Clinical guidelines for the management of hypertension

World Health Organization
Regional Office for the Eastern Mediterranean

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Foreword

The World Health Organization has estimated that high blood pressure causes one in every eight deaths, making hypertension the third leading killer in the world. Globally, there are one billion hypertensives and four million people die annually as a direct result of hypertension. In the Eastern Mediterranean Region, specifically, cardiovascular diseases and stroke are becoming major causes of illness and death. They account for 31% of deaths, and hypertension currently affects 26% of the adult population in the Region. These figures are attributable to ageing populations, high rates of smoking and changes in nutritional and behavioural habits. This necessitates setting priorities for screening, early detection and management of hypertension to be applied and followed among Eastern Mediterranean countries, through community-based programmes.

Primary prevention is the most cost-effective approach to containing the emerging hypertension epidemic. Obesity remains the single most important contributing factor and, in fact, most hypertensive patients in our Region are overweight or obese. Weight reduction reduces blood pressure and improves the effectiveness of drug therapy. A variety of lifestyle modifications have been shown, mostly in observational studies, to lower blood pressure and to reduce the incidence of hypertension. These include reduction of dietary sodium intake, weight loss in the overweight, physical activity, greater dietary potassium intake and a diet with increased fresh fruit and vegetables and reduced saturated fat intake. Smoking increases the risk of heart attack or stroke at least three-fold in hypertensive patients, an effect that can be almost abolished if smoking is ceased. Doctors at primary health care centres have been shown to have the most effective frontline role in advising patients about ceasing smoking.

Good management of hypertension is central to any strategy formulated to control hypertension at the community level. Randomized trials of drugs that lower and control blood pressure clearly show a reduction in mortality and morbidity but at the same time, since hypertension is associated with cardiovascular disease and diabetes, management and control is potentially costly.

This publication presents guidelines that recognize the complementary nature of non-pharmacological approaches to management and pharmacotherapy and which are cost-effective. Developing skills to apply the non-pharmacological approach presents a challenge, as most doctors in our Region must be trained to be able to advise their patients on a non-pharmacological approach. Countries need a cost-effective drug management strategy that promotes adherence to medical therapy, motivates patients, builds trust and strengthens communications between clinicians and patients and their families. It

is hoped that these clinical guidelines will make a positive contribution to the improved management of hypertension in the Region.

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Preface

This publication aims to provide up-to-date, reliable and balanced information for the management and care of arterial hypertension in the WHO Eastern Mediterranean Region. The Regional Consultation on Hypertension Prevention and Control held in Abu Dhabi, United Arab Emirates, 20–22 December 2003, acknowledged the need for a standardized response to the growing challenge of hypertension (see Annex 1). These clinical guidelines respond to the suggestion of WHO and the International Society of Hypertension that regional experts draw up recommendations specifically directed toward the management of patients in their own region, as well as addressing the challenges highlighted at the Regional Consultation.

This publication updates *Prevention and control of cardiovascular diseases* (EMRO Technical Publications Series 22) published in 1995 and *Prevention and management of hypertension* (EMRO Technical Publication Series 23) published in 1996. After reviewing both publications, the Regional Office decided that the rapid developments and changes in management and care of hypertension over the past 10 years merited publication of the latest evidence-based information.

These guidelines are aimed at standardizing the management and care of hypertension, including control of blood pressure and complications in people with established hypertension and identification of individuals with high blood pressure who are at increased risk of complications; and at promoting integration of prevention of hypertension into primary health care settings, including lifestyle measures for prevention and management and cost-effectiveness.

The guidelines are intended to benefit physicians at primary, secondary and tertiary level, general practitioners, internists and family medicine specialists, clinical dieticians and nurses as well as health and policy-makers in the Region. They provide the necessary information for decision-making by health care providers or patients themselves about disease management in the most commonly encountered situations. The information is evidence-based and is clearly stated to facilitate the use of the document in daily practice and living. Also accompanying the publication is a quick reference card, which allows a readily accessible appraisal of hypertension management and care.

This publication has been prepared with the consensus of regional experts, based on the best available evidence for all key recommendations and with the principle that guidelines should be educational rather than merely prescriptive. They are in line with the view recently adopted by the European Society of Hypertension and the European Society of Cardiology (ESH/ESC) of avoiding rigid classification of its recommendations.

However, readers preferring a more critical assessment of the evidence can consult the reference list, which clearly identifies those articles based on randomized studies. It is also recognized that guidelines can be useful tools but are, as their name implies, only a guide. They do not attempt to make rigid clinical decisions for physicians and patients. Each clinician must decide, with his or her patient, the best approach for managing hypertension.

Acknowledgements

Introduction

Hypertension is a major health problem throughout the world because of its high prevalence and its association with increased risk of cardiovascular disease. Advances in the diagnosis and treatment of hypertension have played a major role in recent dramatic declines in coronary heart disease and stroke mortality in industrialized countries. However, in many of these countries, the control rates for high blood pressure have actually slowed in the last few years. It is estimated that by 2010, 1.2 billion people will be suffering hypertension worldwide [1]. In the Eastern Mediterranean Region, the prevalence of hypertension averages 26% and it affects approximately 125 million individuals [2]. Of greater concern is that cardiovascular complications of high blood pressure are on the increase, including the incidence of stroke, end-stage renal disease and heart failure.

Recent data suggest that individuals who are normotensive at age 55 years have a 90% lifetime risk for developing hypertension. The relationship between blood pressure and risk of cerebrovascular disease events is continuous, consistent and independent of other risk factors. The higher the blood pressure, the greater the chance of myocardial infarction, heart failure, stroke and kidney disease [3]. For individuals aged 40–70 years, each increment of 20 mmHg in systolic blood pressure or 10 mmHg in diastolic blood pressure doubles the risk of cardiovascular disease. These alarming data support a need for greater emphasis on public awareness of the problem of high blood pressure and for an aggressive approach to antihypertensive treatment.

Over the past three decades there has been unprecedented production of scientific information in the form of longitudinal and cross-sectional studies and trials. Subsets of the study population have been analysed and the data have been combined into meta-analysis. The abundant and rapid access to information has overwhelmed busy clinicians with published reports and editorials and a multitude of postgraduate educational programmes. In order to help clinicians digest the rapidly developing and abundant information, guidelines have been developed by a variety of governmental, professional and voluntary bodies. Clinical guidelines present a cost-effective way to synthesize and filter study conclusions that can improve the effectiveness and efficacy of treatment. They are also intended to reduce variations in treatment patterns and to assist standard-setting groups. There has been a proliferation of published guidelines proposed by various scientific bodies throughout the world. This has happened because the science base that has been derived from clinical trials is sufficiently broad that different conclusions have been drawn from the results. Differences between published guidelines often reflect the choices and ranking of various forms of evidence used in

supporting the benefits of therapy versus the cost to individual patients and to the general population. Guideline differences may also reflect both cultural attitudes regarding approaches to medical care and limits of available resources. This publication draws upon the wealth of global information available and applies it specifically to the WHO Eastern Mediterranean Region.

Definition and classification

Blood pressure, like height and weight, is a continuous biological variable with no cut-off point separating normotension from hypertension. The continuous relationship between the level of blood pressure and cardiovascular risk makes any numerical definition and classification of hypertension somewhat arbitrary. Therefore, a definition of hypertension is usually taken as that level of arterial blood pressure associated with doubling of long-term cardiovascular risk [4].

The *Seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure* [3] provides a classification of blood pressure for adults aged ≥18 years (Table 1). The classification is based on the mean of two or more properly measured seated blood pressure readings on two or more office visits. Normal blood pressure is defined as levels <120/80 mmHg. Systolic blood pressure of 120–139 mmHg or diastolic blood pressure 80–89 mmHg is classified as prehypertension. These patients are at increased risk for progression to hypertension. Hypertension is defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. Hypertension is divided into two stages.

- Stage 1 includes patients with systolic blood pressure 140–159 mmHg or diastolic blood pressure 90–99 mmHg.
- Stage 2 includes patients with systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg.

Isolated systolic hypertension is defined as systolic blood pressure ≥140 mmHg and diastolic blood pressure <90 mmHg. Accelerated hypertension is characterized by markedly elevated blood pressure (diastolic blood pressure usually >120 mmHg) associated with retinal haemorrhage and exudates (grade 3 Kimmelstiel-Wilson retinopathy). If untreated, it commonly progresses to malignant hypertension, which is characterized by papilloedema (grade 4 Kimmelstiel-Wilson retinopathy). Both

Table 1. Classification of blood pressure for adults aged ≥18 years

BP classification	Systolic BP (mmHg)		Diastolic BP (mmHg)
Normal	<120	and	<80
Prehypertension	120–139	or	80–89
Stage 1 hypertension	140–159	or	90–99
Stage 2 hypertension	≥160	or	≥100

BP: blood pressure

Table 2. Classification of blood pressure for adults

Category	Systolic BP (mmHg)	Diastolic BP (mmHg)
Optimal	<120	<80
Normal	120–129	80–84
High normal	130–139	85–89
Grade 1 hypertension (mild)	140–159	90–99
Grade 2 hypertension (moderate)	160–179	100–109
Grade 3 hypertension (severe)	≥180	≥110
Isolated systolic hypertension	≥140	<90

BP: blood pressure

accelerated and malignant hypertensions are associated with widespread degenerative changes in the walls of resistance vessels including hypertensive encephalopathy, haematuria and renal dysfunction. A more elaborate classification of blood pressure is provided by the European Society of Hypertension and the European Society of Cardiology (ESH/ESC) (Table 2) [5].

