regulating arterial pressure. Hypertension is usually multifactorial, interfering with different pressor mechanisms. Thus, acting on several physiological systems improves blood pressure goal attainment rates. Three main factors that determine BP include renal sodium excretion and the resultant plasma and total body volume, as well as vascular tone and cardiac performance. Each of these factors controls determinants of BP, like cardiac output, intravascular volume and systemic vascular resistance. RAAS plays a central role in elevating BP through these mechanisms. This system regulates the secretion of renin, with feedback systems from sodium balance, arterial BP levels and angiotensin II. The direct vasoconstrictor effect of angiotensin II, resulting from the secretion of renin, can increase systemic vascular resistance, and salt and water retention can again lead to an increase in the extracellular blood volume. The rationale for combining drugs from different classes lies in reaching the goal BP more rapidly, as each drug works at a separate site, blocking different effector pathways.[1,3,7] An overview of the RAAS system is presented (Figure 1).

One of the largest obstacles to achieving goal BP in antihypertensive patients is the patients themselves, the challenge being lack of adherence to the prescribed therapy. BP variability increases with increasing BP levels. The complexity of the drug therapy is an important factor that is associated with noncompliance as the majority of patients need treatment with more than one agent. Multiple clinical trial evidence supports the use of combination therapy, indicating that it results in better clinical outcomes than monotherapy. Co-morbid conditions, such as diabetes mellitus, impose an even greater pill burden, making it critical to address the adherence challenge in order to achieve maximum clinical benefit. Studies have demonstrated that high adherence to antihypertensive therapy (AHT) is associated with a significant decrease in cardiovascular events (CVE), and also results in decreased hospitalisation rates and better cost-effectiveness, compared with low adherence. Additional target organ protection is also provided with 24-hour BP control. Thus, major long-term benefits are realised in patients who comply with their AHT.[5–7,8–10]

Rationale for combination therapy

The development of single-pill combinations of two antihypertensive agents, commonly known as a fixed-dose combination (FDC), is the solution to overcoming nonadherence.[9,11] Combination therapy has the ability to target different physiological systems, there is a synergistic pharmacological effect at lower doses of individual agents and it also attempts to block counter-regulatory responses, achieved through blockage by a single agent.[1,10] This is achieved as hypertension affects multiple regulatory systems, and combining more than one agent causes interference in multiple pathways, as well as a reduction in the activation of counter-regulatory mechanisms.[9] A reduction in metabolic consequences can also be seen because of the use of lower doses of single-drug components. BP control in a large population is often only reached with a combination of drugs from different classes.[1,3,6,12] Components in FDCs can be designed to counteract each other's

