

# South African perspective on limiting hypertension- related organ damage



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## Learning objectives

You will learn:

- That treating all hypertensives to a goal of  $<140/90$ mmHg is vital and protective in this COVID-19 era
- That while regular BP monitoring at this time may be challenging, this review suggests a variety of approaches that the clinician can use to ensure remote diagnosis and monitoring, and ongoing effective treatment
- About South African studies of effective combination therapies that support the clinician's choice of antihypertensive therapies in the population.

## Introduction

Hypertension, in my view, is the 'Cinderella' of cardiovascular (CV) and renal risk factors in the eyes of the public, media and some health professionals. This is despite the undisputed evidence garnered by insurance companies in the 1930s that elevated blood pressure (BP) is linked to CV and renal death.<sup>1</sup> Nonetheless, medical opinion at the time was that elevated BP was a compensatory mechanism to overcome vascular resistance caused by diseased arteries and that it would be foolish to lower it. Yet in fact, the then president of the USA, Franklin D Roosevelt, died of a massive 'unexpected stroke' after the end of World War II when his systolic BP reached 300mmHg!



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It was only in the 1970s that treating hypertension became an evidence-based practice when placebo-controlled studies were performed showing irrefutable evidence that treating it prevented adverse CV outcomes.<sup>2</sup> We now know that treating all hypertensives to a goal BP <140/90mmHg and ideally in high-risk patients to <130/80mmHg is cost effective and prevents CV events and death. The late Professor Bongani Mayosi stated that controlling hypertension was the ‘best buy’ for preventing CV disease in sub-Saharan Africa.<sup>3</sup>

In sub-Saharan Africa (and South Africa) the prevalence of hypertension has reached alarming proportions, with an overall prevalence of 40%.<sup>4,5</sup> Sadly, only 9% of all hypertensives are controlled due to a failure to screen, failure to treat and failure to treat to goal, resulting in over 500 000 premature deaths every year.<sup>6</sup> The reasons for this are complex but physician inertia is a major factor, combined with patient non-adherence and poor health infrastructure and policies. There needs to be an urgent public health initiative to deal with this emergency.

## The COVID-19 pandemic

The COVID-19 pandemic has placed hypertension back in the spotlight; together with diabetes it is the dominant comorbidity across all ages in people dying of the virus, even rather surprisingly eclipsing HIV in recent statistics provided by the Western Cape government (Table 1). Although the data are unadjusted, they provide a telling story of risk factors for severe disease and death. The reasons why hypertension is a risk factor for severity are not known, but it is clear that COVID-19 not only affects the lungs but has an important vascular component. As hypertension is primarily a vascular disease involving endothelial dysfunction, this is the probable link, but further research is required. In the author’s view it is important to diagnose hypertension, treat patients to

target and prevent hypertension-mediated organ damage as this is likely to mitigate the severity of disease. This view also applies to the treatment of other chronic diseases like diabetes.

There are several key issues relating to the care of patients with hypertension arising from the COVID-19 pandemic in South Africa (and the rest of the world):

1. Accessing care
2. BP measurement and diagnosing hypertension
3. Treating to target and appropriate monitoring
4. Identifying and preventing hypertension-mediated organ damage
5. Choice of medication.

*We know now that treating all hypertensives to a goal BP <140/90mmHg and ideally in high-risk patients to <130/80mmHg is cost effective and prevents CV events and death*

**Table 1. Commonest comorbidities in patients dying of COVID-19 in the Western Cape**

Age (years)	Hypertension	Diabetes	HIV
20-39	20%	30%	25%
40-49	28%	51%	33%
50-59	63%	70%	27%
60-69	70%	58%	8%
≥70	74%	46%	3%

## Accessing care

The COVID-19 pandemic has resulted in a dramatic reduction in patients accessing care for chronic diseases for fear of being infected by the virus. In state facilities, clinics have been closed or there is very limited access. For example, the Hypertension Clinic at Groote Schuur Hospital has been closed to routine follow-up or assessment of new patients. The long-term effects of all these changes are still to be determined and are not currently on the public radar.