The diagnosis of hypertension in adults is made when the average of two or more diastolic blood pressure measurements on at least two subsequent visits is ≥90 mmHg, or when the average of multiple systolic blood pressure readings on two or more subsequent visits is ≥140 mmHg. Patients should be clearly informed that a single elevated reading does not constitute a diagnosis of hypertension but is a sign that further observation is required.

Systolic, diastolic and pulse pressures as predictors of risk

Historically, more emphasis has been placed on diastolic than systolic blood pressure as a predictor of cerebrovascular and coronary artery disease. However, observational data have repeatedly confirmed that both systolic and diastolic blood pressures show a continuously graded, yet independent, relationship with risk of stroke and coronary events. The relationship between systolic blood pressure and relative risk of stroke is steeper than that for coronary events, which reflects its closer aetiological relationship with strokes [5].

Normally, systolic blood pressure rises through adult age range, whereas diastolic blood pressure peaks at about age 60 years in men and 70 years in women, and falls gradually thereafter [6]. At least in elderly populations, these observations help explain why a wide pulse pressure has been shown to be a better predictor of adverse cardiovascular outcomes than either systolic or diastolic pressure individually, and help to identify patients with systolic hypertension who are at specifically high risk. Some observational studies have reported that for a given level of systolic blood pressure,

diastolic blood pressure had an inverse association with cardiovascular risk. However in a large meta-analysis, both systolic and diastolic blood pressures were independently predictive of stroke and coronary mortality, and more so than pulse pressure [7]. Therefore in practice, the use of both systolic and diastolic values to categorize blood pressure and thereby overall risk remains a simple and practical approach.

Cardiovascular risk factors

The presence of cardiovascular risk factors, particularly diabetes mellitus, target organ damage and associated cardiovascular and renal disease, substantially increases the risk of hypertension. The level of risk is used to determine the threshold and type

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Box 1. Factors influencing prognosis of hypertension

Risk factors

Level of systolic and diastolic blood pressure

Men aged >55 years

Women aged >65 years

Smoking

Dyslipidaemia

Family history of premature cardiovascular disease (men aged <55 years, women aged <65 years)

Abdominal obesity (abdominal circumference ≥102 cm for men, ≥88 cm for women)

C-reactive protein ≥1 mg/dL

Target organ damage

Left ventricular hypertrophy (LV mass index >125 g/m^2 in men, >110 g/m^2 in women)

Carotid intima-media thickness ≥0.9 mm or atherosclerotic plaque

Serum creatinine >1.3 mg/dL in men, >1.2 mg/dL in women

Microalbuminuria

Diabetes mellitus

Fasting plasma glucose ≥126 mg/dL

Postprandial plasma glucose ≥200 mg/dL

Associated clinical conditions

Cerebrovascular disease (transient ischaemic attack, stroke, haemorrhage)

Heart disease (angina, myocardial infarction, heart failure)

Renal disease (diabetic nephropathy, serum creatinine >1.5 mg in men, >1.4 mg in women, protienuria >300 mg/24 hours)

Peripheral vascular disease

Advanced retinopathy (haemorrhage, exudates, papilloedema)

Table 3. Risk stratification of blood pressure values [5]

	Normal PB 120–129 DBP 80–84	High normal SPB 130–139 DPB 85–89	Grade 1 SPB 140–159 DPB 90–99	Grade 2 SPB 160–179 DBP 100–109	Grade 3 SBP ≥180 DBP ≥110
No other risk factors	AR	AR	LAR	MAR	HAR
1–2 risk factors	LAR	LAR	MAR	MAR	VHAR
≥3 risk factors or TOD or DM	MAR	HAR	HAR	HAR	VHAR
Associated clinical conditions	HAR	VHAR	VHAR	VHAR	VHAR

AR: average risk	HAR: high added risk	SPB: systolic blood pressure
LAR: low added risk pressure	VHAR: very high added risk+	DBP: diastolic blood
MAR: moderate added risk	TOD: target organ damage	DM: diabetes mellitus

of therapeutic intervention. Box 1 indicates the most common risk factors, target organ damage and associated clinical conditions that are used to stratify risk [8].

The ESH/ESC have proposed a classification of the level of added risk associated with different values of blood pressure (Table 3). The terms low, moderate, high and very high added risk are calibrated to indicate an approximate 10-year risk of cardiovascular disease of <15%, 15%–20%, 20%–30% and >30%, respectively or an approximate absolute risk of fatal cardiovascular disease of <4%, 4%–5%, 5%–8% and >8%, respectively [9].

In countries of the Eastern Mediterranean Region, among people aged 25–65 years, the prevalence of smoking ranges from 16% to 35%, overweight/obesity from 40% to 70% and dyslipidaemia from 20% to 45%. In most countries of the Region, more than two out of three adults have one or more of the major risk factors for cardiovascular disease. [2]

Causes of hypertension

The various causes of hypertension are listed in Box 2. Primary (essential or idiopathic) hypertension is systemic hypertension of unknown cause that results from dysregulation of normal homeostatic control mechanisms of blood pressure in the absence of detectable known secondary causes. Over 95% of all cases of hypertension are in this category. Secondary hypertension is systemic hypertension due to an underlying disorder. It accounts for <5% of cases of hypertension [4].

Box 2. Causes of hypertension

Systolic and diastolic hypertension
1. Primary (essential or idiopathic)
2. Secondary
   Renal
   - Renal parenchymal
     – acute glomerulonephritis
     – chronic nephritis
     – polycystic disease
     – diabetic nephropathy
     – hydronephrosis
   - Renovascular
     – renal artery stenosis
     – intrarenal vasculitis
   - Renin-producing tumours
   - Renoprival
   - Primary sodium retention (Liddle syndrome, Gordon syndrome)
   Endocrine
   - Acromegaly
   - Hypothyroidism
   - Hyperthyroidism
   - Hypercalcaemia (hyperparathyroidism)
   - Adrenal
     i. Cortical
     – Cushing syndrome
     – primary aldosteronism
     – congenital adrenal hyperplasia
     – apparent mineralocorticoid excess (liquorice)
     ii. Medullary
     – phaeochromocytoma
   - Extra-adrenal chromaffin tumours
   - Carcinoid
   - Exogenous hormones: estrogen, glucocorticoids, mineralocorticoids, sympathomimetics, tyramine-containing food, monoamine oxidase inhibitors

   Coarctation of the aorta
   Pregnancy-induced hypertension
   Neurological disorders
   - Increased intracranial pressure
     – brain tumours
     – encephalitis
     – respiratory acidosis
   - Sleep apnoea
   - Quadriplegia
   - Familial dysautonomia
   - Acute prophyria
   - Guillain-Barré syndrome
   - Lead poisoning
   Acute stress, including surgery
   - Psychogenic hyperventilation
   - Hypoglycaemia
   - Burns
   - Pancreatitis
   - Alcohol withdrawal
   - Alcohol and drug abuse
   - Sickle cell crisis
   - After resuscitation
   - Postoperative
   Increased intravascular volume

Systolic hypertension
1. Increased cardiac output
   Aortic valvular insufficiency
   Arteriovenous fistula, patent ductus arteriosus
   Thyrotoxicosis
2. Rigidity of aorta
3. Iatrogenic hypertension

   Paget's disease of bone
   Beri-beri
   Hyperkinetic circulation

Diagnosis of hypertension

Background

Uncomplicated hypertension is usually asymptomatic and many of the symptoms often attributed to hypertension such as headache, tinnitus, dizziness and fainting are probably psychogenic in origin. They may reflect hyperventilation, induced by anxiety over the diagnosis of a lifelong disease that threatens well-being and survival. However recent data indicate that, surprisingly, a person's general sense of well-being often improves during initiation of medical treatment of hypertension. These new data suggest that hypertension may not be as asymptomatic as was previously assumed. Even if not totally asymptomatic, hypertension can go unrecognized for years because overt symptoms and signs generally coincide with the onset of target organ damage. Therefore, proper technique of blood pressure measurement is the cornerstone of hypertension detection. This can be achieved with the help of the following guidelines [10].

Blood pressure measurement

Condition of the patient

Posture

- Sitting pressures are usually adequate for routine measurement of blood pressure. Patients should sit quietly with back supported for 5 minutes, with arm bared and supported at the level of the heart.
- In patients aged ≥65 years, diabetic or receiving antihypertensive therapy, check for postural changes by taking readings 1 and 5 minutes after patient stands up.