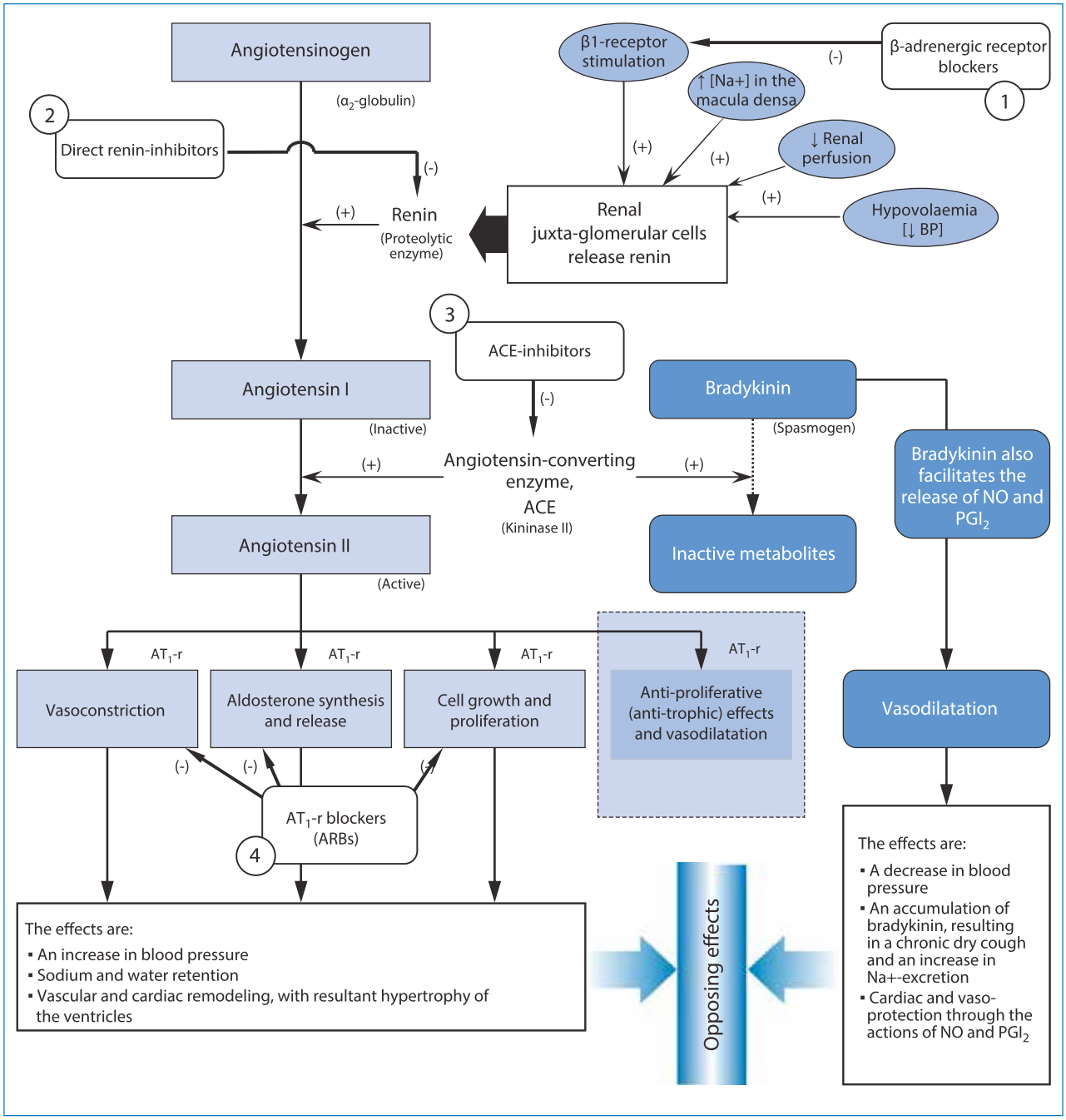


Figure 1: Diagram of the renin-angiotensin-aldosterone system showing the sites of action of the β-adrenergic receptor blockers, the direct rennin inhibitors, the angiotensin-converting enzyme inhibitors and the angiotensin II receptor blockers[22]

side-effects, resulting in an overall neutral effect. Also, BP goals may be reached earlier than would be the case with monotherapy. Furthermore, as the two components can be given at lower dosages, most antihypertensive drugs produce dose-dependent adverse effects.[3,7,8–10] The convenience, tolerability and simplicity associated with FDCs help to accomplish sustained BP targets over a long period, which can result in advantages with respect to cardiovascular outcomes and reducing the risk of a stroke.[1,9,11,13–16]

Thus, the complexity of treatment regimens is reduced with FDCs and is associated with better compliance and persistence with treatment, motivating patients to adhere to lifelong therapy.[1,10]

The Eighth Joint National Committee (JNC 8) recommends selection from four specific medication classes, known as:

- Angiotensin-converting enzyme (ACE) inhibitors
- Angiotensin-receptor blockers (ARBs)
- Calcium-channel blockers.
- Diuretics.[2]

BP goals are based on age, diabetes and chronic kidney disease.

Table 1 provides the different BP goals recommended by the JNC 8.

Most patients require two or more drugs to reach optimal control of their BP, as combining drugs from complementary classes provides approximately a five times greater antihypertensive effect than increasing the dosage of a single drug.

