

# Hypertension – back to basics

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This article outlines the principles of blood pressure, including normal and dysfunctional physiology, mathematical equations of pressure, definitions of hypertension and diagnosis, and hence the rationale for and mechanisms of treating hypertension in order to reduce cardiovascular and cerebrovascular risk.

**Keywords:** hypertension, blood pressure, cardiac output, peripheral vascular resistance

## What is blood pressure?

Blood pressure (BP) is a product of cardiac output (CO) and peripheral vascular resistance (PVR).<sup>1</sup> Hence, changing either or both processes affects BP:

**BP = cardiac output (CO) x peripheral vascular resistance (PVR)**

CO is mainly associated with systolic blood pressure (SBP), while PVR is mainly associated with diastolic blood pressure (DBP). Breaking this mathematical relationship down further, it is evident that the individual components of CO are related to stroke volume and heart rate:

**CO = stroke volume x heart rate**

*Stroke volume* is a function of the three major factors affecting the volume of blood that is pumped out of the left ventricle during each systolic cardiac contraction, namely (i) preload (fluid volume/venous filling), (ii) contractility of the heart, and (iii) afterload (stiffness of the aorta; pressure against which heart has to pump). CO may also increase in many conditions other than hypertension, where the heart rate is increased, e.g. fever, anaemia, exercise, stress, pregnancy, hyperthyroidism, etc., which then presents with elevated SBP in keeping with the formulas outlined above.

*Pulse pressure* is the difference between SBP and DBP:

**Pulse pressure (mmHg) = SBP – DBP**

A normal SBP is 120, a normal DBP is 80, and thus a normal pulse pressure is 40 mmHg. Pulse pressure can rise with any clinical condition that has an increased cardiac output, such as fever, anaemia, hyperthyroidism or pregnancy, which causes elevated SBP. This is corrected by treating the underlying cause.

Ageing is associated with stiffening of the aorta and major blood vessels due to loss of elastic tissue. This increases afterload and may cause an isolated systolic hypertension, which is defined as an SBP > 140 mmHg but with a DBP < 90 mmHg. Clearly this would equate to an increased pulse pressure. The concern is that an elevated pulse pressure is associated with an increased mean arterial BP and increased cardiovascular (CV) risk:

**Mean arterial BP = DBP + 1/3 of pulse pressure =  
± 93 mmHg**

## What is hypertension?

BP is in a typical normally distributed biological variable curve (Bell shaped) with values at the high end of the distribution curve considered to be elevated BP defined as hypertension.<sup>2</sup>

In a large observational study involving one million adults in 61 prospective trials, there was a proportionate increase in CV risk starting at an SBP level of 115 mmHg and a DBP of 75 mmHg. For every 20 mmHg increase in SBP and 10 mmHg increase in DBP, there is a twofold relative increase in stroke mortality and a two-fold relative increase in mortality from coronary artery disease and other vascular diseases.<sup>3</sup> The absolute CV risk also depends on the presence of other CV risk factors and/or target organ damage as shown, e.g., in the ongoing Framingham Heart Study.<sup>4</sup>

This leads to a very interesting question: What is hypertension? (a) Is hypertension a BP level where there is an increase in CV risk? Or (b) Is hypertension a BP level where the benefit of treatment outweighs the harm of the treatment?<sup>2</sup>

Hypertension is currently mostly defined as higher than an arbitrary cut-off level which was chosen for pragmatic reasons to simplify diagnosis and treatment decisions. This arbitrary level of defining hypertension can also be influenced by the absolute or total CV risk of the patient. With a high CV risk, anti-hypertensive drugs may be initiated at lower BP levels.<sup>2,3</sup> BP values defining hypertension could change if and when new information becomes available.

## Classification of hypertension

The European Society of Hypertension/European Society of Cardiology criteria to define BP levels are as follows:<sup>5</sup>

- Optimal: SBP < 120 mmHg/DBP < 80 mmHg
- Normal: SBP 120–129 mmHg/DBP 80–89 mmHg
- High normal: SBP 130–159/DBP 85–89 mmHg
- Stage (Grade) 1 Hypertension: SBP ≥ 140–159/DBP 90–99 mmHg

- Stage (Grade) 2 Hypertension: SBP 160–179 mmHg/DBP 100–109 mmHg
- Stage (Grade) 3 Hypertension: SBP  $\geq$  180 mmHg/DBP  $\geq$  110 mmHg.