Circumstance

- A quiet warm setting is required.
- No caffeine, smoking or alcohol for preceding 30 minutes.
- Question about the most recent meal or evacuation of bowels or bladder. Distended abdominal viscera cause blood pressure elevation presumably because of anxiety, sympathetic stimulation and pain. Older persons typically have lower blood pressure post-prandially.
- No exogenous adrenergic stimulants e.g. nasal decongestants or eye drops for papillary dilatation.
- Home readings under varying circumstances and 24-hour ambulatory readings may be preferable.

Equipment

Cuff size

The bladder size (six sizes are available) should encircle at least 80% of the arm circumference and cover two thirds of the arm length; if not, place the bladder over the brachial artery. If bladder is too small, spuriously high readings may result. The lower edge of the bladder should be within 2.5 cm of the antecubital fossa.

Manometer

Mercury, anaeroid or electronic devices used in measurement of blood pressure should be calibrated frequently and routinely against standards (typically every 6 months) to assure accuracy. Ensure that the equipment used is in working order: clean, calibrated, filled with non-leaking tubing and has a properly sized cuff.

Ultrasonic

For infants use ultrasonic equipment e.g. Doppler method.

Technique and precautions

Number of readings

- On each occasion, take at least two readings separated by as much time as is practical. If readings vary by more than 5 mmHg, take additional readings until two or more are close. Multiple measurements should be taken in patients with irregular pulse (e.g. atrial fibrillation) and in older patients with systolic hypertension.
- For diagnosis, obtain at least two sets of readings at least a week apart. Although it is traditional to average blood pressure measurements at a given visit, recent guidelines state recording individual blood pressure measurements with the lowest reading in any position (including standing) to be considered as the "blood pressure taken at that visit".
- Initially, take pressure in both arms. If pressure differs by >10/5 mmHg, use arm with higher pressure.
- If arm pressure is elevated, take pressures in one leg.

Performance

- Inflate the bladder quickly to a pressure of 20 mmHg above systolic as recognized by disappearance of the radial pulse. Important diagnostic information will be missed if the "auscultatory gap" is not detected.
- Deflate the bladder 3 mmHg every second. At least one Korotkoff sound should be heard at each 2 mmHg gradation of the mercury column.
- Record the Korotkoff phase V (disappearance) except in children in whom use of phase IV (muffling) may be preferable.

- If Korotkoff sounds are weak, have the patient raise the arm then open and close the hand 5–10 times, after which the bladder should be inflated quickly.
- Listen over the brachial artery by using the bell of the stethoscope with minimal pressure exerted on the skin. At the conclusion of blood pressure measurement, there should be no lasting indentation in the area where the stethoscope was placed. Too great pressure with the stethoscope overestimates the systolic blood pressure and underestimates the diastolic blood pressure.

Recordings

- Note the pressure, patient position, the arm used and cuff size (e.g. 140/90, seated, right arm, large adult cuff).
- Office blood pressure measurements taken by trained professionals should be the blood pressure used for diagnosing and treating hypertension in all but a few special situations.

Home (self) blood pressure measurements

Home readings of blood pressure tend to be better correlated with both the extent of target organ damage and the risk of future mortality than are readings taken in the physician's office. They are also helpful in evaluating symptoms of hypotension particularly if they are intermittent and infrequent [11,12]. Many machines are now available for the purpose that are convenient, inexpensive and relatively accurate.

Home readings are on average 12/7 mmHg less than office measurements, even in normotensive subjects. However, many factors that contribute to blood pressure variability including circadian variation, food and alcohol ingestion, exercise and stress are more difficult to control in the home environment.

Technique and precautions

When giving instruction about self-measurement of blood pressure at home, the following points should be made [10].

- Advise only the use of validated devices.
- Advise that the patient keep the arm at heart level during measurement.
- Recommend semi-automatic rather than mercury sphygmomanometric devices to avoid the difficulty of patient instruction and error from hearing problems in elderly individuals.
- Instruct the patient to take measurement when seated after several minutes of rest.
- Inform them that values may differ between measurements because of spontaneous blood pressure variability.
- Avoid requesting an excessive number of measurements; ensure that some of the measurements are made before drugs are taken to provide information on treatment effect.

Ambulatory blood pressure monitoring (ABPM)

Indications

Ambulatory blood pressure is usually several mmHg lower than office blood pressure. Office values of 140/90 mmHg correspond to 24-hour average values of approximately 125/80 mmHg. Clinical decisions may be based on day, night, or 24-hour mean values, but 24-hour values are preferable. The following situations are ones in which a better knowledge of what is happening to a patient's blood pressure over 24 hours can lead to different therapeutic decisions [10].

Evaluation of newly diagnosed hypertensive patients without target organ damage

In these patients, therapeutic decisions will depend mainly on how blood pressure is evaluated. ABPM may reveal that some of these patients have isolated office (white-coat) hypertension.

Isolated office hypertension

The condition refers to persistently elevated office blood pressure readings (≥140/90 mmHg at several visits) while 24-hour ambulatory blood pressure values are normal (<120/80 mmHg). Diagnosis can also be based on home blood pressure mean values <135/85 mmHg, after several days recording. Isolated office hypertension is encountered in about 10% of the general population and accounts for a non-negligible population of individuals in whom hypertension is diagnosed. Several, but not all, studies have reported this condition to be associated with target organ damage and metabolic abnormalities, which suggests that it may not be an entirely innocent phenomenon. Lifestyle changes and a close follow-up should be implemented in all patients with isolated office hypertension. Drug treatment is instituted when there is evidence of target organ damage or high cardiovascular risk profile.

A less frequent phenomenon is the "reverse of isolated office hypertension". This refers to individuals with normal office blood pressure (<140/90 mmHg) but elevated ambulatory blood pressure values (isolated ambulatory hypertension). These individuals display a greater than normal prevalence of target organ damage.

Refractory hypertension

This may be the result of a genuinely resistant hypertension, non-compliance or an exaggerated white-coat hypertension. The best clue to this exaggerated white-coat effect is a persistently elevated office pressure in the absence of target organ damage. Such patients can be evaluated either with ABPM or initially with home monitoring. Another cause of refractory hypertension is the sleep apnoea syndrome. A clue to this may be

that although the average blood pressure level and heart rate fall during the night, their variability increases.

Intermittent symptoms possibly related to blood pressure

Episodes of light-headedness, particularly in patients who are on antihypertensive medication, may be a manifestation of transient hypotension. This can potentially be detected by ABPM.

Episodic hypertension

Episodic symptoms accompanied by transient elevation in blood pressure may occur in a variety of conditions, including phaeochromocytoma and panic attacks.

Episodic hypotension

ABPM may be helpful in cases of idiopathic orthostatic hypotension because many patients who are orthostatic during the day are hypertensives during the night. There are huge swings of blood pressure during the day depending to a large extent on changes of posture and physical activity, and relatively stable but high pressure at night when the patient is supine. In contrast, the heart rate is relatively constant throughout day and night.

Autonomic neuropathy is common in type 1 diabetes and has been attributed to interruption of both vagal and sympathetic control of the circulation. The former is manifested by a relatively fixed heart rate and the latter by orthostatic hypotension. In common with patients with idiopathic orthostatic hypotension, blood pressure remains high at night.

Compared with casual blood pressure measurements, ABPM measurements are a better predictor of left ventricular hypertrophy (LVH), cardiac function and optic, carotid, renal and peripheral vascular damage resulting from elevated blood pressure. Most normotensive patients and perhaps 80% of hypertensives have at least 10% drop in blood pressure during sleep compared with daytime average. There is about a 3-fold increased risk of cardiovascular events among those with non-dipping blood pressure or pulse patterns.

Technique and precautions [13]

When measuring 24-hour blood pressure, care should be taken to follow certain procedures.

- Use only devices validated by international standardized protocols.
- Use cuffs of appropriate size and compare the initial values with those from a sphygmomanometer to check that the differences are not greater than ±5 mmHg.

**Table 4. Blood pressure thresholds for definition of hypertension
with different types of measurement** [5]

Type of measurement	Systolic BP (mmHg)	Diastolic BP (mmHg)
Office	140	90
24-hour ambulatory	125	80
Home (self)	135	85

BP: blood pressure

- Set the automatic readings at no more than 30-minute intervals and have most hours represented in case some readings are rejected because of artefacts.
- Instruct the patients to engage in normal activities but to refrain from strenuous exercise, and to keep the arm extended and still at the time of measurement.
- Ask the patient to provide information in a diary about unusual events and on duration and quality of night sleep. There is evidence that subjects in whom nocturnal hypotension is blunted and thus exhibit a relatively high night-time blood pressure may have an unfavourable prognosis.
- Obtain another ambulatory blood pressure measurement if the first examination has <70% of the expected values because of a high number of artefacts.

The blood pressure thresholds for definition of hypertension with office, 24-hour ambulatory and home measurements are given in Table 4.

