ESSENTIAL HYPERTENSION

Elevated blood pressure is one of the most important causes of cardiovascular disease.

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Cardiovascular diseases are a leading cause of death and disability worldwide. Almost 70% of the cerebrovascular disease burden (stroke burden) and about 50% of the ischaemic heart disease burden are due to elevated blood pressure levels. In more than 95% of cases of hypertension, no single reversible cause can be found (essential hypertension).

A basic definition of blood pressure (BP):
BP = cardiac output x peripheral resistance
(cardiac output = stroke volume x heart rate)

DEFINING HYPERTENSION

Physiologically, hypertension can be viewed as an increase in BP due to an increase in cardiac output and/or peripheral resistance. The problem is to separate 'normal' blood pressure from high BP. Traditionally hypertension is defined as a BP $\geq$ 140/90 mmHg because, for most people, this is the level above which the benefits of treatment outweigh the risks. However, there is a continuous association between increasing BP and risk of cardiovascular disease (CVD): stroke, coronary heart disease (CHD), peripheral arterial disease (PAD), heart failure, renal failure, dementia and death. This risk starts at a level of 115/75 mmHg and doubles with every 20/10 mmHg increase in BP above the level of 115/75 mmHg. Hypertension is also recognised at a level of $\geq$ 130/85 mmHg in patients with the features of the metabolic syndrome. One way to evaluate the impact of BP on cardiovascular events, is to calculate an individual's absolute CVD risk. Someone may have a normal BP, yet be at a very high CVD risk. More than 80% of hypertensives will have additional CVD risk factors which will influence their absolute CVD risk. Some prefer the term BP-related diseases rather than the term hypertension to demonstrate that BP level is only one component of CVD risk.

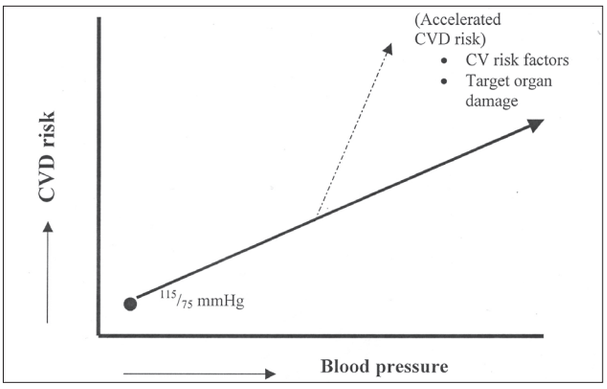

Fig. 1. The relationship between CVD risk and BP.

Fig. 1 demonstrates two important points:

- There is a direct, continuous rise in CVD risk (CHD, PAD, stroke, heart failure, renal disease) and rising BP, starting at a pressure of 115/75 mmHg.
- With the presence of other risk factors (elevated glucose, elevated LDL, elevated total cholesterol, elevated triglycerides, low HDL, smoking) or with target organ damage (microalbuminuria, proteinuria, left ventricular hypertrophy (LVH), previous stroke, previous myocardial infarct, previous PAD) the CVD risk accelerates.

In Fig. 2, the levels of normal BP (< 120/80 mmHg) and prehypertension are demonstrated.

In recent guidelines the term prehypertension was created to identify individuals who have an increased risk of developing hypertension. This is not a disease category, but such individuals should be evaluated for other CVD risk factors (especially the metabolic syndrome) and then followed up regularly, and lifestyle management should be initiated. These people do not necessarily need drug treatment, unless their absolute CVD risk is high. Many people with prehypertension will eventually develop hypertension.

How common is hypertension?

Hypertension affects 1 in 4 (± 25%) of adults. The prevalence rises with age, so that 60 - 70% of people older than 70 years will have hypertension. The Framingham Heart Study showed that at the age of 55, people have a 90% chance of developing hypertension if they are expected to live to the age of 80 years (the residual lifetime risk of hypertension).

In the USA, hypertension prevalence in the population has been shown to be on the increase, a trend which has also been shown in some other countries. The age-related rise in systolic BP (due to loss of elasticity of large arteries) is primarily responsible for the increased prevalence of hypertension with increasing age. Systolic BP has increasingly been recognised as an important risk factor (even more important than diastolic BP) for CVD. This concept was neglected in the past.

Other causal factors that may contribute to the rise in hypertension with age are:

- increasing body weight
- excessive sodium intake
- excessive alcohol intake
- reduced physical activity
- inadequate intake of fruit, vegetables and potassium in the diet.