Table 1: Rational blood pressure goals according to the JNC 8[2]

Populations aged < 60 years	Populations of all ages with diabetes	Populations of all ages with CKD, with or without diabetes	Populations aged > 60 years
< 140/90 mmHg	< 140/90 mmHg	< 140/90 mmHg	< 150/90 mmHg

CKD: chronic kidney disease

Table 2: Advantages and disadvantages of fixed-dose combination therapy[10,20]

Advantages	Disadvantages
Simplification of the regimen	Individualised dose flexibility is lost
Improved adherence	Specialised dosing is lost when treating specific co-morbid conditions
Reduced pill burden	The likelihood of dose-dependent reactions is increased
There is a potential reduction in costs, when compared to taking the individual drugs separately	

Thus it is recommended that:

- Therapy is initiated with two drugs from different classes when the BP is > 20 mmHg (systolic) or > 10 mmHg above the diastolic target.
- A third drug is selected when the target BP is still not reached, titrating the third drug up to the maximum recommended dose. (This excludes the combined use of an ACE inhibitor and an ARB.)
- Consideration is given to initiating AHT with more than one drug in patients at high cardiovascular risk, identified by increased BP and other risk factors.
- Low-dose combination therapy is used as the initial treatment. A meta-analysis showed that this resulted in greater cardiovascular benefits than the initiation of monotherapy.[2,3,14,17–19]

Advantages and disadvantages of fixed-dose combinations

The use of combination therapy has various advantages, e.g. a convenient dosing format and improvement of patient compliance.[10,20] There are also disadvantages when compared to single-drug therapy. Table 2 provides a summary of the advantages and disadvantages of FDC therapy.

Available options for combination therapy

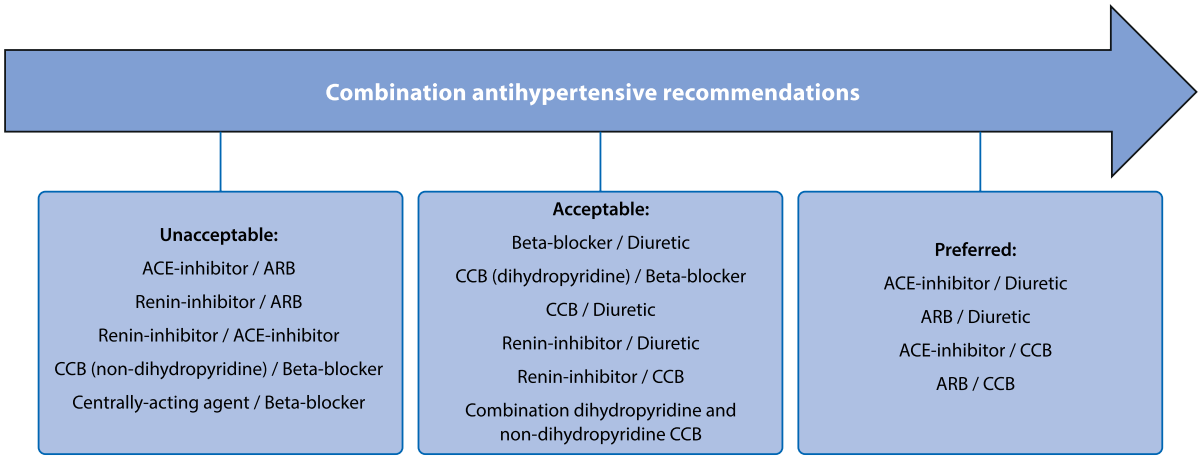
Combined drug therapy started in 1960 with the combination of hydrochlorothiazide (HTCZ) and triamterene.[16] Benefits from their complimentary action result from the use of combination antihypertensive drugs.[10] However, the number of combinations is extensive, and is thus subdivided into preferred combinations, and acceptable, unacceptable or ineffective combinations. This subdivision is based on the outcome of the combination, the efficacy of the antihypertensive drug, and its safety and/or tolerability[1] (Figure 2). An overview of the available combinations in South Africa is presented in Table 3.