Systolic blood pressure measurement during exercise or use of laboratory stressors

A rise in exercise systolic blood pressure to >200 mmHg during the first 6 minutes of exercise predicts a 3-fold greater likelihood of hypertension over the next 5–15 years and a doubling of cardiovascular death rates in middle-aged men. However, whether or not an excessive rise in blood pressure during exercise adds diagnostic precision to blood pressure at rest depends on the response of the cardiac output: if the exercise-induced rise in cardiac output is impaired in hypertensives, exercise blood pressure no longer has independent prognostic power [14]. On the whole, systolic blood pressure measurement during exercise, though potentially valuable, is not recommended as a routine procedure in hypertensives [5].

Pseudo-hypertension [4]

This term refers to the rare situation where blood pressure measurements by the usual indirect sphygmomanometry are much higher than direct intravascular measurements. These differences are usually attributed to very stiff and calcified arteries that are

nearly impossible to compress with the bladder in the usual blood pressure cuff. The Osler manoeuvre (palpating the walls of the brachial artery when blood flow has been interrupted by inflating the cuff higher than systolic pressure) has been recommended as a simple, but neither sensitive nor specific, measure to diagnose the condition. More precise methods involve intra-arterial measurements and perhaps an infusion of an intravenous antihypertensive agent to calibrate the difference between direct and indirect blood pressure measurements. The benefit of lowering blood pressure in older patients with stiff arteries is well established.

Evaluation of hypertensive patients

Background

During the initial office evaluation of a hypertensive patient a comprehensive history should be obtained. Careful physical examination with focus on signs suggesting secondary hypertension and target organ damage is done and routine laboratory tests are recommended. Further (extended) evaluation depends on the initial findings and results.

Clinical history

A clinical history for hypertension should include the following assessments [5].

- Duration and previous level of high blood pressure.
- Symptoms indicative of secondary hypertension:
  - renal disease: urinary tract infection, haematuria, analgesic abuse, family history of polycystic kidney;
  - phaeochromocytoma: episodes of sweating, headache, anxiety, palpitation;
  - aldosteronism: episodes of muscle weakness and tetany;
  - drug/substance intake: oral contraceptives, liquorice, carbenoxolone, nasal drops, cocaine, amphetamines, steroids, non-steroidal anti-inflammatory drugs, erythropoietin, cyclosporine.
- Risk factors:
  - dietary habits/obesity (particularly abdominal obesity);
  - smoking;
  - amount of exercise;
  - personality;
  - personal and family history of cardiovascular disease, hypertension, hyperlipidoemia and diabetes mellitus.
- Symptoms of target organ damage:
  - brain and eyes: headache, vertigo, impaired vision, transient ischaemic attacks, sensory or motor deficits;
  - heart: palpitation, chest pain, shortness of breath, swollen ankles;
  - kidney: thirst, polyuria, nocturia, haematuria;
  - peripheral arteries: cold extremities, intermittent claudication.

- Previous antihypertensive therapy:
  - drugs used, efficacy and adverse effects.
- Personal, family and environmental factors that may influence blood pressure and cardiovascular risk, as well as the course and outcome of therapy.

Physical examination

In addition to methodological blood pressure measurement (see above), physical examination should search for the following signs of hypertension [3].

- Signs suggesting secondary hypertension:
  - features of Cushing syndrome;
  - skin stigmata of neurofibromatosis (phaeochromocytoma);
  - diminished and delayed femoral pulse and reduced femoral blood pressure (aortic coarctation, aortic disease);
  - palpation of enlarged kidneys (polycystic kidney);
  - ausculatation of precordial or back murmurs (aortic coarctation or aortic disease) or abdominal murmurs (renovascular hypertension).
- Signs of target organ damage:
  - brain: murmurs over neck arteries, motor or sensory defects;
  - retina: funduscopic abnormalities;
  - heart: cardiac enlargement, arrhythmias, gallop sounds, pulmonary crackles, dependent oedema;
  - peripheral arteries: absence, reduction, or asymmetry of pulses, cold extremities, ischaemic skin lesions.

Laboratory investigation

Laboratory investigations should be directed at providing evidence of additional risk factors, searching for secondary hypertension and assessing presence or absence of target organ damage. They include routine tests, recommended tests (based on recent studies) and specific tests for extended evaluation of hypertensive complications and causes of secondary hypertension [3,5].

- Routine tests:
  - electrocardiogram (ECG)
  - plasma glucose (preferably fasting)
  - serum total cholesterol
  - serum high-density (cholesterol) lipoprotein (HDL)

- – fasting serum triglycerides
- – serum uric acid
- – serum creatinine
- – serum potassium
- – haemoglobin and haematocrit
- – urinalysis (dipstick test and urinary sediment examination).
- • Recommended tests:
  - – echocardiogram
  - – carotid (and femoral) ultrasound
  - – C-reactive protein
  - – microalbuminuria (essential in diabetics)
  - – quantitative proteinuria (if dipstick is positive)
  - – funduscopy (in severe hypertension).
- • Extended evaluation (domain of the specialist):
  - – complicated hypertension: tests of cerebral, cardiac and renal function
  - – search for secondary hypertension: measurement of renin, aldosterone, corticosteroids, catecholamines, arteriography, renal and adrenal ultrasound, computed tomography (CT) and brain magnetic resonance imaging (MRI).

Signs of target organ damage

Hypertensive cardiac damage

Atrial (S4) gallop is a common and vital clue to the presence of hypertensive heart disease.

Hypertensive cardiac damage is also identified by left ventricular hypertrophy (LVH). The ECG is the most cost-effective way to diagnose and exclude LVH [15]. However, compared with echocardiography, CT or MRI, it is only 10%–50% sensitive and 80% specific. The expense of these more accurate methods of screening for LVH, however, limits their use. A limited echocardiogram that accurately calculates LV size and provides information about ventricular geometry is a reasonable choice [16]. ECG evidence of LVH is associated with about a 3-fold increase in cardiovascular events. In several studies, LVH was the most powerful of any of the traditional cardiovascular risk factors in predicting the occurrence of heart failure, stroke, myocardial infarction and death in patients with hypertension. In patients with stage 1 hypertension, the detection of LVH would lead to reclassification of the patient to stage 2 and indicate the need for antihypertensive drug therapy earlier than if the patient was free of target organ damage.

LVH is associated with intimal hyperplasia of the epicardial coronary arteries, increased coronary vascular resistance, increased severity and frequency of ventricular arrhythmias and reduced diastolic relaxation. Severe diastolic dysfunction may result in flash pulmonary oedema, despite a normal ejection fraction. The relationship between echocardiographically determined LV mass and cardiovascular risk is continuous, the threshold of 125 g/m^2 for men, and 110 g/m^2 for women is most widely used for conservative estimates of LVH. Classification into concentric or eccentric hypertrophy and concentric remodelling by using the wall to radius ratio (values >0.45 define concentric pattern) has been shown also to have risk-predicting value [17].

Early data indicate a better prognosis among patients with echocardiographically determined LVH whose LV mass index is reduced by pharmacological treatment of hypertension compared with those whose index increases over time.

Hypertensive vascular damage

Hypertensive vascular damage can be identified by changes in the optic fundi. These are important in the assessment of both the severity and duration of elevated blood pressure. The clinical Keith-Wagener-Barker classification (1939) describes the combined effects of hypertension and arteriosclerosis on the retinal vessels [18]. It divides such changes into four grades.

Grade 1. Arterial tortuousity, localized arterial spasm or narrowing, silver wiring.

Grade 2. Extensive or generalized arteriolar narrowing resulting in changes in arteriovenous crossing (arterial nicking).

Grade 3. Haemorrhages or exudates.

Grade 4. Papilloedema.

In hypertensive patients presenting early in the course of the disease, haemorrhages, exudates and papilloedema are rarely observed. Grade 1 and 2 arteriolar changes are often noted, but no evidence is available that these can be used as evidence of target organ damage or have a significant prognostic value.

Ultrasound examination of the carotid arteries with measurement of the intima-media thickness and detection of plaques has been shown to predict the occurrence of both stroke and myocardial infarction. The relationship between carotid artery intima-media thickness and cardiovascular events is continuous but a threshold ≥0.9 mm can be taken as an estimate of significant alteration [19].

Hypertensive vascular damage can also be identified by measuring large artery compliance [20,21]. The increasing interest in systolic blood pressure and pulse pressure as predictors of cardiovascular events, stimulated by evidence of the beneficial effects of lowering blood pressure in the elderly and in isolated systolic hypertension, has

encouraged the development of techniques for determining large artery compliance. Two of these techniques have been well developed: namely the pulse wave velocity measurement and the augmentation index measurement device (SphygmoCor®). Both are of interest, particularly in view of the claim that aortic blood pressure (and therefore the pressure exerted on the heart and brain) may be different from that which is usually measured at the arm and may be a better predictor of outcomes.

Endothelial dysfunction or damage is an early marker of cardiovascular damage [22,23]. Current studies on circulating markers of endothelial damage may soon provide simpler tests of endothelial dysfunction. Such markers include nitric oxide and its metabolites, endothelines, cytokines and adhesion molecules.