There is also a genetic component to the development of hypertension, as hypertension runs in families, emphasising the influence of a complex genetic BP dysregulation.

PATHOPHYSIOLOGY

Important mechanisms of BP regulation which become abnormal in hypertension are:

Sodium and fluid balance

- The kidneys play a central role in essential hypertension: renal sodium excretion is impaired at any degree of raised BP (probably part of a generalised membrane abnormality).
- Salt sensitivity is an important mechanism.
- Stimulation of the renal sympathetic nervous system and activation of the renin-angiotensin system in hypertension promote sodium and fluid retention – elevated angiotensin II is an important mechanism.
- Obesity is strongly associated with hypertension – it is associated with stimulation of the sympathetic nervous system and the renin-angiotensin system.
- Low numbers of nephrons at birth are linked to hypertension, probably due to an altered mechanism of sodium handling. Genetic factors and fetal/maternal nutritional factors during pregnancy could play an important role in low nephron numbers.

Vasomotor tone of peripheral arteries

Increased peripheral arterial resistance is the hallmark of essential hypertension. Vascular smooth muscles can either contract (vasoconstriction) or be permanently narrowed by remodelling of the arterioli. Angiotensin II levels, sympathetic nervous system stimulation and many other factors cause constriction and/or narrowing and thus increase peripheral resistance. Genetic factors also have an influence on the reactivity of peripheral arteries.

Endothelial dysfunction (common in obesity, in diabetics and in people with CVD risk factors) contributes to abnormal vascular resistance.

Ageing and pulse pressure

Systolic BP rises progressively with age in industrialised societies (it does not happen in societies with low consumption of calories and salt) and diastolic BP remains constant or may decrease, creating an increase in pulse pressure: isolated systolic hypertension. In this condition the main haemodynamic defect is decreased distensibility of the large arteries (e.g. aorta). This condition creates a high CVD risk due to repetitive pounding of the blood vessels with each cardiac cycle and the return of the pulsatile wave from the periphery to the heart. In the Framingham study (as in other studies) systolic BP level has been shown to be a powerful predictor of CVD disease.

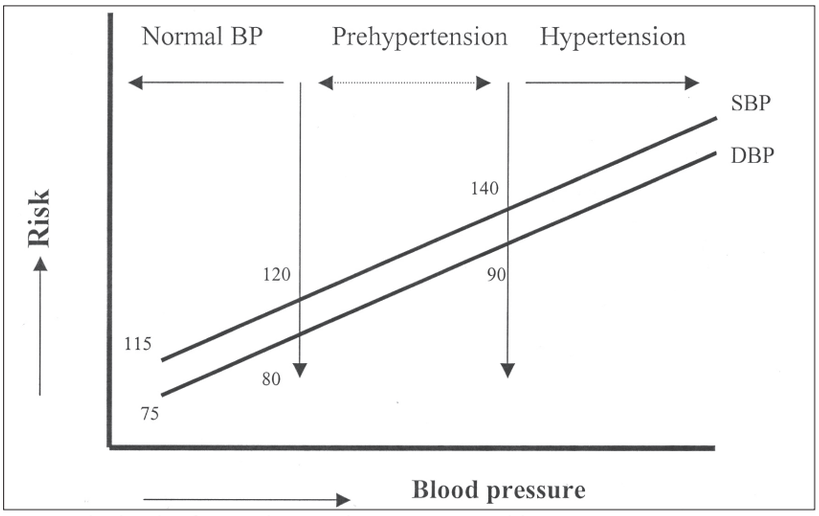

Fig. 2. The levels of normal BP, prehypertension and hypertension.

Almost 70% of the cerebrovascular disease burden (stroke burden) and about 50% of the ischaemic heart disease burden are due to elevated blood pressure levels.

Traditionally hypertension is defined as a BP ≥ 140/90 mmHg because, for most people, this is the level above which the benefits of treatment outweigh the risks.

INITIAL EVALUATION FOR HYPERTENSION

The focus should be on 3 goals:
- the accurate assessment of BP
- the evaluation of CVD risk and
- looking for a secondary and preventable cause of raised BP.

Accurate assessment of BP

This is essential to ascertain risk and to monitor management.