The South African Guidelines follow a similar classification of BP to the European Guidelines. The American guidelines have a different classification and consider a BP of  $\geq$  130/80 mmHg as hypertension.

### How should hypertension be diagnosed?

The basic concept in hypertension diagnosis is that the diagnosis is based on multiple BP measurements taken during many instances and using the mean value of all these readings. Ideally an elevated BP as measured in the clinic (consulting rooms) should be confirmed by an out-of-office measurement such as 24-hour ambulatory monitors or home BP measurements.

#### Blood pressure measurement methods

*Conventional clinic BP (office BP) (This represents a snapshot of total BP load)*

In general, this method is less reliable, but the accuracy can be increased by doing repeated measurements at different times of the day and on different days and all the measurements are then used to generate a mean value. At least two BP measurements on at least two occasions using a standard measurement technique, validated equipment, including the correct cuff size, should be the minimum practice.

Measure both arms initially (take highest for the value) and measure BP in one leg to exclude coarctation of the aorta. A marked difference between the two arms indicates the presence of significant atherosclerosis and is associated with an increased CV mortality especially using a cut-off of 15 mmHg.<sup>6</sup>

Patients with diabetes mellitus, the elderly, especially frail and other people with orthostatic hypotension due to autonomic insufficiency, should have their BP taken 1–3 minutes after standing up. Orthostatic hypotension is defined as a drop in SBP of 15 mmHg or more and a drop of DBP of 10 mmHg or more, especially if accompanied by symptoms such as dizziness.

#### *Unattended automated clinic measurement*

In this method, an automated electronic apparatus is used to obtain multiple readings with the patient sitting alone in a quiet room. The automated machine takes 3–5 measurements every five minutes (or at any other time intervals) and the machine then averages all the values. The BP readings taken with this method correlate closely with awake ambulatory readings.<sup>6</sup> This method increases the accuracy of the diagnosis of hypertension but must be done properly. The diagnosis of white coat hypertension can also be made with this method.

#### **Out-of-office blood pressure measurements**

##### *24 hour ambulatory BP measurements*

Advantages of this method are that it is the most accurate method to diagnose hypertension and is therefore considered

the gold standard. This method also provides night-time values to demonstrate dipper status which normally occurs when BP falls during sleep. In hypertension, a non-dipper pattern is associated with a worse prognosis. In addition, it provides the total BP load over 24 hours and is useful when episodic hypertension is suspected (e.g. pheochromocytoma). It can diagnose or confirm white coat hypertension – where the BP is elevated in the clinic but normal outside the clinic – as well as masked hypertension – where the BP is normal in the clinic but elevated outside the clinic.

#### **24 hour ambulatory bp measurements: normal values**

Over 24 hours: < 130/80 mmHg  
Daytime: < 135/85 mmHg  
Night-time: < 120/70 mmHg

#### **Home (self) blood pressure measurements**

This method is increasingly used for diagnosis and monitoring BP response to therapy. A normal value is < 135/85 mmHg. It is not possible to obtain nocturnal measurements with this method.

The best and most accurate way to confirm a diagnosis of hypertension is to use at least two different methods.<sup>5</sup> True normotension is diagnosed when office BP and one out-of-office measurements are normal.

#### **Hypertension phenotypes based on blood pressure:**

1. Dipper pattern: The normal BP pattern is associated with a BP decline at night during sleep. If a hypertensive patient has this BP pattern, it is associated with lower CV risk.
2. Non-dipper pattern: This phenotype does not have a decline of BP at night during sleep and is associated with an increased CV risk. Non-dipper is also associated with obstructive sleep apnoea, obesity, poor sleep quality, high salt intake, chronic kidney disease (CKD), diabetic neuropathy and orthostatic hypotension.
3. White coat pattern: In this phenotype, the BP values taken in the office (clinic) are higher than the BP values obtained outside the office (in ambulatory or home measurements). There could be a slight increase in CV risk in these people and this condition may not be as innocent as previously thought.
4. Masked hypertension pattern (This phenotype is also known as reverse white coat): It has an incidence of 15 to 30% of people with normal BP values in the clinic but elevated BP when tested out-of-office.<sup>7</sup> Exactly how and when to test for masked hypertension remains unclear. It is seen in the elderly but can also be seen in young males with psychological stress. Masked hypertension is associated with a significantly increased CV risk. People with masked hypertension sometimes present with left ventricular hypertrophy of unknown origin with a normal clinic BP measurement.
5. Variable hypertension (especially visit-to-visit): Variable BP readings have been associated with an increased stroke risk.
6. Isolated systolic hypertension (ISH): This phenotype is mainly seen in the elderly with reduced elasticity of arteries: SBP > 140; DBP < 90 mmHg with increased pulse pressure. It carries an increased CV risk and requires treatment.