Hypertensive renal damage

Hypertensive renal damage can be identified by certain laboratory tests. Blood urea nitrogen, serum creatinine, serum electrolytes and urinalysis (particularly for proteinuria) are the only measures of renal function that are currently routinely recommended for evaluation of all hypertensive patients. However, these are very insensitive indicators of the onset and progression of hypertensive nephrosclerosis. The presence of mild renal insufficiency has been defined as serum creatinine values ≥1.5 mg/dL in men and ≥1.4 mg/dL in women or estimated creatinine clearance values <60–70 mL/minute [24]. A slight increase in serum creatinine and urate may sometimes occur when antihypertensive therapy is instituted or intensified but this should not be taken as a sign of progressive renal deterioration.

Hyperuricaemia, defined as serum urate levels >7 mg/dL, is frequently seen in untreated hypertensives and has also been shown to correlate with the existence of nephrosclerosis [25].

The detection of microalbuminuria as defined by the presence of albumin in the urine above the normal range of <30 µg/day but below the detectable range with the conventional dipstick methodology of 300 µg/day is also warranted. Microalbuminuria occurs in 5%–40% of non-diabetic persons with essential hypertension and is a marker of blood pressure control. Blood pressure control with all agents (except dihydropyridine calcium channel blockers and central or peripheral sympathetic blockers) reduces albuminuria. The amount of microalbuminuria is proportional to the severity of systolic, diastolic and mean blood pressure elevation. Moreover, microalbuminuria predicts the development of ischaemic cardiovascular events related to the development of atherosclerosis. It is an indicator of increased vascular permeability and hence altered barrier function of the endothelium. When albumin leaks into the interstitial space, cellular injury occurs due to free radicals and cytokine production, which is enhanced by the presence of albumin. Subjects with microalbuminuria and type 2 diabetes mellitus have an approximate total mortality of 8% and a cardiovascular mortality of 4%, annually. These values are up to

four times higher than those of patients without microalbuminuria. Similar increases in cardiovascular mortality are also present in people with microalbuminuria and without diabetes [26].

Routine assessment of microalbuminuria in diabetic patients is well advised, but in hypertensives without diabetes mellitus its value is still debatable. Perhaps all hypertensives with trace proteinuria (300–500 µg/day) when measured by conventional dipsticks could have a spot urine measurement of the albumin/creatinine ratio. This may allow more precise evaluation of the patient's prognosis at the initial visit [27].

Hypertensive brain damage

Hypertensive brain damage is suggested by the following features [28].

- History of transient ischaemic attack, stroke or impairment of cognition (suggestive of repeated lacunar infarcts).
- Physical finding of focal neurological defects.

CT is the standard procedure for diagnosis of stroke but, except for prompt recognition of an intra-cranial haemorrhage, CT is progressively being replaced by MRI techniques. Diffusion-weighted MRI, particularly in fluid-attenuated inversion recovery (FLAIR) sequences, is far superior to CT in identifying lacunar infarcts. The limited availability and time-consuming nature and cost of MRI do not allow its widespread use, but liberal application may be acceptable in patients with neurological disturbances, particularly memory loss [29].

Secondary hypertension [3,4]

Evaluation

There are several clinical and laboratory features that will suggest a diagnosis of secondary hypertension on initial evaluation for elevated blood pressure. However, most of these features are non-specific and, in view of the low frequency of secondary hypertension, the selection of patients for further evaluation should be based on reasonable and reliable indices, as follows:

- onset of hypertension before age 25 or after age 55 years;
- severe hypertension, blood pressure >180/110 mmHg at baseline;
- sudden onset or change from normal blood pressure to severe hypertension in <1 year;
- refractory hypertension;
- poor response to prior effective drug therapy;
- paroxysmal attacks of hypertension with palpitation, pallor, perspiration and tremor;

Table 5. Laboratory investigation for identifiable causes of secondary hypertension

Diagnosis	Diagnostic procedure	
	Initial	Additional
Chronic renal disease	Urinalysis, serum creatinine, renal sonography	Isotope renogram, renal biopsy
Renovascular disease	Captopril-enhanced isotopic renogram, duplex ultrasonography	Magnetic resonanace or CT angiogram, aortogram
Coarctation	Blood pressure in legs	Echocardiography, aortography
Primary aldosteronism	Plasma and urinary potassium, plasma renin and aldosterone	Plasma or urinary aldosterone after saline load, adrenal CT scans and scintiscan
Cushing syndrome	Monitoring plasma cortisol after 1 mg dexamethazone at bedtime	Urinary cortisol after variable doses of dexamethazone, adrenal CT scans and scintiscan
Phaeochromocytoma	Plasma metanephrine, spot urine for metanephrine	Urinary catechols, plasma catechols, adrenal CT scans and scentiscan

CT: computed tomography

- multiple system complaints on initial evaluation;
- asymmetry of the peripheral pulses with lower blood pressure in the lower extremities;
- abnormal bruit over the renal artery with a diastolic component;
- bilateral flank masses;
- presence of end-organ damage: grade 2 or more retinopathy, LVH, serum creatinine >1.5 mg/dL;
- laboratory abnormalities: hyperglycaemia, hypokalaemia, hypercalcaemia.

If suggestive clues for identifiable cause of secondary hypertension are found, additional investigation should be performed. The diagnostic methods listed in Table 5 as initial are usually adequate screening procedures. If they are abnormal, the listed additional procedures should be performed along with whatever other tests are needed to confirm the diagnosis.

Renal disorders

Renal parenchymal disease [4,30]

Renal parenchymal disease is the most common cause of secondary hypertension in adults and accounts for 2% to 4% of all cases of hypertension. It can be acute or chronic, unilateral or bilateral, and does not have to be associated with renal insufficiency. The most common renal parenchymal disorders associated with hypertension are chronic glomerulonephritis, polycystic kidney disease and hypertensive nephrosclerosis.

Clinical picture

Several mechanisms have been proposed for elevated blood pressure in renal parenchymal disease:

- inability of the reduced renal mass to excrete salt and water (the most important mechanism);
- activation of renin-angiotensin-aldosterone system;
- accumulation of endogenous inhibitors of nitric oxide synthase.

Investigation

Assessing the presence of protein, erythrocytes and leucocytes in the urine as well as measuring serum creatinine concentration are the appropriate functional screening tests. If these tests are positive, a detailed investigation for kidney disease should follow. Renal parenchymal disease may be excluded if urinalysis and serum creatinine concentration are repeatedly normal. Renal ultrasound has now almost completely replaced intravenous urography in the anatomical exploration of the kidney. It provides all the necessary anatomical data about kidney size and shape, cortical thickness, urinary tract obstruction and renal masses.

Renovascular disease [4,31,32]

Renovascular disease is the second most common cause of secondary hypertension. Two clinical subgroups comprise the majority of patients with renovascular hypertension.

1. Atherosclerotic disease, making up nearly 70% of total renovascular hypertension, usually involves the proximal third of the renal artery. Lesions generally arise bilaterally, although one side may predominate. Left untreated, most lesions progress leading to complete occlusion and renal failure.
2. Fibromuscular dysplasia of the renal arteries accounts for about 25% of all renovascular hypertension and occurs almost exclusively in young patients, especially females. About 70% of affected individuals display medial fibroplasias and an additional 20%

show perimedial fibroplasias. Both of these types exhibit classical beaded appearance on angiography. The natural history usually consists of slow progression of stenosis without frank occlusion.

Less common causes of renovascular hypertension include renal artery aneurysm, embolism or thrombosis, polyarteritis nodosa, radiation fibrosis and extrinsic compression of the renal arteries by tumours.

In all these conditions, restriction of renal arterial flow to either or both kidneys activates the renin-angiotensin-aldosterone system.

Clinical picture

The two most common modes of presentation are:

- recent-onset hypertension in a young woman with no family history of hypertension;
- late-onset or exacerbation of hypertension in an older man, with strong evidence of coronary, cerebrovascular or peripheral vascular insufficiency.

Although the detection of an abdominal bruit slightly increases the odds of significant stenosis, the presence or absence of bruit has limited predictive value (present in only 40% of cases). Other potential clues include marked hypertensive retinopathy, worsening of renal function after angiotensin-converting enzyme (ACE) inhibitor therapy, progressive worsening of uraemia despite blood pressure control, history of unilateral small kidney from incidental studies, history of smoking and history of pulmonary oedema in a difficult to control hypertension.

Investigation

The clinical index of suspicion of renovascular hypertension is divided into three categories (Box 3). Those with characteristics listed under moderate are considered to have a 5%–15% likelihood of the diagnosis and therefore are in need of a non-invasive screening test. A positive screening test calls for renal arteriography. Those with characteristics listed under high have >25% likelihood of the diagnosis, so that renal arteriography should be the initial test.