In the author's view, it is essential to screen for chronic diseases opportunistically when patients come to the clinic for other ailments.

BP measurement is mandatory, but all guidelines require several BP measurements at separate visits before a diagnosis of hypertension can be made, unless the BP is severely elevated. The use of 24-hour ambulatory measurement (ABPM) is ideal to establish the diagnosis (see below), but patients are reluctant to come to the practice for two visits and follow-up. Home BP measurement is also a very useful strategy and patients are advised to purchase or borrow a validated home BP monitor and record their BPs. Follow-up can then be done remotely. Home BP can also be monitor established patients remotely.

## BP measurement and diagnosis of hypertension

American Heart Association/American College of Cardiology hypertension guidelines published in 2018<sup>7</sup> controversially redefined hypertension as a BP  $\geq 130$ mmHg systolic and/or diastolic  $\geq 80$ mmHg. However, the European Society of Cardiology/European Society of Hypertension and the International Society of Hypertension (ISH) subsequently published a comprehensive guideline in 2018 and 2020, respectively, in which the definition of hypertension was left unchanged at  $\geq 140/90$ mmHg.<sup>8,9</sup> The South African Practice Guidelines support the latter definition.<sup>10</sup>

All hypertension guidelines now emphasise the need for appropriate BP measurement techniques and the increased use of out-of-office BP measurement to diagnose (and monitor) hypertension.<sup>7-9</sup> Traditionally, the diagnosis of hypertension was based on a series of office BP measurements, repeated over a period of weeks or even months. However, office BP is not as accurate as both

home BP measurement and 24-hour ABPM because of the white-coat effect, making the latter options better predictors of hypertensive organ damage. Furthermore, 24-hour ABPM gives information about nocturnal BP, which is one of most important predictors of adverse CV outcome.<sup>11</sup> A simple algorithm (Figure 1) recommends incorporating both office and out-of-office BP in the initial diagnosis.<sup>12</sup> As noted above, during the COVID-19 pandemic the use of home BP monitoring is preferred and allows for remote monitoring.