### **Causes of hypertension**

*Essential hypertension* (primary or idiopathic) occurs in > 90% of cases. The exact cause of raised BP is unknown, but genetic and environmental factors – high salt intake, decreased potassium intake (as a surrogate for reduced vegetable intake), excessive alcohol intake, smoking, increased calorie intake and sedentary lifestyle all play a role.

*Secondary hypertension* may be caused by various conditions. These include:

1. Renal disease: CKD is both a cause of hypertension and a consequence of hypertension when damaged as a target organ disease (TOD).
2. Coarctation of the aorta.
3. Endocrine: over secretion of hormones, e.g. Cushing's, Conn's, pheochromocytoma.
4. Drugs, e.g. nonsteroidal anti-inflammatory drugs (NSAIDs), alcohol, anabolic steroids, cocaine, contraceptives.

### Epidemiology of hypertension<sup>5</sup>

Hypertension is diagnosed in 30–45% of adults older than 25 years overall and this high prevalence is consistent across the world, irrespective of income status. The prevalence of hypertension increases with increasing age with a prevalence of more than 60% in people older than 60 years.<sup>5</sup> People aged 80 years have a 90% chance of developing hypertension. Globally, hypertension is increasing, irrespective also of country income status. The major burden of hypertension has shifted to middle- and low-income countries such as sub-Saharan Africa and Asia where most hypertension cases are observed and where the age of hypertension diagnosis has also shifted to younger patients.

Hypertension is the single biggest contributor to CV disease and premature death and is responsible for  $\pm$  50% of global myocardial infarctions, stroke, and heart failure and  $\pm$  18% of global deaths. Hypertension contributes significantly to renal disease, dementia and to foetal and maternal health. It causes a two-fold increase in risk of coronary heart disease (CHD) and a four-fold increase in risk of stroke and heart failure. Hypertension is responsible for about 35% of atherosclerotic CV events.

### Absolute cardiovascular risk in hypertension<sup>3</sup>

In different patients with similar BPs of 145/95 mmHg, the CV risk can vary considerably. The absolute CV risk of hypertension is thus determined by:

1. Level of BP: The higher the BP level, the higher the CV risk.
2. The presence of other CV risk factors:  $\pm$  80% of hypertensive people have other CV risk factors.
3. Presence of end-organ damage due to hypertension:
  - Left ventricular hypertrophy (LVH)/heart failure.
  - Proteinuria/renal impairment/renal failure.
  - Abnormal fundus of the eyes such as soft and hard exudates or bleedings.
  - The presence of an atherosclerotic plaque in an artery, e.g. carotid, femoral artery.
  - The presence of existing ischaemic heart disease or stroke or peripheral arterial disease (PAD).

### Target organ damage

Complications of hypertension are numerous and include the following organ systems:

1. Heart: LVH – a powerful risk for atherosclerotic complications and heart failure – myocardial infarction (MI), heart failure, arrhythmias (especially atrial fibrillation), aortic valve insufficiency.

2. Aorta: Atherosclerosis, aneurysm and dissection may be caused by hypertension.
3. Peripheral arteries: Atherosclerosis: hyaline arteriosclerosis may occur in small arterioles including in the kidney and retina.
4. Renal: CKD is both a cause of hypertension and a sign of TOD.
5. Brain: Stroke, TIA and possibly dementia.

### Severe hypertension<sup>8</sup>

Severely elevated BP causing acute organ damage used to be called malignant hypertension or hypertensive crises. Different levels may cause different injuries. Very high BP (BP > SBP 180/DBP 110–120 mmHg) may cause acute injury to the heart, brain and kidneys, with damage to the microcirculation. Both the absolute level of BP, and the rate at which the pressure rises determine the organ damage.

1. Hypertension urgency: BP severely elevated but there is no TOD.
2. Hypertension emergency: BP severely elevated plus signs of acute TOD. It is reiterated that the speed at which BP rises is important. The basis for the development of complications is endothelium damage by fibrinoid necrosis of blood vessels.
  - Retina: Exudates, haemorrhages, papilloedema.
  - Kidney: Blood in urine (RBC casts) resembles glomerulonephritis picture.
  - Cardiovascular complications are acute MI, acute stroke, and acute heart failure that usually presents with acute pulmonary oedema.
  - Blood: Microangiopathic haemolytic anaemia (RBC fragmented).