Preferred combinations

Renin-angiotensin-aldosterone system inhibitors and calcium-channel blockers

Different combinations included under this group include the combination of an ACE inhibitor, ARB, or direct renin inhibitor with a calcium-channel blocker. The rationale behind this combination lies in the management of the side-effects between the two pharmacological groups: [1,3,10,16]

- The RAAS blocker counteracts the calcium-channel blocker-induced activation of the sympathetic nervous system, e.g. tachycardia, and the RAAS.
- Calcium-channel blockers cause a negative sodium balance which adds to the antihypertensive effects of the RAAS blocker.
- The RAAS clocker minimises the dose-dependent peripheral oedema caused by the calcium-channel blockers.



[ACE: Angiotensin-converting enzyme; ARB: Angiotensin-receptor blocker; CCB: Calcium-channel blocker]

Figure 2: Recommended antihypertensive combination therapy

Table 3: Fixed-dose combinations available in South Africa[23]

Combination	Fixed dose combination examples	Trade name	Price
ACEI–CCB	Trandolapril/Verapamil	Tarka®	R308.00 (180 mg/2 mg). R308.00 (240 mg/4mg)
ARB–CCB	Amlodipine/Valsartan	Exforge®	R270.22 (5 mg/320 mg). R270.22 (10 mg/320 mg)
	Valsartan/HCTZ/Amlodipine	Co-Exforge®	R270.22 (320 mg/25 mg/10 mg)
	Telmisartan/Amlodipine	Twynsta®	R201.06 (40 mg/5 mg). R228.87 (40 mg/10 mg). R201.06 (80 mg/5 mg). R228.87 (80 mg/10 mg)
ACEI–Diuretic	Captopril/HCTZ	Zapto-Co®	R90.19 (50 mg/25 mg)
	Benazepril/HCTZ	Cibadrex®	R282.05 (10 mg/12.5 mg)
	Enalapril/HCTZ	Co-Renitec®	R92.11 (20 mg/12.5 mg)
		Pharmapress Co®	R92.91 (20 mg/12.5 mg)
	Lisinopril/HCTZ	Adco-Zetomax®	R57.43 (10 mg/12.5 mg). R93.04 (20 mg/12.5 mg)
		Hexal-Lisinopril Co®	R57.45 (10 mg/12.5 mg). R94.46 (20 mg/12.5 mg)
		Lisinopril Co Unicorn®	R54.29 (10 mg/12.5 mg). R87.83(20 mg/12.5 mg)
		Lisoretic®	R54.29 (10 mg/12.5 mg). R87.94(20 mg/12.5 mg)
		Lisozide®	R58 (10 mg/12.5 mg). R95 (20 mg/12.5 mg)
	Quinapril/HCTZ	Accumax Co®	R77.25 (10 mg/12.5 mg). R116.82 (20 mg/12.5 mg)