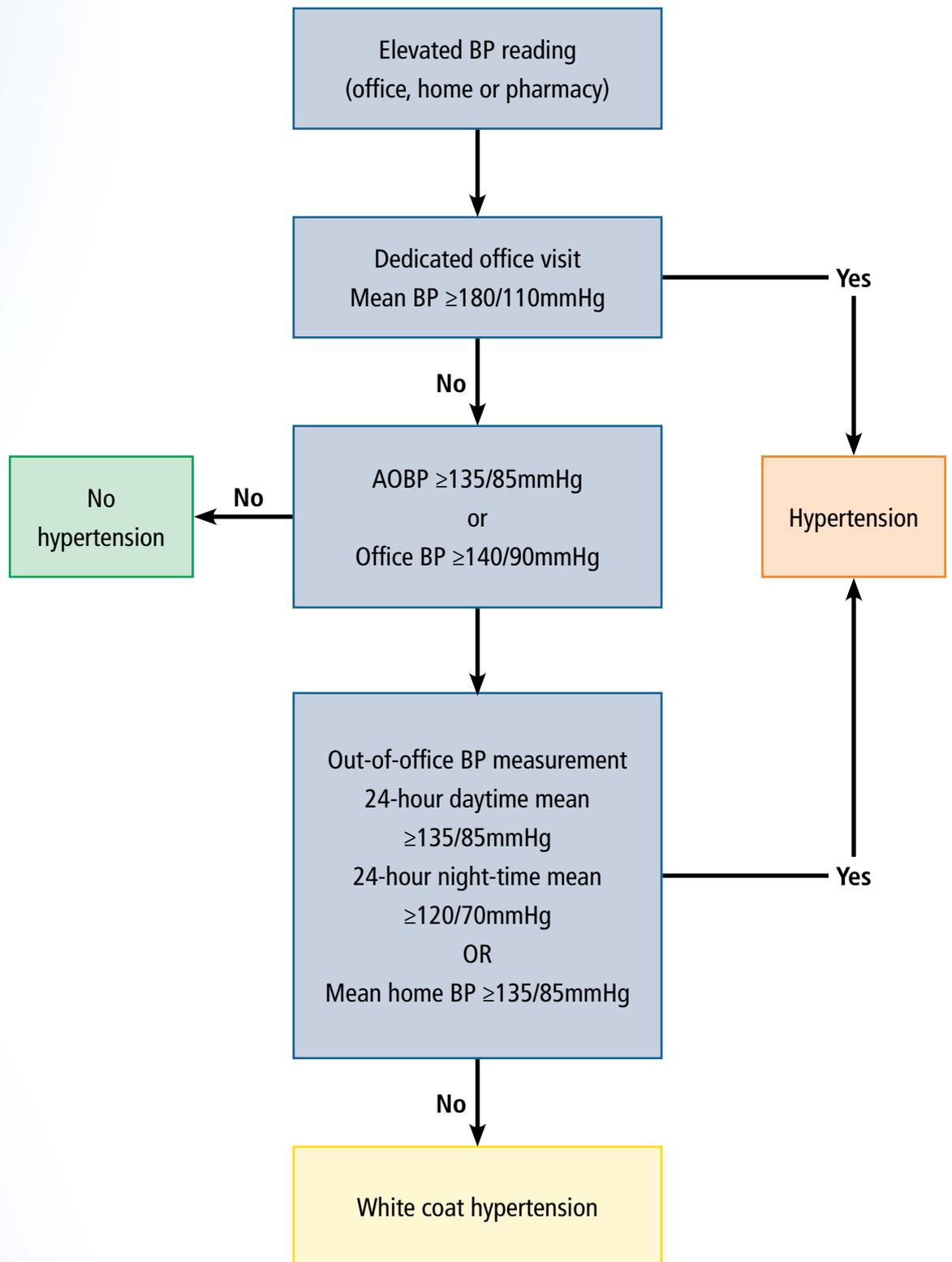
Home BP monitoring should be done over seven days with three BP readings taken in the morning and evening, and an average of all readings taken to define hypertension. The threshold values for the diagnosis of hypertension are shown in Table 2.<sup>10</sup> Out-of-office BP measurement is also important in assessing patients with apparent treatment resistance, who may have super-added white-coating.

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AOBP: automated office BP

Figure 1. Hypertension diagnostic algorithm<sup>10</sup>

**Table 2. Thresholds for the diagnosis of hypertension by different methods<sup>10</sup>**

	Clinic	Home	Ambulatory
<b>Predicts outcome</b>	Yes	Yes	Strongly
<b>Initial diagnosis</b>	Yes	Yes	Yes
<b>Cut-off BP levels (in mmHg)</b>	140/90	135/85	120/70 (mean night) 135/85 (mean day)
<b>Evaluation of treatment</b>	Yes	Yes	Limited but valuable
<b>Assess diurnal rhythm</b>	No	No	Yes

*Although it is widely recognised that hypertension is the dominant cause of both haemorrhagic and ischaemic stroke, a less well-recognised problem is the insidious and silent development of small-vessel disease in the brain, which is commonly present in middle-aged to elderly hypertensives*

### Assessment of hypertensive organ damage

The principal effects of hypertension are seen in the small vessels of the brain, kidneys and eyes, and the pressure effects on the heart. Assessment of organ damage can be undertaken by clinical examination and basic tests.