### Hypertension management principles

The total management of hypertension should include a change in lifestyle as well as drug treatment, with one aim:

#### **To reduce the risk of cardiovascular and renal complications.**

The basis of effective management to reduce CVD risk, is to reach target or goal BP and to remain in target or goal BP ranges. This is the concept of target treatment time.<sup>6</sup>

### Lifestyle management of hypertension<sup>5</sup>

Healthy lifestyle choices can prevent or delay the onset of hypertension and can reduce CV risks.<sup>5</sup> They can also augment the effects of drug therapy and assist in reducing the pill load in some patients. Dietary changes include reducing sugar and refined starch and increasing fruit and vegetables, in concert with increasing moderate intensity exercise to at least 150 minutes per week. Sodium intake should be reduced by not adding salt to food and avoiding salt-rich (preserved) food. Smoking should be stopped, and alcohol consumption and weight should be reduced.

One meta-analysis showed modest reductions in SBP and DBP when lifestyle changes were made.<sup>9</sup> This is one of many

demonstrating the added benefit of lifestyle changes in lowering BP as an adjunct drug therapy.

### Drug treatment of hypertension

Eventually most patients, in addition to lifestyle modification, require drug treatment to control their BP. Licensed anti-hypertensive drugs have been tested in randomised clinical trials and are all associated with reductions in CV events to varying degrees (Table I).

The big question is how to improve BP control in treated patients? The European Hypertension Guidelines<sup>5</sup> encourage the use of combination drug therapy in most patients, especially in the context of lower BP targets. Single-pill combination (SPC) therapy of two drugs from different classes, was endorsed by the WHO in July 2019. SPCs improve patient adherence to drug therapy and their use creates a treatment algorithm that is simple, pragmatic and can be applied to all patients regardless of race, gender or age.

### When should drug treatment be initiated in hypertension?

The European, NICE (UK) and South African guidelines recommend drug therapy when BP exceeds SBP 140 mmHg and/or DBP 90 mmHg. The big issue is whether treatment should be initiated at a lower baseline BP. When the total CV risk is high (due to other CVD risk factors present or signs of TOD) it could be prudent to initiate drug treatment at a lower level of BP, e.g. SBP > 130 mmHg and DBP > 80 mmHg. This is a controversial issue and is endorsed by the USA guidelines and some others. The bottom line is that people with a high predicted total CV risk should be treated even when the BP does not exceed 140/90 mmHg, such as at BP > 130/90 mmHg.

### Treatment schedule for hypertension

The European Society of Hypertension and the International Hypertension Society suggest that treatment is prescribed as follows:

**Step 1:** Start with a combination of two drugs, preferably in a single pill, of a RAS-blocker (ACE inhibitor or an angiotensin-receptor-blockers [ARB]) and a calcium channel blocker (CCB) such as amlodipine. One can commence therapy with both components at half-dose. If this is inadequate, the dose of both components may be doubled to their maximum recommended doses.

A RAS-blocker plus a diuretic is an alternative combination. The diuretic is useful in the elderly, Black patients, incipient heart failure and CCB intolerance.

**Step 2:** If adequate reduction of BP is not achieved, then a triple combination of a RAS-blocker plus a CCB plus a diuretic should be used. Triple drug therapy in a single pill is currently available.

**Step 3:** Resistant hypertension: BP not adequately controlled despite three drugs, including a diuretic, at full dose. Consider using an aldosterone antagonist (e.g. spironolactone) at doses of 12.5 mg to 25 mg. This agent should not be used if serum potassium is above 5 mmol/l or if there is renal impairment.

#### Potential causes of resistant hypertension

1. Measurement issues, e.g. BP measured with an inappropriate cuff size.
2. Treatment issues: Inadequate or non-up titration of anti-hypertensive doses.
3. Doctor inertia to increase drug dose or to initiate combination therapy.
4. Secondary hypertension causes such as hyperaldosteronism, Cushing's and renal disease.
5. Obstructive sleep apnoea.
6. Drugs such as NSAIDs, cocaine, liquorice.