		Accuretic®	R163.69 (10 mg/12.5 mg). R207.75 (20 mg/12.5 mg)
		Adco-Quinaretic®	R72.16 (10 mg/12.5 mg). R110.33 (20 mg/12.5 mg)
	Perindopril/Indapamide	Acesyl Co®	R96.85 (2 mg/1.25 mg). R132.72 (4mg/1.25 mg)
		Ariprel Plus®	R110.58 (4mg/1.25 mg)
		Coversyl Plus®	R212.22 (4mg/1.25 mg)
		Pearinda Plus 4®	R111.29 (4mg/1.25 mg)
		Perindopril Co Unicorn®	R116.13 (4mg/1.25 mg)
		Preterax®	R193.32 (2 mg/0.625 mg)
		Prexum Plus®	R130.52 (4mg/1.25 mg)
		Vectoryl Plus®	R111.32 (4mg/2.5 mg)
ARB–diuretic	Irbesartan/HCTZ	Co-Irbewin®	R162.41 (150 mg/12.5). R162.41 (300 mg/12.5 mg)
		Coaprovel®	R241.70 (150 mg/12.5 mg)
		Isart Co®	R122.79 (150 mg/12.5 mg). R122.79 (300 mg/12.5 mg)
	Losartan/HCTZ	Ciplazar Co®	R91.98 (50 mg/12.5 mg). R91.98 (100 mg/25 mg)
		Cozaar Comp®	R108.37 (50 mg/12.5 mg)
		Fortzaar®	R115.40 (100 mg/25 mg)
		Hytenza Co®	R75.64 (50 mg/12.5 mg). R86.80 (25 mg/100 mg)
		Lohype Forte Plus	R94.38 (100 mg/25 mg)
		Losaar Plus®	R72.50 (50 mg/12.5 mg). R78.20 (100 mg/25 mg)
		Losacar Co®	R78.10 (50 mg/12.5 mg)
		Losartan Co Unicorn®	R80.01 (50 mg/12.5 mg). R82.99 (100 mg/25 mg)
		Lozaan Co®	R87.86 (50 mg/12.5 mg). R95.25 (100 mg/25 mg)
		Netrasol Co®	R73.80 (50 mg/12.5 mg). R85.00 (100 mg/25 mg)
		Sartoc-Co®	R90.98 (50 mg/12.5 mg)
		Zartan Co®	R82.50 (50 mg/12.5 mg). R82.50 (100 mg/25 mg)
	Telmisartan/HCTZ	Co-Micardis®	R224.75 (40 mg/12.5 mg). R224.75 (80 mg/12.5 mg). R143.37 (80 mg/25 mg)
		Co-Pritor®	R143.37 (40 mg/12.5 mg). R143.37 (80 mg/12.5 mg)
	Valsartan/HCTZ	Co-Diovan®	R222.16 (80 mg/12.5 mg). R162.42 (160 mg/12.5 mg)
		Co-Diovan Plus®	R222.18 (25 mg/160 mg)
		Co-Migroben®	R136.88 (80 mg/12.5 mg). R136.88 (160 mg/12.5 mg)
		Co-Tareg®	R136.88 (160 mg/25 mg). R136.88 (80 mg/12.5 mg)
		Co-Tareg160 Plus®	R136.88 (160 mg/12.5 mg)
		Co-Zomevek®	R136.88 (160 mg/25 mg)
β-adrenoceptor antagonist diuretic	Atenolol/chlortalidone	Tenchlor®	R102.85 (100 mg/25 mg). R59.36 (50 mg/12.5 mg)
		Tenoretic®	R319.98 (100 mg/25 mg)