Office (clinic) BP

- To get a clear picture of a patient's usual BP, multiple readings on several occasions are necessary, because BP can vary considerably over a 24-hour period. Using the auscultatory method and a mercury sphygmomanometer is the method of choice. Aneroid and electronic devices are also increasingly used. All devices should be regularly inspected and validated to ensure accuracy of measurement.
- A correct cuff size is important: a cuff bladder encircling at least 80% of the arm is needed.
- Measure BP at least twice with a 5-minute interval between measurements. Patients should be sitting (preferred position) and have had no exercise, not drunk caffeine or smoked for at least 30 minutes prior to measurement.
- Standing BP measurements are necessary for those at risk of postural hypotension (diabetes mellitus, the elderly, patients on multiple drugs).

Ambulatory blood pressure (ABP)

ABP gives a better prediction of risk than office measurements. ABP measurements give the best time-integrated BP burden and therefore correlate best with target organ damage (e.g. LVH).
Normal ABP:
- daytime < 135/85 mmHg
- nighttime < 120/70 mmHg
- 24-hour BP < 130/80 mmHg.

Comparison of ABP monitoring and home BP measurement with casual (clinic) BP measurement has demonstrated 4 groups of BP responses:
- Normotensive by all methods: true normotensives.
- Hypertensives by all methods: true hypertensives (sustained hypertensives).
- Hypertensives by clinic (casual) measurements but normotensive by ambulatory measurements and home measurements: white coat hypertension. This is best diagnosed with ABP (elevated office reading, normal rest of day and night). Patients with this condition may not always benefit from drug treatment, but should be placed on lifestyle management and followed up biannually or annually with 24-hour ABP.
- Masked hypertensives (reversed white coat hypertension) are normotensive by clinic (casual) measurement and hypertensive by ABP or home BP measurement. This condition seems to be more common than thought and is seen as an explanation for many cases of LVH of unknown origin. Suspicion of this condition should be raised in patients with a family history of hypertension in both parents, central obesity, with multiple cardiovascular risk factors and in those with BP readings that at times are normal and at times elevated. Masked hypertension needs treatment.

ABP is also useful in certain circumstances to evaluate the efficacy of therapy for dose adjustments. For example, sometimes it is necessary to have an evening dose of an antihypertensive agent or to rule out hypotensive episodes.

ABP is also useful to evaluate resistant hypertension. The use of ABP demonstrated that BP normally varies according to a circadian rhythm, typically decreasing by 10 - 20% at night during sleep (dippers) and that in non-dippers, the end-organ damage and prognosis of hypertension may be worse than that in dippers.

Home BP measurement

There is increasing evidence that home readings of BP adequately predict cardiovascular events and are particularly useful for monitoring the effects of treatment. It also engages patients in their own management, which may improve compliance to therapy. In patients with a home BP < 130/80 mmHg despite an elevated clinical BP without target organ damage, drug therapy may be withheld and lifestyle management initiated.

Evaluation of global CVD risk

Both clinical examination and special investigations are done to determine CVD risk in an individual patient with elevated BP. Cardiovascular risk is determined by 3 factors:
- BP level
- presence of other CVD risk factors
- presence of target organ damage (TOD).

These 3 groups of risk factors have an additive effect on cardiovascular risk.

BP level

Cardiovascular disease risk increases progressively and linearly from levels as low as 115/75 mmHg. The level of systolic BP is an additional independent risk factor. Remember that for every 20 mmHg that systolic BP rises, the CVD risk doubles.

Major CVD risk factors

Cigarette smoking; dyslipidaemia (elevated total cholesterol, LDL, TG, low HDL); diabetes mellitus; obesity;

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In most patients, several drug classes and combinations need to be rotated to optimise treatment at acceptable tolerance.

age (> 55 years for men, > 65 for women); chronic renal disease – glomerular filtration rate (GFR) < 60 ml/min, urine protein > 150 mg/24 h. Each of these risk factors compounds the risk from hypertension.

Target organ damage

- **Heart:** left ventricular hypertrophy; angina; previous myocardial infarction; previous myocardial revascularisation procedures; heart failure; dysrhythmias (especially atrial fibrillation, ventricular extrasystoles).
- **Brain:** previous stroke; transient ischaemic attack; dementia.
- **Renal:** GFR < 60 ml/min; urine protein > 150 mg/24 h.
- **Peripheral arterial disease (atherosclerosis).**

Calculating CVD risk

By considering these 3 groups of risk (BP, CVD risk factors, TOD) patients can be placed in risk groups:

- **Low risk:** only BP elevated. About 2% of hypertensive patients fall in this group.
- **Moderate risk:** 60% of hypertensive patients fall in this group. They have 1 or more additional CVD risk factors, other than diabetes, and have no TOD.
- **High risk:** These patients have clinical evidence of TOD or CVD. All patients with type 2 diabetes mellitus and all with renal insufficiency are also placed in the high-risk group. More than 30% of hypertensive patients fall in this group.

