

# Hypertension: a review of antihypertensive medication

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## Abstract

This article provides an overview of the changes that have taken place in the diagnosis and management of hypertension over the past decade. Hypertension remains a very common condition seen in South Africa. The approach to the management of hypertension includes necessary lifestyle modifications and a decisive, stepwise escalation process in the pharmacotherapeutic management thereof. Thiazide diuretics are still being promoted by most guidelines to be the initial (first-line) drug of choice, with the addition of other suitable antihypertensive agents, if necessary, and according to any relevant comorbid conditions.

**Keywords:** hypertension, antihypertensive agents, fixed-dose combination therapy, angiotensin II-receptor blockers, angiotensin-converting enzyme inhibitors, calcium-channel blockers

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S Afr Pharm J 2020;87(5):20-27

## Introduction

Hypertension is a haemodynamic disorder, associated with a rise in peripheral vascular resistance that can, in turn, lead to myocardial infarction, renal failure, strokes and death, if not identified early and treated correctly.<sup>1-3</sup> 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 2000.<sup>4</sup> Most patients with hypertension do not attain the 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. Factors found to be associated with high BP are the result of a complex relationship between genetic and environmental elements, which can lead to activation or inhibition of one or more of the processes involved in the normal control of BP.<sup>1,3,5-7</sup> Dietary factors and physical inactivity contribute to the genetic predisposition, while environmental factors include smoking, drinking, obesity and alcohol, thus making hypertension a preventable cause of morbidity and mortality. The advantages of populations with hypertension leading a healthy lifestyle cannot be stressed enough, and this includes a controlled diet and regular exercise. The primary goal of treatment is to abolish the risks factors associated with hypertension, without reducing the patient's quality of life.<sup>1-4</sup>

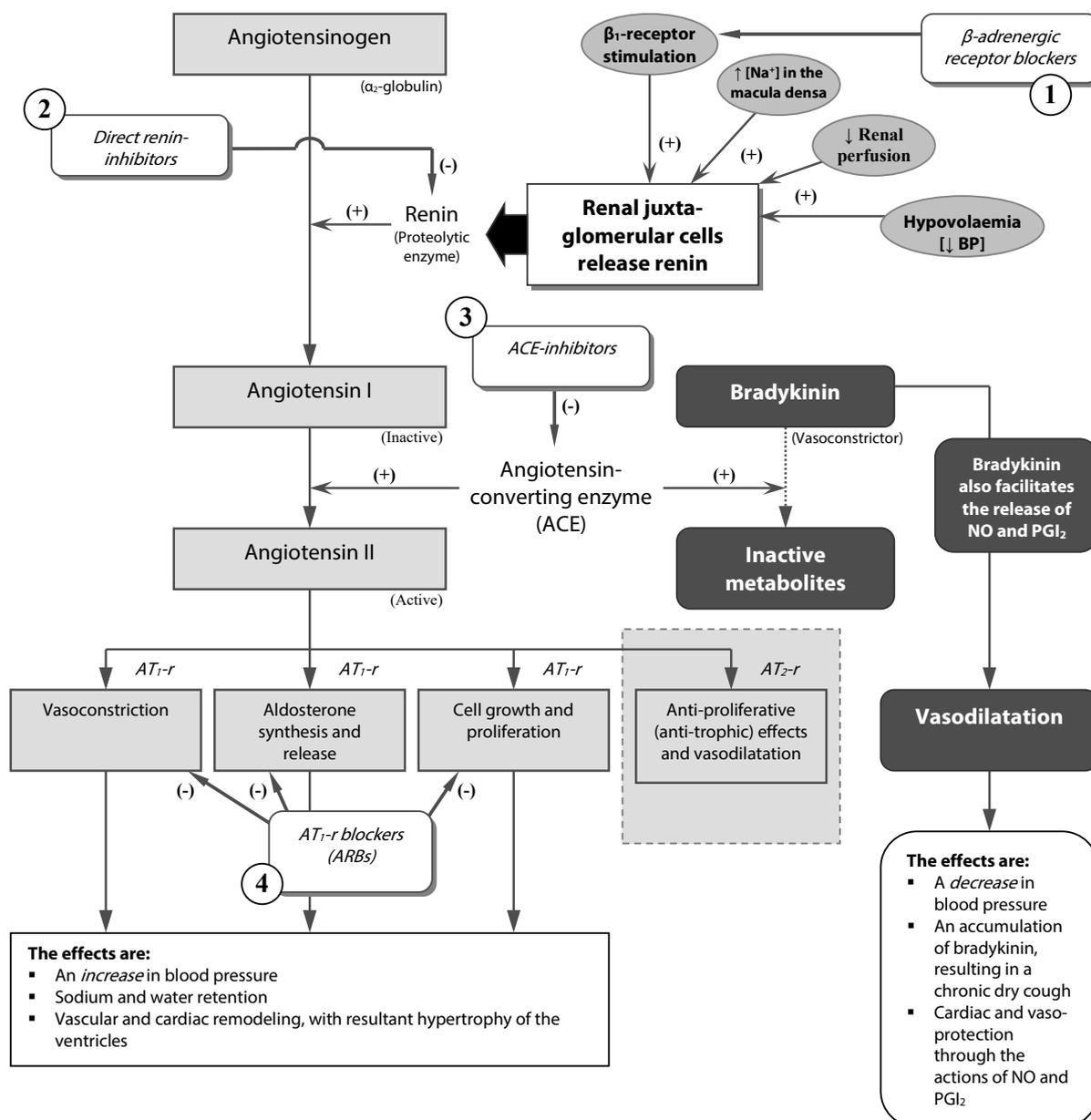
The renin-angiotensin-aldosterone system (RAAS), as well as the sympathetic nervous system, is involved in regulating arterial BP. Hypertension is usually viewed as a multifactorial condition, which interferes with different pressor mechanisms and acts on several physiological systems. The three main factors that determine BP are renal sodium excretion (and the resultant impact on plasma and total body volume), vascular tone and cardiac performance. Each of these factors controls the vital determinants of BP, such as cardiac output, intravascular volume and systemic vascular