Non-invasive tests

Captopril plasma renin activity. The patient should be on normal sodium dietary intake and off diuretics and ACE inhibitors. After sitting for 30 minutes, venous blood is obtained for basal plasma renin activity then 50 mg of captopril is given orally. After 60 minutes, another blood sample for stimulated plasma renin activity is obtained. A positive result is indicated by stimulated plasma renin activity ≥12 ng/mL per hour, absolute increase in plasma renin activity of ≥10 ng/mL per hour and 150% increase in plasma

Box 3. Clinical index of suspicion of renovascular hypertension as a guide to selecting patients for laboratory investigation [4]

Low (not to be tested)

    Borderline, mild or moderate hypertension in the absence of clinical clues

Moderate (non-invasive tests recommended)

    Severe hypertension (diastolic BP>120 mmHg)

    Hypertension refractory to therapy

    Abrupt onset of sustained, moderate–severe hypertension at age <20 or >50 years

    Hypertension with a suggestive abdominal bruit (long, high-pitched and localized to the region of the renal artery)

    Moderate hypertension in a smoker, in presence of occlusive vascular disease or with unexplained but stable elevation of serum creatinine

    Normalization of BP by an ACE inhibitor in a patient with a moderate or severe hypertension

High (consider arteriography)

    Severe hypertension with progressive renal insufficiency or refractoriness to aggressive treatment

    Accelerated or malignant hypertension

    Hypertension with recent elevation of serum creatinine either unexplained or induced by an ACE inhibitor

    Moderate to severe hypertension with asymmetry of renal size

BP: blood pressure
ACE: angiotensin-converting enzyme

renin activity (≥400% if baseline plasma renin activity is <3 ng/mL per hour). The test depends on the abrupt inhibition of the circulating angiotensin II by the ACE inhibitor with subsequent intensification of ischaemia in the stenotic kidney.

Captopril isotopic renography (scintigraphy). One hour after 50 mg oral captopril, a renogram is obtained using labelled hippurate (a measure of renal blood flow) and diethylenetriaminepentaacetic acid or mercaptoacetyltriglycine (measures of glomerular filtration rate [GFR]). The ACE inhibitor produces a fall in GFR on the affected side more than a reduction in renal blood flow. If a significant difference develops between the two kidneys, the procedure is repeated without captopril to document the ischaemic origin of the difference in GFR or blood flow. A positive scan correlates with successful angioplasty or surgical intervention in ≥90% of cases and decreases the need for renal vein renin measurements.

Renal duplex ultrasound has a high sensitivity. Colour Doppler ultrasound with calculation of peak systolic velocity and resistance indices in the renal artery is able

to detect stenosis of the renal artery, particularly those close to the origin of the vessel. However, the procedure is highly observer-dependent.

Breath-hold 3D, gadolinium-enhanced magnetic resonance angiography may become the diagnostic procedure of choice in the future. Another imaging procedure with similar sensitivity is spiral-computed tomography. The cost of these procedures is currently prohibitive.

Invasive tests

Intra-arterial digital subtraction angiography has become the invasive test of choice to demonstrate definitively the renal artery anatomy and determine whether an arterial lesion is present.

Renal vein renin ratio determination (requiring sampling from both renal veins and inferior vena cava) to assess the functional significance of renal artery stenosis is of controversial value.

Treatment

1. Percutaneous renal angioplasty is the first treatment option for renovascular disease. It improves 60%–70% of patients, more with fibromuscular dysplasia than with atherosclerosis. Early work with balloon dilatation was limited by vessel dissection and early restenosis. This was especially true for ostial lesions, which are probably primarily of aortic atherosclerotic origin. Several studies have now demonstrated the technical effectiveness of renal artery stenting. Although this may be done at time of renal arteriography for all flow-limiting lesions, the procedure is recommended only if the lesion is functionally significant. This is revealed either by a positive captopril renogram or a renal vein renin ration >1.5 between the two renal veins.

2. Surgical treatment is indicated for failed angioplasty, very distal lesions, bifurcation lesions, coexisting renal artery aneurysm or severe aortic atherosclerosis. Renal artery reconstruction is the vascular procedure of choice. Other options include venous bypass, endarterectomy and ex-vivo reconstruction and auto-transplantation for distal lesions. However, if the kidney is small (<7.5–8 cm in diameter) with poor function but with high renin production, nephrectomy is the proper treatment.

3. When medical treatment is indicated, calcium antagonists are the drugs of choice. ACE inhibitors may aggravate ischaemia of the affected kidney by removing the high levels of angiotensin II that are supporting its circulation.

Endocrinal disorders

Primary aldosteronism [4,33,34]

The most common cause of primary aldosteronism is an aldosterone-producing adenoma, which accounts for 70% to 80% of cases. Less commonly the condition is due to bilateral hyperplasia (20%), nodular adrenocortical hyperplasia, renin-responsive adenoma and glucocorticoid-remediable aldosteronism. A variety of other conditions also exhibit mineralocorticoid excess, including enzymatic deficiencies (11-OH-hydroxylase deficiency, 17-OH-hydroxylase deficiency and 11-OH-dehydrogenase deficiency syndromes) and chronic liquorice ingestion containing glycyrrhetinic acid.

Clinical picture

Patients with primary hyperaldosteronism present principally with hypertension. Non-specific weakness, fatigue, polyuria, or cramps may be associated due to hypokalaemia.

Investigation

24-hour urinary aldosterone excretion during salt loading (200 mEq/day for 3 days). An excretion rate >14 μg of aldosterone in 24 hours establishes the diagnosis and distinguishes the condition from essential hypertension. Plasma aldosterone is unreliable since about 40% of patients with primary aldosteronism have plasma aldosterone values that fall within the range for essential hypertension.

Other tests that have been used for the diagnosis are suppressed plasma renin activity (<1 ng/mL per hour) that fails to rise above 2 ng/mL per hour after salt and water depletion and upright posture, and an elevated plasma aldosterone to renin ratio (but these have limitations).

Serum K is usually low in patients with secondary hypertension, but 7%–38% of patients have normal serum K levels, particularly those with bilateral adrenal hyperplasia.

Fludrocortisone suppression test. In patients with primary aldosteronism, 4-day administration of fludrocortisone further suppresses plasma renin activity without suppressing plasma aldosterone below 5 ng/dL.

Imaging studies to detect adenomata include CT and MRI. All adenomata ≥1.5 cm in diameter can be located accurately. However, ≤8% of the normal population may have non-functioning incidental adrenal adenomas (incidentalomas). An adenoma is likely in the presence of spontaneous hypokalaemia <3.0 mEq/L, plasma 18-hydroxycoricosterone values >100 mg/dL and an anomalous postural decrease in plasma aldosetrone concentration.

Adrenal venous aldosterone levels should be measured when the biochemical findings are highly suggestive of an adenoma but the adrenal CT or MRI is ambiguous.

Treatment

1. Medical therapy is indicated in patients with adrenal hyperplasia, bilateral adrenal adenomas and those who are poor surgical risks. A combination of a diuretic (e.g. furosemide 80–160 mg/day) with either spironolactone 100–200 mg/day or amiloride hydrochloride 12–20 mg/day corrects the hypokalaemia and normalizes the blood pressure within 2–4 weeks.
2. Surgical excision with unilateral total adrenalectomy is indicated for unilateral aldosterone-producing adenomas. Preoperative drug treatment is needed to correct blood pressure and hypokalaemia for at least 8–10 weeks.

Cushing syndrome [4,35,36]

Spontaneous Cushing syndrome can be classified into:

- corticotrophin-dependent, due to pituitary tumour (70%–80% of cases) or ectopic adrenocorticotropic hormone (ACTH) syndrome;
- corticotrophin-independent, usually due to unilateral cortisol-producing adenoma or carcinoma. Rarely, the condition is due to bilateral adrenal hyperplasia.

Hypertension occurs in about 80% of patients with Cushing syndrome. The excess cortisol production may overwhelm the ability of the renal 11 β-hydroxysteroid dehydrogenase to convert active cortisol into an inactive cortisone at the renal mineralocorticoid receptor level, so that cortisol persists and stimulates the mineralocorticoid receptors to retain sodium and expand the extracellular fluid volume. Cortisol also stimulates the synthesis of renin substrate and the expression of angiotensin II receptors and also potentiates the response of vascular smooth muscle to vasoconstrictor agents.

Investigation

24-hour urinary free cortisol or overnight dexamethazone suppression test is the initial screening test. A 24-hour urinary free cortisol >40 µg or serum cortisol >5 µg/dl in a blood sample withdrawn at 08:00 after giving 1.0 mg of dexamethasone at 23:00 the previous night suggests the diagnosis. This should prompt measurement of plasma ACTH at 08:00.

Plasma ACTH. A low plasma ACTH level is suggestive of an adrenal tumour or hyperplasia and should be evaluated further by abdominal CT.