There are a number of tables (statistical tools) to calculate CVD risk, into which these risk factors are integrated. One that is widely used is the Framingham risk score. The tables calculate the absolute risk which estimates an individual's probability of an adverse cardiovascular event occurring in a defined period of time of 5 or 10 years (e.g. 20% risk over next 10 years).

Look for a secondary potentially reversible cause for hypertension

Routine searching for a secondary cause for hypertension may not be cost effective in all patients. The following circumstances constitute indications to search for a secondary cause:

- Finding a clue on the initial examination, e.g.:
  - palpable mass in abdomen (polycystic kidney)
  - abnormal renal function (chronic kidney disease)
  - Cushingoid appearance (excess glucocorticoid)
  - unequal pulses and BP readings between arms and/or legs (coarctation)
  - snoring, daytime somnolence (sleep apnoea)
  - hypokalaemia not due to diuretics (primary aldosteronism)
  - attacks of tachycardia, headache, pallor (phaeochromocytoma)
  - thyroid or parathyroid disease.
- Refractory/difficult to treat hypertension. The term resistant hypertension is used when the BP is elevated > 140/90 mmHg despite 3 or more antihypertensive drugs. Non-adherence to treatment is an important cause to exclude before embarking on trying to find a secondary cause of hypertension.

TARGET BP LEVELS (GOAL BP)

Target BP levels are listed in Table I. For most patients to reach these targets you require:

- a motivated compliant patient (adherence to treatment)
- the use of 2 or more drug classes.

MANAGEMENT OF HYPERTENSION

The primary goal of treatment of hypertension is to prevent CVD and death.

Non-drug management (lifestyle modifications)

If a healthy lifestyle is implemented in childhood, many cases of hypertension will be prevented. Once hypertension is established, lifestyle modifications alone are rarely sufficient to replace medications completely, but lifestyle modifications very often lead to a decrease in medication requirements. Lifestyle modification includes:

- Weight loss.
- Moderate dietary sodium reduction – reducing salt can not only independently reduce BP, but also improve the efficacy of ACE-inhibitors, angiotensin receptor blockers (ARBs) and beta-blockers. Processed foods are an important source of salt and should be avoided.
- Increased consumption of vegetables and fruit – the DASH trial (Dietary Approach to Stop Hypertension) confirmed the effectiveness of these dietary measures.
- Cessation of smoking.
- Reduced alcohol consumption: a maximum of 2 units of alcohol per day for a man and 1 unit of alcohol per day for a woman. Consumption of alcohol should preferably be stopped altogether.
- Regular aerobic exercise – BP can be lowered for up to 16 hours after 1 hour of aerobic exercise.
- Relaxation techniques, such as meditation, biofeedback etc. can acutely lower BP but have little effect on chronic hypertension.

Table I. **Target BP levels**

Patient risk	Target BP
Most patients at relatively low risk	< 140/90 mmHg
With coronary artery disease	< 130/80 mmHg
With diabetes mellitus	< 130/80 mmHg
With chronic renal disease	< 130/80 mmHg
With significant proteinuria (> 1 g/d)	< 125/75 mmHg
Isolated systolic hypertension	< 140 mmHg systolic BP diastolic BP not below 65 mmHg (very low DBP in the elderly may impair myocardial perfusion)

- Stress management is beneficial to the patient's well-being, but rarely sufficient to control hypertension.

Drug treatment

The aim with drug treatment of hypertension is to:

- lower blood pressure to achieve normal levels of BP or goal BP levels
- reduce cardiovascular and renal complications
- increase longevity
- improve quality of life.

How effective is treating raised BP?

Placebo-controlled trials of antihypertensive drugs in middle-aged and older hypertensive patients showed that:

- reduction of diastolic BP of 5 - 6 mmHg sustained for 5 years reduced stroke by nearly 40%, coronary events by 15% and heart failure substantially (± 50%).
- in older patients with isolated systolic hypertension reduction of BP reduced stroke by about 30%, CAD by ± 20%, and heart failure significantly.
- achieving a sustained 12 mmHg reduction in systolic BP over 10 years will prevent 1 death for every 11 patients treated; if there is CVD or TOD, 1 death will be prevented for every 9 patients treated.

Which drugs to use

A number of classes of anti hypertensive drugs have been shown in outcomes-based clinical trials to reduce CVD events and deaths.