resistance. The 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 lead to an increase in the extracellular blood volume. The rationale for combining drugs from different classes lies in reaching the BP target more rapidly, as each drug will work on a separate site, blocking different effector pathways.<sup>1,3,7,8</sup> An overview of the RAAS system is presented in Figure 1.<sup>9</sup>

Hypertension is a growing global problem that is associated with numerous underlying pathophysiological conditions.<sup>10</sup> These include ventricular hypertrophy, endothelial dysfunction, metabolic syndrome, a procoagulant state, oxidative stress, inflammation and a genetic predisposition to cardiovascular events.<sup>11</sup> The high prevalence of hypertension is a particular concern in developing countries as it contributes to the present and anticipated pandemic of cardiovascular disease (CVD). CVD was previously ranked as the second highest cause-of-death category in South Africa, resulting in major cost implications for developing countries.<sup>12</sup> The control of hypertension and trying to curb the risk factors, such as cigarette smoking, dyslipidaemia and diabetes mellitus, is a major challenge.<sup>13</sup> This indicates that there is a great need for antihypertensive agents that achieve more than the mere lowering of BP, and which provide advantages in the prevention and management of CVD.<sup>14</sup>

## Guidelines

The seventh and eighth reports, respectively, of the Joint National Committee on the prevention, detection, evaluation and



**Figure 1:** Diagram of the renin-angiotensin-aldosterone system, showing the sites of action of the  $\beta$ -adrenergic receptor blockers, the direct renin inhibitors, the angiotensin-converting enzyme inhibitors and the angiotensin II AT<sub>1</sub>-receptor blockers<sup>9</sup>  
ARBs – angiotensin-receptor blockers, ACE – angiotensin-converting enzyme

treatment of *high blood pressure* (JNC 7 and JNC 8), and the South African hypertension guidelines were drawn up to promote the evidence-based, accessible and comprehensive management of hypertension by healthcare professionals, and serve as valuable resources in both the public and private healthcare sectors in South Africa.

### JNC 7

The rates of detection, treatment and control of high BP have improved over the last two decades, but not by much. Only 34% of hypertensive people had BP readings at goal level in the 1999–2000 National Health and Nutrition Examination Survey, compared with 27% in the one conducted from 1991–1994.<sup>15</sup> Therefore, it was with great need that the JNC 7 committee drew up a revised document, as the previous system was too

complicated for a number of reasons. For example, risk Group A (no risk factors) included only premenopausal women. Male gender and postmenopausal status were defined as risk factors.