A high plasma ACTH level >200 pg/mL is suggestive of ectopic ACTH production and should prompt a search for ACTH-producing tumours such as small-cell bronchial

carcinoma or carcinoid tumours. A high plasma ACTH level, but <200 pg/mL, suggests the diagnosis of either a pituitary tumour or ectopic ACTH production. Differentiation can be made by low-dose and high-dose dexamethasone suppression tests. In the low-dose test, dexamethasone is administered at 0.5 mg orally every 6 hours for 48 hours. The high-dose test is then done using a dose of 2.0 mg orally every 6 hours for 48 hours. A 24-hour urinary free cortisol and morning serum cortisol are measured at baseline and on the second day of each dose. Non-suppression on the low-dose test and suppression on the high-dose test (≥50% reduction in plasma cortisol and ≥90% reduction in urinary free cortisol) support the diagnosis of pituitary tumour or hypothalamic-pituitary dysfunction. Non-suppression on both the low- and high-dose tests is suggestive of ectopic ACTH production.

A normal plasma ACTH level will require a corticotrophic-releasing hormone infusion test or metyrapone response test. Both tests demonstrate the responsiveness of the hypothalamic-pituitary axis in the presence of cortisol excess. The corticotrophic-releasing hormone infusion test involves measurement of serum cortisol and plasma ACTH in response to corticotrophic-releasing hormone infusion. The metyrapone response test involves the administration of metyrapone to block cortisol synthesis and thereby stimulates endogenous release of ACTH. An increase in plasma ACTH in response to either test suggests the diagnosis of a pituitary tumour or hypothalamic-pituitary dysfunction. Lack of response to either test suggests ectopic ACTH production.

Head CT or MRI and inferior petrosal sinus sampling for ACTH level estimation may help identify the pituitary cause of the syndrome.

Treatment

1. The majority of patients have discrete pituitary adenomas that can be resected by transsphenoidal microsurgery.
2. If an adrenal tumour is responsible, it should be removed surgically.
3. Medical treatment for inoperable cases includes metyrapone, bromocriptine and ketoconazole.

Phaeochromocytoma [4,37,38]

This is a catecholamine-producing tumour of the sympathoadrenal system. Nearly 80% of the tumours are limited to the adrenal gland, usually unilaterally. The tumours are likely to be bilateral or multiple in paediatric presentations or in familial forms such as neurofibromatosis and multiple endocrine neoplasia types 2A or 2B. About 10%–20% arise in other intra-abdominal sites and <5% appear in intrathoracic sites or the bladder. Less than 10% are malignant. Most tumours secrete both norepinephrine and epinephrine although the former usually predominates.

Clinical picture

Patients usually present with clusters of symptoms that occur in paroxysms. These spells may occur many times a day or may be separated by weeks or months. Often there is a characteristic trigger such as change in posture, certain foods, trauma, pain or drugs.

The three most common symptoms are headache, palpitation, and sweating. Other symptoms may occur including anxiety, weakness and tremor. When norepinephrine is the primary hormone produced, pallor usually occurs but if substantial amounts of epinephrine are produced, flushing develops.

Episodic hypertension develops as a result of catecholamine release from the tumour and the sympathetic nerves. Although some blood pressure readings may be normal, most measurements are in the hypertension range but with wide variability.

Investigation

24-hour urinary excretion of total catecholamines (norepinephrine, epinephrine or dopamine) or their metabolites (vanillylmandelic acid or metanephrine). Since any single hormone may or may not be elevated, an array of these substances should be measured. Urinary creatinine should also be measured to verify that collection represents the 24-hour excretion. To reduce the incidence of false positive results, the patient should be in a non-stressful situation when the sample is obtained. Newer chromographic techniques usually obviate the need for dietary restrictions, although some drug interferences remain.

Plasma catecholamines levels (norepinephrine plus epinephrine) are measured when the urinary assays are borderline. If the levels exceed 2000 pg/mL in the basal state, the presence of phaeochromocytoma is highly likely. If the levels are less than 1000 pg/mL, the diagnosis is highly unlikely. In patients with plasma catecholamine levels between 1000 and 2000 pg/mL, the clonidine suppression test may be useful.

Clonidine suppression test. Plasma catecholamine levels are obtained at baseline and hourly for 3 hours after 0.3 mg of clonidine is given orally. The normal response to clonidine is suppression of plasma catecholamine level by at least 50% from baseline to <500 pg/mL. Non-suppression of elevated plasma catecholamines by clonidine is strongly suggestive of phaeochromocytoma.

Glucagon stimulation test. Plasma catecholamine levels <1000 pg/mL in a patient with clinical features suggestive of phaeochromocytoma is about the only indication for this test. Plasma catecholamine levels are obtained at baseline and 3 minutes after intravenous injection of 2 mg glucagon. A positive result is indicated by a 3-fold increase in plasma catecholamine levels or an absolute level >2000 pg/mL. A blood pressure rise of at least 20/15 mmHg is desirable but not essential to confirm the diagnosis. The test is potentially

dangerous and rarely indicated. Phentolamine 5 mg intravenous bolus after a 0.5 mg test dose should be readily available to terminate a life-threatening pressor response.

CT and MRI of the abdomen are used to localize the tumour after the diagnosis is established by the above tests. Patients with biochemical diagnosis and negative localization studies should have 131-I-metaiodobenzylguanidine followed by total body scan to provide both anatomical localization and functional characterization of extra-adrenal phaeochromocytomas and metastases. The agent requires active concentration in the sympathoadrenal tissues by the catecholamine re-uptake mechanism; therefore drugs that block catecholamine re-uptake (e.g. tricyclic antidepressant, cocaine, etc.) may result in false-negative results.

Treatment

1. Phaeochromocytomas should be resected. Preoperative management usually includes several weeks of α-blockers (especially phenoxybenzamine) and rehydration to avoid abrupt hypotension from withdrawal of the elevated catecholamines once the tumour pedicle is clamped. β-blockers can control arrhythmias during the perioperative period but should be administered only in conjunction with α-blockers to avoid unopposed α-agonist influence.

2. It the tumour is unresectable, chronic medical therapy can be used with the α-blocker phenoxybenzamine or with α-methyltyrosine, an inhibitor of catechol synthesis.

Pharmacological causes of hypertension [3]

Drugs that cause hypertension are divided into three categories.

Vasoconstrictors

Phenylephrine, pseudoephedrine, β-agonist bronchodilators, alcohol excess, anti-adrenergic agent withdrawal and monoamine oxidase inhibitor co-administered with tyramine-containing foods or medications.

The intake of large amounts of alcohol has been associated with secondary hypertension, presumably because of increased sympathetic activity and inhibition of sodium transport across cell membranes with consequent increases in intracellular Ca^{2+} concentration [39].

Volume expanders

Glucocorticoids, estrogens (oral contraceptives), non-steroidal anti-inflammatory agents (NSAIDs).

Oral contraceptive pills cause hypertension in 5% of their users over a 5-year period. The likelihood of developing hypertension increases among those aged over 35 years,

those who are obese, those who drink large quantities of alcohol or those who have had hypertension during a prior pregnancy. Hypertension is usually mild but it may be severe and can persist after the drug has been discontinued. Possible mechanisms causing hypertension include renin-angiotensin-aldosterone mediated volume expansion, sodium retention and induction of insulin resistance and hyperinsulinaemia.

Women given the pill should have their blood pressure monitored. If it rises, an alternative contraceptive should be offered. If the pill remains the only acceptable contraceptive, the elevated blood pressure should be reduced with appropriate therapy. Those who stop taking the drug should be evaluated for secondary hypertension after at least 3 months have elapsed to allow for the changes in renin-angiotensin-aldosterone system to remit.

Postmenopausal estrogen use does not appear to induce hypertension.

Miscellaneous

Psychotropic drugs that interfere with antihypertensive agents, cyclosporine, tacrolimus, erythropoietin.

The immunomodulating drugs cyclosporine and tacrolimus can cause hypertension in >50% of instances. Possible mechanisms of hypertension include direct nephrotoxicity, production of renal vasoconstrictor eicosanoids, failure of vasodilator prostaglandin synthesis, interference with endothelial-derived relaxing factor or increased renal sympathetic activity. Because of cyclosporines binding to the intracellular calcium-binding protein cyclophilin, the resulting hypertension is particularly sensitive to treatment with dihydropyridines e.g. nifedipine. In contrast, ACE inhibitors may worsen their renal function and diuretics may exacerbate hypomagnesaemia.

Evaluation for hypertensive crisis [40,41,42]

Hypertensive crises are acute life-threatening syndromes associated with very high blood pressure or sudden marked increases in blood pressure. They may be separated into the following groups.

- **Hypertensive emergencies**, which are associated with severe symptoms of progressive target organ damage. They require immediate reduction of blood pressure (within 1 hour usually with parenteral agents).
- **Hypertensive urgencies**, which are asymptomatic and not associated with target organ damage. They require slower reduction of blood pressure by oral agents.

When the rise in blood pressure causes acute damage to retinal vessels, the term accelerated-malignant hypertension is used. The separation between accelerated and malignant phases has been based on the presence of retinal haemorrhages or exudates (accelerated) and papilloedema (malignant). Since the clinical features and survival rates

of those with or without papilloedema are so similar there is no sound reason for such separation.

Pathophysiology

Any hypertensive disease can initiate a crisis. Some conditions, including phaeo-chromocytoma and renovascular hypertension, do so at a higher rate than does primary hypertension. However, because of the marked prevalence of the latter, most hypertensive crises appear in the setting of pre-existing primary hypertension.