- Diuretics: low-dose 6.125 - 12.5 max 25 mg per day, e.g. hydrochlorothiazide. In multiple trials, low-dose thiazides have consistently reduced stroke, myocardial infarctions and mortality in hypertensives.
- Beta-blockers (low-dose). There are indications that beta-blockers in uncomplicated hypertension may have limited value. In fact, some argue that for primary prevention beta-blockers are obsolete. However, in patients with hypertension and coronary artery disease, beta-blockers may be valuable.
- ACE-inhibitors.
- Calcium channel antagonists (long-acting).
- Angiotensin receptor blockers (ARBs).

The question of which drug class is the best suited to start therapy is largely obsolete. **Lowering BP to goal is more important than the use of a specific drug.** Use as many drugs as necessary to reach target. The majority of patients will need 2 or more drugs to achieve goal BP. In most patients, several drug classes and combinations need to be rotated to optimise treatment at acceptable tolerance.

Certain compelling indications require certain specific drug classes, e.g. a patient with hypertension and ECG criteria of LVH needs an ARB; a patient with hypertension and proven coronary artery disease needs an ACE-inhibitor. Specific risk profiles of patients may direct one to use a specific type of antihypertensive drug. Table II gives a guideline basis for compelling indications for individual drug classes.

If the treatment of hypertension is viewed from a cost aspect, start with a thiazide-like drug. If goal is not reached, add an ACE-inhibitor and/or a long-acting calcium channel blocker. Many authorities recommend that low-dose thiazides should be a component of any combination because of low cost and proven efficacy.

Combination therapy

The best combination of drugs is not known, but recent indications are that a long-acting calcium channel antagonist and an ACE-inhibitor may be better than a combination of a beta-blocker and a diuretic.

How to improve compliance and quality of life

- Treatment and drug dosage adjustments should be based on home readings, which engages patient participation.
- Use long-acting agents which require once-a-day dosing.
- Use drugs with a low side-effect profile.
- Use low-dose combinations from different classes to achieve a synergistic effect on lowering BP but avoiding dose-dependent side-effects.
- Use fixed-dose combinations to reduce the number of pills.
- Use lifestyle modifications to augment drug effects.

How long should we wait before adjusting doses?

In the majority of low-risk patients (only elevated BP, no target organ damage) it is safe to wait 6 weeks before changing the dose. It is best to evaluate high-risk patients after 1 - 2 weeks and change the dose or add other drugs.

MANAGEMENT ESSENTIALS

Reduction of BP

- Control of BP to goal levels.
- Systolic BP should be controlled to below 140 mmHg – if SBP is lowered to 20 mmHg below the usual SBP of the patient, the CVD disease risk can be halved.
- Reduction of the 24-hour BP load (use ABP and/or home measurement of BP).
- Lifestyle management: augment drug effects.

End-organ protection

- LVH – reversal is associated with reduction of cardiovascular events.
- Proteinuria reduction can slow renal deterioration.
- Reduction in dementia may occur.

Reduction of atherosclerosis

- Control other risk factors with appropriate drugs: > 80% of hypertensives have other risk factors.
- Reduce cholesterol with a statin.

Aspirin

Consider low-dose aspirin in all hypertensives when the BP is controlled. Many argue that aspirin should be routinely given to all people above the age of 50 years regardless of BP level.

Table II. **Clinical trial and guideline basis for compelling indications for individual drug classes**

Compelling indication	Recommended drugs					
	Diuretic	BB	ACEI	ARB	CCB	Aldo ANT
Heart failure	√	√	√	√		√
Post-myocardial infarction		√	√			√
High coronary disease risk	√	√	√		√	
Diabetes	√	√	√	√	√	
Chronic kidney disease			√	√		
Recurrent stroke prevention	√	√				

BB = beta-blockers; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; Aldo ANT = aldosterone antagonist.

IN A NUTSHELL

Recently it became clear that the risk for cardiovascular events starts at a BP level of 115/75 mmHg. Thereafter the risk is a continuous linear one.

The presence of other risk factors (elevated glucose, elevated cholesterol, smoking) and target organ damage increases the CVD risk.

Attaining goal BP (< 140/90 mmHg or < 130/80 mmHg in high-risk patients) should be pursued even if it implies using multiple drugs.

Lowering BP is more important than the type of drug used.

Further CVD risk reduction should be possible by treating risk factors, especially adding a statin to control cholesterol.

Further reading

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