Additionally, there was little value in distinguishing between stage 2 and stage 3 hypertension, as the treatment was the same for both.<sup>15,16</sup> Another important issue that the committee highlighted was that the old category of so-called normal to high BP (130/85–139/89 mmHg) led to complacency in patients, and did not adequately alert them to their risk.<sup>16,17</sup>

The JNC 7 report was published in 2003, with the following important highlights:<sup>16,17</sup>

- A systolic BP (SBP) of greater than 140 mmHg is a more important CVD risk factor than diastolic BP (DBP) in patients aged 50 years and older

- The CVD risk doubles for each increment of 20/10 mmHg, beginning at 115/75 mmHg.
- Prehypertensive individuals (SBP 120–139 mmHg or DBP 80–89 mmHg) should undergo lifestyle modification interventions to reduce the likelihood of disease progression.
- Thiazide diuretics should be used either alone, or as part of drug treatment, for uncomplicated hypertension.
- The initiation of therapy should involve more than two agents, one of which should include a thiazide diuretic, especially when the hypertension is complicated by other high-risk conditions, such as diabetes and chronic kidney disease, and in patients with a BP higher than 20 mmHg above the SBP goal, or more than 10 mmHg above the DBP goal.

### JNC 8

The JNC 8 report is a simplified treatment guideline for hypertension, whereby patients are categorised according to their age, and whether or not they have diabetes or chronic kidney disease (CKD). The actual definitions of hypertension and prehypertension are not addressed in these guidelines, but the thresholds for pharmacological treatment are highlighted. The latter includes agents from four medication classes, namely the angiotensin-converting enzyme (ACE) inhibitors, angiotensin II-receptor blockers (ARBs), calcium-channel blockers (CCBs) and thiazide-type diuretics.<sup>16</sup>

The JNC 8 guidelines was published 10 years after the JNC 7 report was launched. This guideline features a few changes:

- Discourages concurrent use of ACE inhibitors and ARBs, and promotes their use in all patients with CKD and hypertension.
- Initiating patients of African descent without CKD on CCBs and thiazides, and not the ACE inhibitors.
- Target goal blood pressure be reached within a month of initiating treatment by either pushing the dose of the initial drug higher or using a combination of medications.<sup>32</sup>

### South African hypertension guidelines

The Southern African Hypertension Society published the fifth hypertension guideline, which implements a national standard to improve the quality of care for persons living with hypertension. The main aim of the document is to diminish the impact of hypertension and related CVD on patients who are at risk in South Africa.<sup>14</sup>

#### Classification of blood pressure

According to the JNC 7 guidelines and the South African hypertension guidelines, the seven categories of BP defined in the JNC 6 were simplified and reduced to four. BP should be recorded with an approved device in a patient who has been seated for at least five minutes prior to taking the measurement. The patient should not have smoked, or taken any caffeinated drink or food in the preceding 30 minutes. To document postural hypotension in patients aged 60 years and older, and those with other comorbid conditions, e.g. diabetes mellitus, BP should also be recorded after

the patient has been standing upright for at least one minute.<sup>15,18</sup> The cuff size appropriate to the size of the patient's arm is an important parameter, and both the SBP and DBP should be recorded.

Self-monitoring of BP and ambulatory BP monitoring can be used in the following selected instances:<sup>15</sup>

- Suspected "white coat" readings (higher readings in the office compared to readings outside), or masked hypertension (normal readings in the office and higher readings outside).
- In patients with comorbid conditions according to which they are classified as a so-called high risk group, in order to guide antihypertensive medication.
- Refractory hypertension.
- To improve compliance with treatment (the self-monitoring of BP only).