### Current recommendation of blood pressure targets (goals) according to European guidelines

**Step 1:** Aim for a BP of < 140/90 mmHg for all patients, including the elderly.

**Step 2:** If the patient can tolerate pharmacotherapy without harm (e.g. deteriorating renal function), aim for a BP of SBP < 130 mmHg and DBP below 80 mmHg in patients younger than 65 years. For patients older than 65 years, a goal of < 140/90

**Table I:** Anti-hypertensive drugs

Class	Types	Examples	Comments
Diuretics	Thiazide-like	Indapamide Chlorthalidone	Available in SA Currently not available in SA
	Thiazide	Hydrochlorothiazide	
	Mineralocorticoid antagonist	Spironolactone; Eplerenone	Aldosterone inhibitors
	Potassium-sparing diuretics	Amiloride	
RAS-blockers	Angiotensin-converting enzyme inhibitors (ACE-I)	Captopril Ramipril	
	Angiotensin-receptor-blockers (ARB)	Candesartan Telmisartan	
Calcium channel blockers	Dihydropyridines (DHP)	Amlodipine; Nifedipine	
	Non-dihydropyridine (NDHP)	Verapamil	
Beta blockers*		Carvedilol,** Bisoprolol,** Metoprolol**	Used 4 <sup>th</sup> line*** or if compelling reasons e.g. MI or heart failure associated with hypertension

\*Beta blockers should not be first-line treatment of hypertension except for post-myocardial infarction or heart failure with hypertension

\*\*When heart failure is present, there are only three proven beta blockers that reduce mortality

\*\*\*Atenolol has been shown not to be as effective in reducing cardiovascular endpoints as the other anti-hypertensive drugs and is especially poor for reduction of stroke

mmHg should be adequate. (Be careful with immobile frail elderly patients.) There are some indications that a lower target for the elderly may be beneficial. Measure BP in the elderly in the standing position because of the high prevalence of orthostatic hypotension in this age group.

If using home and ambulatory BP measurements, aim for BP of < 135/85 mmHg.

The important issue is to not only aim for the target BP, but to keep the BP at target at all times.

### Effect of treatment

The Thomopoulos et al. meta-analysis<sup>10</sup> of 68 randomised clinical trials involving 245 885 patients who received anti-hypertensive drugs has shown the following results for a reduction of SBP of 10 mmHg and DBP of 5 mmHg over five years of treatment:

Relative risk reduction of stroke: 36% (95% CI 29–43%) with numbers-needed-to-treat (NNT) of 53 (95% CI 45–65) to prevent the first stroke over five years.

Relative risk reduction of coronary heart disease (CHD): 18% (95% CI 14–24%) with NNT of 133 (95% CI 100–171) to prevent the first CHD event over five years.

Relative risk reduction heart failure: 38% (95% CI 25–49%) with NNT of 53 (95% CI 42–79) to prevent the first heart failure over five years.

Relative risk reduction of CV death: 16% (95% CI 8–23%) with NNT 125 (95% CI 88–249) to prevent the first CV death over five years.

The relative risk reductions are very similar for hypertensive patients with and without diabetes mellitus. The absolute risk reductions are higher and better with higher CV risk patients.

A rather contentious issue is to what level should the DBP be reduced before possible ischaemic damage to the myocardium occurs? The conventional target DBP should probably not be lower than 60 mmHg. There is, however, insufficient trial data to be absolutely sure.

### Conclusion

The following may serve as a framework for the management of a patient with hypertension:

1. Diagnosis of hypertension: multiple readings are necessary using clinic or 24-hour ambulatory or home measurements. The clinic (office) BP measurement is regarded as screening for hypertension and an out-of-office measurement is necessary for confirmation of diagnosis.

2. Look for obvious secondary causes: Sometimes the phenotype of the patient will aid the diagnosis, e.g. the Cushing's-phenotype.
3. Test for other CV risk factors: More than 80% of hypertension patients have other CV risk factors. Treat these if present alongside BP treatment, e.g. the use of statins in hypertension is associated with additional reductions in MI.
4. Test for TOD using a resting ECG for LVH and urine dipstick for the presence of proteinuria. These are the minimum tests.
5. Regarding treatment, start with lifestyle changes which may aid in the treatment and contribute to BP reduction. Eventually patients will need drug therapy. Lifestyle changes may also enable one to reduce the pill load. Typical measures which can be taken are the reduction of salt intake, cessation of smoking, exercise, reduction of alcohol intake and increased vegetable and fruit intake.
6. Achieve goal BP levels and maintain BP below target or goal levels. Review the progress of the patient regularly. Control of BP is essential and preferably must be achieved within at least the first three months to maximise the benefits of treatment.

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