Elevated BP leads to the development of left ventricular hypertrophy (LVH). LVH can be detected clinically by a pressure-overloaded apex and a fourth heart sound, but assessment can be unreliable. An echocardiogram is not routinely available to the general practitioner; an electrocardiogram (ECG) is a basic test that is often overlooked in the assessment of hypertensive organ damage. The presence of ECG-detected LVH in the Framingham study significantly increased the risk of CV events by 40%. The specificity is good, but it lacks sensitivity for a variety of reasons. LVH is best determined by any one of the following three criteria:

- a. The Sokolow-Lyon criteria - adding the amplitude of the S wave in V1 plus the R wave in V5 or V6. If the sum is  $\geq 35$ mm, LVH is present
- b. Cornell voltage criteria (the sum of the amplitude of the R wave in aVL plus the S wave in V3 (plus V6 in females)  $\times$  QRS duration  $> 2.440$ mm/ms
- c. The R wave in aVL  $> 11$ mm.<sup>8</sup> Because of the complexity of the Cornell voltage, it is recommended that the practitioner use the Sokolow-Lyon and the R wave in aVL assessment.

Assessment of hypertensive kidney damage requires the results of the urinary albumin/

creatinine ratio (first voided urine best), serum creatinine and calculation of the estimated glomerular filtration rate (eGFR). Patients' risk for kidney damage and progression of disease and the need for referral are shown in Figure 2.<sup>13</sup> Essentially, the lower the eGFR and higher the albuminuria the more severe the kidney damage and the higher the risk of progression. Dipstick urine tests can also be used to assess albuminuria.

Retinopathy is an important sign of organ damage as the small vessels of the eye can be directly visualised, but this assessment is not routinely recommended during the COVID-19 pandemic due to the close personal contact required.

Although it is widely recognised that hypertension is the dominant cause of stroke, both haemorrhagic and ischaemic, a less well-recognised problem is the insidious and silent development of small-vessel disease in the brain, which is commonly present in middle-aged to elderly hypertensives.<sup>14</sup> Although magnetic resonance imaging (MRI) is not routinely recommended as part of assessing organ damage, it should be considered if there are early signs of cognitive decline, unsteady gait, speech or swallowing disturbances, and/or subtle long-track signs such as spasticity, hyperreflexia and/or abnormal reflexes. The MRI may show cerebral white matter lesions, microbleeds and/or lacunar infarcts in the internal capsule, midbrain, pons, cerebellum and medulla.

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Overall, the importance of finding hypertensive organ damage is that it establishes the diagnosis of hypertension and signifies a patient at greater risk for adverse CV outcomes. Specialist referral is often recommended if significant damage is detected. It

is also important to reassess these parameters annually to determine if there is regression or stabilisation of the hypertension-mediated organ damage. If there is, this signifies a good long-term prognosis.

				Persistent albuminuria categories		
				Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				ACR* <30mg/g <30mg/mmol	ACR* 30–300mg/g 3–30mg/mmol	ACR* >300mg/g >30mg/mmol
eGFR categories (ml/min per 1.73m <sup>2</sup> ) Description ad range	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			Refer
	G3b	Moderately to severely decreased	30–44		Refer	Refer
	G4	Severely decreased	15–29	Refer	Refer	Refer
	G5	Kidney failure	<15	Refer	Refer	Refer

ACR – Albumin-to-creatinine ratio; eGFR – Estimated glomerular filtration rate

Figure 2. Assessing risk and referral in relation to ACR and eGFR<sup>13</sup>

*The South African Hypertension Society recommends a universal target <140/90mmHg and, if tolerated, <130/80mmHg in individuals at high risk*

### Target BP

The South African Hypertension Society recommends a universal target <140/90mmHg and, if tolerated, <130/80mmHg in individuals at high risk.<sup>10</sup> This decision was largely pragmatic, based on the high levels of

uncontrolled BP in the population, simplicity of the recommendation and the resources needed to screen and treat the increased numbers of patients. This is also supported by the recent ISH guidelines 2020 (Table 3).<sup>9</sup>