BP can be staged according to actual BP and other comorbid conditions. Table I provides an overview of the BP categories.<sup>15,16</sup>

| Category               | Systolic blood pressure (mmHg) | Diastolic blood pressure (mmHg) |
|------------------------|--------------------------------|---------------------------------|
| Normal                 | < 120                          | < 80                            |
| Prehypertension        | 120–139                        | 80–89                           |
| Hypertension (stage 1) | 140–159                        | 90–99                           |
| Hypertension (stage 2) | ≥ 160                          | ≥ 100                           |
| Hypertension (stage 3) | > 180                          | > 110                           |

The following are the new optimal BP levels in patients 60 years of age or older, with or without comorbidities, according to the JNC 8:

- The BP goal is < 150/90 mmHg in patients aged 60 years or older, and who do not have diabetes or CKD.
- The new BP goal is < 140/90 mmHg in patients aged 60 years and older who have diabetes, CKD or both.
- Optimal BP is < 140/90 mmHg in patients aged 18–59 years of age, without any comorbidities.

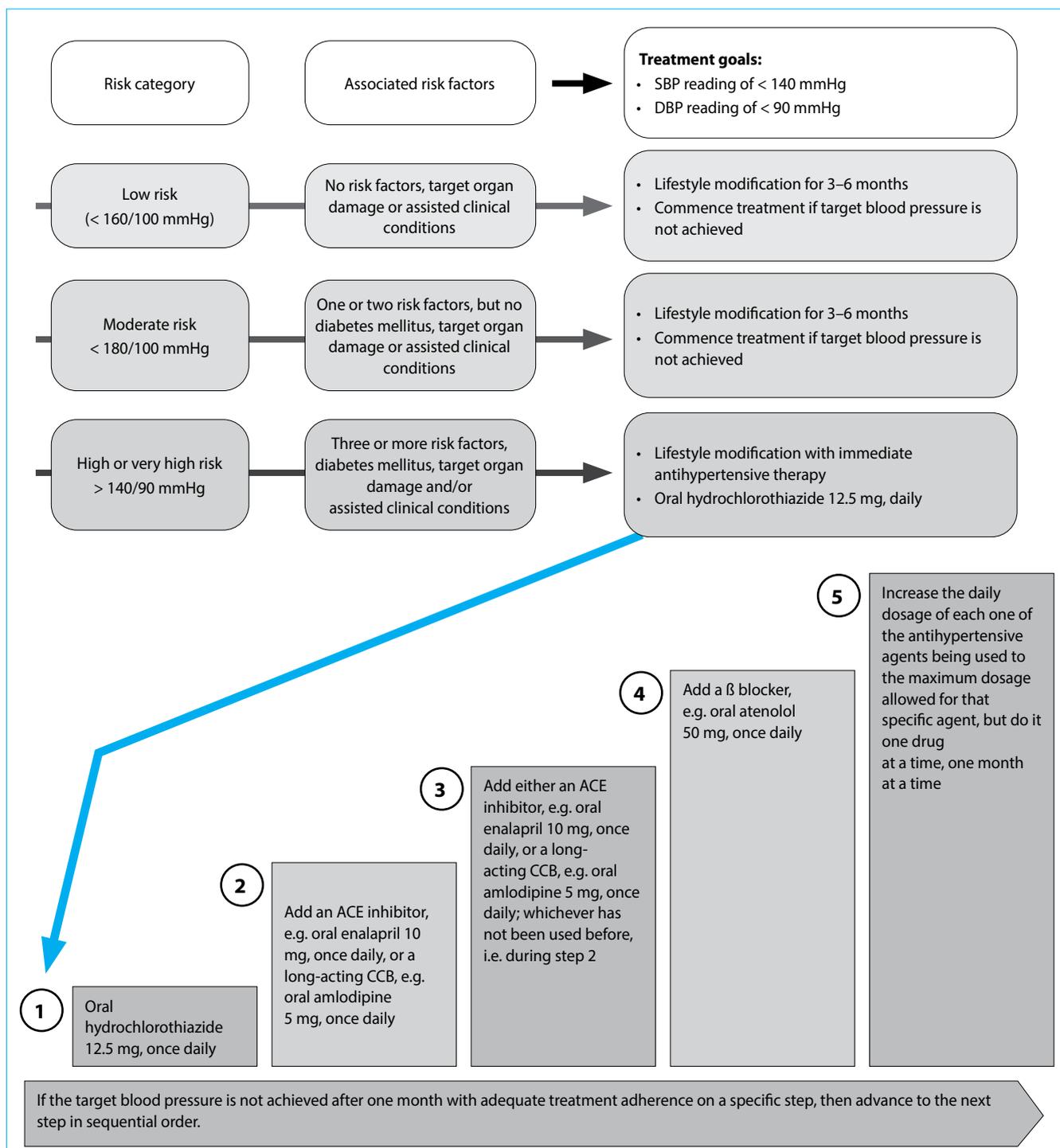
### Non-pharmacological treatment

The South African hypertension guidelines and the JNC 8 highlight the fact that the non-pharmacological management of hypertension has not changed from that outlined in the previous JNC 7 guideline. Lifestyle modification remains the key non-pharmacological management.