ACE: angiotensin-converting enzyme, ARBs: angiotensin-receptor blockers, HCTZ: hydrochlorothiazide

Until recently, FDCs of the calcium-channel blockers and a RAAS inhibitor have only been available with the use of an ACE inhibitor and calcium-channel blocker combination. This subsequently changed with the development of a combination of an ARB plus amlodipine.[16] However, similar end-points have been illustrated with ACE inhibitors and an ARB when used in combination. The ACE inhibitors were shown to be more cardioprotective, while the ARBs conferred better stroke prevention.[1]

Of the calcium-channel blockers, amlodipine seems to be best choice in terms of the dihydropyridine calcium-channel blocker, with its distinctive pharmacokinetics and pharmacodynamics: [7,16]

- A long half-life of 35 hours, thereby adequately controlling BP over 24 hours and allowing once-daily dose administration.
- The reduced incidence of cardiovascular events.
- Improved vascular structure, e.g. intima-media thickness of the carotid arteries.

The combination of ACE inhibitor with a calcium-channel blocker is beneficial in a patient with co-morbid conditions, such as hypertension and diabetes. The combination of an ARB and a calcium-channel blocker has advantages beyond BP lowering, i.e. on the morbidity and mortality of patients with hypertension and other co-morbid conditions.[10]

Renin-angiotensin-aldosterone system inhibitors and diuretics

The majority of available FDCs is either an ACE inhibitor or an ARB inhibitor with a low-dose thiazide-type diuretic, usually a HCTZ.[16] The diuretics reduce the intravascular volume, thereby activating the RAAS, thus producing vasoconstriction with salt and water retention. This is antagonised by the RAAS inhibitor.[1,3] The addition of the RAAS inhibitor also counteracts diuretic-induced hypokalaemia and glucose intolerance.[1,3] The combination of perindopril and indapamide has been shown to reduce the incidence of strokes in the elderly by 30%.[1]

Acceptable combinations

Beta blockers and diuretics

The combination of beta blockers and diuretics results in similar side-effects that may augment the likelihood of the development of glucose intolerance, fatigue, sexual dysfunction and the onset of new diabetes.[1] Earlier literature suggesting that a β blocker should be used in patients with a diuretic was demonstrated to be inferior to the use of a calcium-channel blocker or a potassium-sparing diuretic in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) study.[1,21]

Calcium-channel blockers and diuretics

The use of amlodipine with a thiazide has the risk of producing new-onset diabetes and hyperkalaemia. However, the use of amlodipine, compared to that of valsartan, results in a similar reduction in both morbidity and mortality, thus the combination may be classified to be acceptable.[1,3]

Dual calcium-channel blockade

The combination of a dihydropyridine and verapamil plus diltiazem reduces BP, without augmented side-effects. This combination may be useful in patients with documented angio-oedema (that developed from RAAS inhibitors) and advanced renal failure with the risk of hyperkalaemia. No long-term safety studies are as yet available.[1]

Unacceptable or ineffective combinations

Dual renin-angiotensin-aldosterone system blockade

The combination of an ACE inhibitor and an ARB does not show any added BP lowering against using either one as monotherapy. The combination does not have any improved cardiovascular end-points, just a small BP reduction of 2.4/1.4 mmHg, when compared to using either an ACE inhibitor or an ARB on its own. The combination also results in more side-effects than monotherapy on its own.[1,3]

Renin-angiotensin-aldosterone system blockers and beta blockers

There are no known additional BP reduction rates following the combination of RAAS blockers and beta blockers in the treatment of hypertension. Thus, this combination should not be used for that purpose. However, it has been shown to reduce reinfarction rates and to be cardioprotective in patients suffering from a myocardial infarction or with heart failure.[1,3]

Beta blockers and antiadrenergic drugs

The combination of a β blocker and an antiadrenergic drug, such as clonidine or methyldopa, does not have any additional beneficial effect on BP end-points. On the contrary, they may even produce a rebound effect in the BP, when discontinued abruptly. Also the combination can also cause a bradycardia or a heart block.[1,3]

Conclusion

The primary goal of reducing BP is to decrease the long-term risks of cardiovascular morbidity and mortality. The use of FDC therapy as first-line treatment may help to achieve these goals as most patients with hypertension require more than one drug.

The JNC 8 guidelines provide evidence-based recommendations for the management of hypertension. Similar treatment goals are defined for all hypertensive populations. The rationale is < 140/90 mmHg, except for some subpopulations when the evidence review supports different goals. For example, the JNC 8 recommends a target BP < 150/90 mmHg for populations aged 60 years and older. Selection from the four specific medication classes is recommended, i.e. the ACE inhibitors, or ARBs, calcium-channel blockers or diuretics. The use of combination antihypertensive drugs benefits from the complimentary action of the different combined classes. However, the number of combinations is extensive, and is thus subdivided into preferred combinations, and acceptable, unacceptable or ineffective combinations. The preferred recommended antihypertensive combinations are an ACE inhibitor combined with a diuretic, an ARB plus a diuretic, an ACE inhibitor in combination with a calcium-channel blocker and an ARB plus a calcium-channel blocker. These combinations are the most acceptable based on the outcome of the combination, their efficacy, safety and tolerability.

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