**Table 3. ISH BP targets 2020<sup>9</sup>**

Essential	Target BP to reduce by at least 20/10mmHg, ideally to <140/90mmHg
Optimal	<65 years: <130/80mmHg if tolerated (but >120/70mmHg) ≥65 years: <140/90mmHg if tolerated and consider individualised target in context of frailty, independence and likely tolerability
Aim	Control BP within three months

## Treatment

Lifestyle changes should be prescribed in all patients, in addition to pharmacological treatment. Other risk factors need to be addressed and treated. Drug treatment should be started in all patients with established hypertension with moderate to high risk. The only exception is stage 1 hypertension with no other major risk factors, organ damage or overt CV or kidney disease, where lifestyle changes may be considered for 3-6 months.<sup>10</sup> Pharmacological treatment should be started in all patients with BP >160/100mmHg.

All guidelines agree that the first-line drug classes for treatment of hypertension are angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs) and thiazide/thiazide-like diuretics.<sup>7-10</sup> Initiation of combination treatment, preferably in a single pill, is advised in the majority of patients if the BP is 20/10mmHg above goal. This has been shown to result in prompt control and a greater reduction in CV events.<sup>15</sup> Most preferred combinations are ACE inhibitor/ARB plus either CCB or diuretic. However, in black patients a CCB plus diuretic has been shown to be effective, but serum potassium must be monitored for development of hypokalaemia.<sup>16</sup>

In the author's view, the most effective single-pill combination is either an ACE inhibitor or ARB in combination with a CCB. This is

effective in the old, in the young, in diabetics, in the obese and across all ethnic groups. Lercanidipine/enalapril is advantageous in those prone to peripheral oedema, and the concerns about lack of 24-hour BP control due to the shorter action of enalapril were not confirmed by a recent study undertaken in South Africa.<sup>17</sup>

Concerns have been raised about the use of ACE inhibitors and ARBs during the COVID-19 pandemic. Both classes raise ACE2, which is the binding site of the virus to enter the lung, and may increase the severity of the infection.<sup>18</sup> However, ACE2 prevents the inflammatory response in the lungs and may have a protective effect against the development of respiratory failure. Observational studies have reported no harm or benefit in hypertensive patients infected with COVID-19 who have been using these agents,<sup>19</sup> and all expert opinion and guidelines strongly suggest that ACE inhibitors and ARBs be continued or initiated in hypertensive patients.  $\beta$ -blockers are not part of first-line treatment, but in patients with coronary heart disease, heart failure, supraventricular tachycardia and, especially, atrial fibrillation, they are preferred. In patients with resistant hypertension, low-dose spironolactone 25mg daily is indicated provided there is no hyperkalaemia or the eGFR is <45ml/min/1.73m<sup>2</sup>.<sup>7-10</sup>

## Conclusion

The COVID-19 pandemic has underlined the harmful effects of hypertension on patients, and there is a greater need to target better BP control and the prevention or reversal of hypertension-mediated organ damage.

The pandemic has also caused significant impediments to the diagnosis and monitoring of hypertensive patients, and the author has suggested a variety of approaches to deal with this.

*Lercanidipine/enalapril is advantageous in those prone to peripheral oedema, and concerns about the lack of 24-hour BP control due to the shorter action of enalapril were not borne out by a recent study undertaken in South Africa*

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## Key learnings

- In South Africa, reasons for poor blood pressure control include physician inertia, patient non-adherence, and poor health infrastructure and policies
- Hypertension is a risk factor for severe COVID-19 disease and death
- Appropriate BP measurement techniques and use of out-of-office BP measurement improve diagnosis and monitoring of hypertension
- Assessment of hypertension-mediated organ damage can be undertaken by clinical examination and basic tests
- In black patients a CCB plus diuretic has been shown to be effective, but serum potassium must be monitored for development of hypokalaemia.

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