#### Lifestyle modification

A healthy lifestyle remains the foundation of managing hypertension, regardless of BP level. In addition to decreasing BP, it enhances antihypertensive drug efficaciousness and decreases total CV risk.

Thus, the following measures assist the patient to ensure a better, healthier life:



**Figure 2:** Standard treatment guideline for antihypertensive therapy according to the Standard Treatment Guideline and Essential Medicines List for South Africa<sup>27</sup>

ACE – angiotensin-converting enzyme, CCB - calcium-channel blocker

- **Achieving and maintaining an ideal body weight:** The ideal body weight is a body mass index of 18.5–24.9 kg/m.<sup>19,20</sup>
- **Limiting total sodium intake:** Sodium intake should be limited to < 2 400 mg/day or < 1 teaspoon of salt.<sup>9,21,22</sup>
- **Limiting alcohol intake:** Alcohol should be limited to two standard drinks per day for men, and one standard drink per day for women and men of a lesser stature.<sup>23</sup>
- **Following the nutrition guidelines published by the World Health**

**Organization (WHO):** The WHO guideline accentuates a diet that is low in total fat, with a high intake of fruit and vegetables (five portions per day), regular low-fat dairy products, fish rather than red meat, products that are low in saturated fat, a high intake of high-fibre wholegrain foods, low salt and the sparing use of sugar and sugar-containing foods.<sup>24</sup>

- **Partaking in regular, moderate-intensity exercise:** It is important to exercise for at least 30 minutes on most or preferably all days of the week, e.g. brisk walking.<sup>25,26</sup>

- *Avoiding the use of all tobacco products:* All tobacco products should be avoided, including snuff.

## Pharmacological treatment

According to the South African hypertension guidelines, the following factors should be considered when selecting an antihypertensive:<sup>14</sup>

- the cost of the drug class,
- patient-related factors, such as the presence of major risk factors, conditions favouring use and contraindications, and
- associated clinical conditions and target organ damage.

Figure 2 outlines the management of hypertension according to the Standard Treatment Guidelines and *Essential Medicines List for South Africa: Hospital Level, Adults*.<sup>27</sup>

## An overview of the changes

The ensuing discussion provides an overview of changes in the management of hypertension according to the JNC 7 and JNC 8.

### Point 1: Do not ignore systolic hypertension

High SBP, i.e. > 140 mmHg, is considered to be much more important than high DBP as a cardiovascular risk factor in patients aged 50 years and older.<sup>16,28</sup> The Multiple Risk Factor Intervention Trial (MRFIT) screened more than 316 000 men, and the investigators concluded that SBP was a stronger risk factor than DBP.<sup>16,28</sup> In addition to the MRFIT trial, another five were performed: the Hypertension Detection and Follow-up Program (HDFP), Hypertension-Stroke Cooperative Study, Medical Research Council (MRC) Study, the Australian National Blood Pressure therapeutic trial in mild hypertension (ANBP) and the Department of Veteran Affairs (VA) Cooperative Study Group on Antihypertensive Agents. Patients aged 30–69 years received medication to lower their DBP to < 90 mmHg, and the results indicated a reduction in cerebrovascular events, heart failure and overall mortality in patients. The JNC 8 panel considered keeping the DBP at a target goal of < 90 mmHg in young patients. However, there was insignificant evidence for the benefits of a SBP goal lower than 140 mmHg in patients younger than 60 years. The JNC 7 and 8 highlight two very important facts: the importance of controlling DBP in patients younger than 60 years in terms of reducing cardiovascular risk, and the need to control SBP in patients aged 60 years and older.<sup>15,16</sup>

### Point 2: Older patients will eventually become hypertensive

At some stage of our lives, everybody will eventually become hypertensive if he or she lives long enough. According to the Framingham Heart Study data, normotensive people aged 55 years have a 90% lifetime risk of developing hypertension. These data also indicate that people with a BP reading between 130/85 mmHg and 139/89 mmHg have a drastic 37.3% chance of developing sustained hypertension within four years if they are younger than 65 years, and 49.5% if they are older than that.<sup>16,29</sup>

### Point 3: Prehypertension creates hypertension

The risk of cardiovascular disease doubles with each increment of 20/10 mmHg above 115/75 mmHg for people aged 40–70 years.<sup>30</sup> People with a SBP of 120–139 mmHg, or a DBP of 80–89 mmHg, are now considered to be prehypertensive, and healthy lifestyle modifications, such as losing weight, exercise and reducing dietary sodium intake, might be able to delay or prevent the onset of hypertension.<sup>16</sup>

### Point 4: Use thiazides

Thiazides seem to be comparable to or better than other classes of drugs for many patients, and this group of drugs form the basis of antihypertensive therapy in most outcome trials.<sup>31</sup> JNC 8 recommended thiazide-type diuretics as initial therapy for most patients because of their evidence based efficacy and can be used as monotherapy or in combination with other drug classes.<sup>32</sup>

### Point 5: Patients will need more than one medication

It is most likely that patients with hypertension will need at least two antihypertensive medications to achieve their BP goal (< 140/90 mmHg for most patients, or < 130/80 mmHg for patients with diabetes mellitus and/or renal disease). Another drug from a different class should be added when the use of a single drug in adequate dosages fails to achieve the BP goal. It is necessary for most patients that one of the drugs is a thiazide diuretic as this boosts the effects of other classes of drugs.<sup>15,16</sup>

### Point 6: Patients with higher blood pressure should start with two drugs

It is essential to consider starting therapy with two agents, one of which should be a thiazide-type diuretic, if the patient's BP is higher than the BP goal by more than 20 mmHg (SBP) or 10 mmHg (DBP). The rationale is simple as many patients who are started on a single agent never achieve optimal control because their dosage is never adjusted upwards, or a second drug is never added. However, it is important to be cautious as patients can be at risk of orthostatic hypotension, e.g. those with diabetes or autonomic dysfunction, or those who are very old.<sup>15,16</sup>

### Point 7: Work with the patient to build compliance

Compliance is one of the most important key aspects in ensuring that effective therapy can take place. Patient motivation is very important when aiming to follow a healthy lifestyle.<sup>16</sup>

Therefore, healthcare professionals should take the following into cognisance:

- Try to understand the patient's attitudes, culture, beliefs and previous experiences with the healthcare system. In particular, determine his or her concerns and fears about therapy.<sup>16</sup>
- Ensure that the patient understands and agrees with the goals of therapy.<sup>16</sup>
- Remove barriers to care, such as the cost of treatment.<sup>16</sup>
- Ensure treatment strategies are tailored specifically for the patient and patient preference.<sup>32</sup>

**Table II: Guideline for the management of high blood pressure in adults**

| Class of drug   | Example of drug  |
|---|--|
| First-line and second-line treatment should be limited to four classes of medicines. Initiate one of these medications, either alone or in combination:   |  |
| Angiotensin-converting enzyme inhibitors  | Captopril<br>Enalapril<br>Lisinopril<br>Perindopril<br>Quinapril<br>Ramipril<br>Trandolapril |
| Angiotensin II-receptor blockers  | Eprosartan<br>Candesartan<br>Lorsartan<br>Valsartan<br>Irbesartan<br>Telmisartan             |
| Thiazide-type diuretics   | Hydrochlorothiazide<br>Indapamide  |
| Beta blockers   | Atenolol<br>Bisoprolol<br>Metoprolol<br>Propranolol  |
| Calcium-channel blockers  | Amlodipine<br>Diltiazem (extended release)   |
| Alpha and beta blocking agents  | Carvedilol   |
| If the BP goal is not achieved with the first drug of a particular class, the dosage of the initial drug should be titrated to the maximum recommended dosage to achieve the BP goal. <sup>32</sup>   |  |
| If the BP goal is not achieved with one drug from a particular class, a second drug should be added from the list above, and titrated up to the maximum recommended dose of the second drug to achieve the BP goal. <sup>32</sup>               |  |
| If the BP goal is not achieved with two drugs from a selected class, a third drug should be selected from the list above (different class), and it should be ensured that the combined use of ACE inhibitors and ARBs is avoided. <sup>32</sup> |  |
| The third drug should be titrated up to the maximum recommended dosage to achieve the BP goal.  |  |
| If all of the above medication fails, then a later-line alternative can be added from the list below.   |  |
| <b>Later-line alternatives</b>  |  |
| Add one of the following medications below to the therapy regimen:  |  |
| Loop diuretics  | Bumetanide<br>Furosemide<br>Torsemide  |
| Potassium-sparing diuretics   | Amiloride<br>Triamterene   |
| Aldosterone-receptor blockers   | Eplenerone<br>Spironolactone   |
| α blockers  | Doxazosin<br>Prazosin<br>Terazosin   |
| Direct vasodilators   | Hydralazine  |
| Peripherally acting adrenergic antagonists  | Reserpine  |

The following information is more specific to the JNC 8 guidelines.<sup>32</sup> First-line and later-line treatment should be limited to four classes of medicine:

- thiazide-type diuretics,
- CCBs,
- ACE inhibitors,
- ARBs

Second- and third-line alternatives include higher dosages or a combination of:<sup>32</sup>

- thiazide-type diuretics
- CCBs,
- ACE inhibitors,
- ARBs.

Numerous medications are now selected as later-line alternatives, such as:<sup>32</sup>

- $\beta$ -receptor blockers
- loop diuretics
- $\alpha$ -receptor blockers
- direct vasodilators
- aldosterone antagonists
- $\alpha$ -1 blockers and  $\beta$  blockers
- vasodilating  $\beta$  blockers
- central  $\alpha$ 2-receptor agonists
- peripherally acting adrenergic antagonists

Table II provides an overview of available medicines in South Africa, and includes some management principles.<sup>15,27,32</sup>

When titrating a drug treatment, it is very important to maximise therapy by employing the following steps:<sup>32</sup>

- maximise the first medication before adding a second medication, or
- add the second medication before reaching the maximum dosage of the first medication, or
- start with two medication classes separately, or as a fixed-dose combination.

## Recommendations

The following recommendations are necessary when selecting a medication for a patient.

Patients of African descent without CKD should use CCBs and thiazides alone or in combination, instead of ACE inhibitors, when initiating therapy. It was indicated in a single large trial, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), that a thiazide-type diuretic was shown to be more effective in improving cerebrovascular heart failure and combined cardiovascular outcomes, than an ACE inhibitor.<sup>33</sup> A CCB was also tested and the outcome was no different to that of a thiazide diuretic. In addition, a significant 51% increase in the risk of a stroke was seen in patients who used an ACE inhibitor as initial therapy, compared to a CCB.<sup>32,34</sup>

Patients with CKD, regardless of ethnic background, should use an ACE inhibitor or ARB alone or in combination as first-line therapy, or in addition to first-line therapy. Mean arterial pressure and different targets were used according to age in the African American Study of Kidney Disease (AASK) and Modification of Diet in Renal Disease (MDRD) trials, and only a DBP goal was used in the Ramipril Efficacy In Nephropathy 2 (REIN-2) trial. Treatment to achieve a lower BP goal that significantly lowered kidney or cardiovascular disease end-points, compared to a goal of lower than 140/90 mm Hg, was not shown in any of the trials.<sup>32,35,36</sup>

CCBs and thiazide-type diuretics should be used in patients aged 75 years and older with impaired kidney function, rather than ACE inhibitors and ARBs, owing to the resultant risk of hyperkalemia, increased creatinine and further renal impairment.<sup>32</sup>

## Conclusion

Hypertension is a haemodynamic disorder, associated with a rise in peripheral vascular resistance, that can, in turn, lead to myocardial infarction, renal failure, strokes and death, if not identified early and treated effectively. Guidelines used in the diagnosis and management of hypertension include the JNC 7 and JNC 8, the South African Standard Treatment Guidelines, Essential Medicines List and the South African hypertension guidelines. As part of the stepwise treatment in the management of hypertension, thiazide-type diuretics are still considered to be the initial first step, with an antihypertensive drug added according to the risk profile of the patient and/or the response to treatment.

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