The primary pathophysiological abnormality is alteration of autoregulation in certain vascular beds, especially cerebral and renal, which is often followed by frank arteritis and ischaemia in vital organs. Autoregulation refers to the ability of blood vessels to dilate or constrict to maintain normal organ perfusion. Normal arteries from normotensive individuals can maintain blood flow over a wide range of mean arterial pressures, usually 60–150 mmHg. Chronic elevations of blood pressure cause compensatory functional and structural changes in the arterial circulation and shift the autoregulatory curve to the right. This allows hypertensive patients to maintain normal perfusion and avoid excessive blood flow at higher blood pressure levels. When blood pressure increases above the autoregulatory range, the tightly constricted vessels can no longer withstand the pressure and are suddenly dilated. Such "breakthrough" of blood flow hyperperfuses the tissues under high pressure causing leakage of fluid into the perivascular tissue. The medium and small arteries and arterioles show acute and chronic inflammatory changes associated with necrosis. Breakthrough of cerebral blood flow results in cerebral oedema and the syndrome of hypertensive encephalopathy. In previously normotensive persons whose vessels have not been altered by prior exposure to high pressure, breakthrough occurs at a mean blood pressure of about 120 mmHg but in hypertensive patients, breakthrough occurs at a mean level of about 180 mmHg. In children with acute glomerulonephritis and in women with eclampsia, hypertensive encephalopathy may develop at blood pressure as low as 150/100 mmHg.

Clinical picture

Hypertensive crisis can be recognized by the association of extremely elevated blood pressure with physical or laboratory findings of target organ damage. However, as indicated above, in formerly normotensive or minimally hypertensive individuals such as children and pregnant women, the condition may occur at relatively low blood pressure levels. The following clinical features help diagnose a hypertensive crisis.

- Severe elevation of blood pressure >180/120 mmHg. The rapidity in rise of blood pressure is more important than the absolute level in producing vascular damage.
- Funduscopic examination reveals haemorrhages, exudates and papilloedema.

- Hypertensive encephalopathy manifesting by headache, irritability, alteration in consciousness, focal deficits and seizures.
- Cardiac enlargement and congestive heart failure.
- Renal insufficiency, with protein and red cells in urine, and azotaemia. Acute oliguric renal failure may develop.
- Nausea and vomiting.
- Elevated levels of plasma renin from diffuse intrarenal ischaemia resulting in secondary aldosteronism and consequent hypokalaemia.
- Microangiopathic haemorrhagic anaemia with red cell fragmentation and intravascular coagulation.

Prognosis

Before effective therapy was available, <25% of patients with malignant hypertension survived 1 year and only 1% survived 5 years. With effective therapy, including renal dialysis, >90% survive to 1 year and about 80% survive 5 years. Death in patients with severe hypertension is usually from stroke or renal failure when it occurs in the first few years after onset. If therapy keeps patients alive for >5 years, death will usually be due to coronary artery disease.

Evaluation for hypertension in special groups and circumstances

Pregnant women

Hypertension during pregnancy is defined as blood pressure >140/90 mmHg on two measurements at least 4 hours apart, or a diastolic blood pressure >110 mmHg at any time during pregnancy or up to 6 weeks postpartum. It affects about 10% of pregnancies.

Hypertension during pregnancy can be classified into five categories [43,44].
1. Chronic hypertension. This refers to hypertension appearing prior to pregnancy or before 20 weeks of gestation. It persists for more than 12 weeks postpartum.
2. Pre-eclampsia. This denotes hypertension associated with proteinuria (>300 mg/24 hours) developing after 20 weeks gestation. It is more common in nulliparous women, multiple gestations, women with hypertension for 4 years or more, those with a family history of pre-eclampsia, hypertension in previous pregnancy and renal disease. It may progress to eclampsia (seizures).
3. Chronic hypertension with superimposed pre-eclampsia. This is recognized by new onset of proteinuria after 20 weeks gestation in a woman with hypertension. In a woman with hypertension and proteinuria prior to 20 weeks gestation, it is recognized by sudden 2–3-fold increase in proteinuria or the development of thrombocytopenia, elevated alanine aminotransferase or aspartate aminotransferase.

4.   Gestational hypertension. This is characterized by the development of hypertension without proteinuria after 20 weeks gestation. It may represent a pre-proteinuric phase of pre-eclampsia, or the recurrence of chronic hypertension that abated in mid-pregnancy, and may evolve into pre-eclampsia.

5.   Transient hypertension. This is a retrospective diagnosis with normalization of blood pressure by 12 weeks postpartum. It may recur in subsequent pregnancies and is predictive of future primary hypertension.

Children and adolescents [45]

Hypertension affects 0.26%–2% of children. It is defined as average systolic or diastolic blood pressure equal to or greater than the 95th percentile for age, sex and height on at least three separate occasions. Blood pressure between the 90th and 95th percentiles is considered high normal or borderline hypertension.

The most common causes of hypertension change during childhood, with secondary causes of hypertension predominating in the youngest patients and those in whom systemic hypertension is most severe. Essential hypertension is being increasingly recognized, especially in adolescents with mild–moderate elevation of blood pressure.

The most common cause of secondary hypertension in children is renal parenchymal disease (60%–80%) often the result of reflux nephropathy, pyelonephritis and obstructive uropathy. Renovascular hypertension (8%–10%) and coarctation of the aorta (2%) are less frequent. Rare causes include endocrinal and central nervous system disorders.

The long-term significance of blood pressure readings above the 95th percentile in an asymptomatic child remains uncertain, since tracking of blood pressure as children grow older does not tend to be persistent. The positive predictive value of a blood pressure reading above the 95th percentile in a 10-year old body being at a hypertensive level at age 20 years is only 0.44. Nonetheless hypertensive children, as defined above, should be given a limited investigation for target organ damage and secondary causes. If these tests are negative, the children should be carefully monitored and given non-pharmacological therapy. Those with severe hypertension (levels above the 99th percentile) should be rapidly and completely evaluated and given appropriate pharmacological therapy.

The elderly [46,47,48]

About 55% of men and women aged 65–74 years have hypertension. Chronic renal disease or atherosclerotic renovascular disease are likely to be found. The elderly achieve even greater reductions in coronary disease and heart failure by effective therapy than younger hypertensives.

The elderly may display two features that reflect age-related cardiovascular changes.

- Pseudo-hypertension from markedly sclerotic arteries that do not collapse under the cuff, presenting much higher cuff pressures than are present within the vessels. If the arteries feel rigid but there are few retinal or cardiac findings to go along with marked hypertension, direct intra-arterial measurements may be needed before therapy.
- Postural and postprandial hypotension, which is seen in about 20% of the elderly. This usually reflects a progressive loss of baroreceptor responsiveness with age.

Women

Women have lower systolic blood pressure levels than men during early adulthood while the opposite is true after the sixth decade of life. Diastolic blood pressure tends to be just marginally lower in women than men regardless of age. However, after the fifth decade of life, the incidence of hypertension increases more rapidly in women than men and the prevalence of hypertension in women is ≥ that in men during the sixth decade of life [49].

The effect of menopause on blood pressure is controversial, but postmenopausal women are more than twice as likely to have hypertension as premenopausal women. This may be attributed to estrogen withdrawal, overproduction of pituitary hormones, weight gain or a combination of other as yet undefined neurohormonal influences [50]. The effect of postmenopausal hormone replacement therapy on blood pressure is likely to be modest. All hypertensive women treated with hormone replacement therapy should have their blood pressure monitored closely at first and then at 6-month intervals.

Patients with diabetes mellitus [51,52,53,54,55]

The association of diabetes mellitus and hypertension is more than that predicted by chance. About 50% of type 1 patients and 80% of type 2 diabetes mellitus have hypertension. The development of hypertension increases all the microvascular and macrovascular complications of diabetes. It is associated with about a doubling of the prevalence of MA, LVH and ECG signs of myocardial ischaemia. The absence of nocturnal fall in blood pressure may reflect autonomic neuropathy or incipient diabetic nephropathy. When hypertensive, patients with diabetes mellitus may confront the following unusual problems [56,57,58].

- The development of progressive renal insufficiency may leave few functional juxtaglomerular cells and as a result, the syndrome of hyporeninaemic hypoaldosteronism may appear, usually manifesting by hyperkalaemia.
- If hypoglycaemia complicates antidiabetic therapy, severe hypertension may occur as a result of stimulated sympathetic nervous activity.
- High doses of both diuretics and β-blockers may worsen diabetic control by inducing further insulin resistance. β-blockers may also blunt the catecholamine response to severe hypoglycaemia and so prevent the development of its warning signs (except sweating).

- Diabetic neuropathy may add to the postural hypotension and impotence that frequently complicate antihypertensive therapy.
- Diabetic nephropathy will impair sodium excretion and diminish the effectiveness of diuretics.
- ACE inhibitors can be especially effective in reducing the high intraglomerular pressures that are probably responsible for the progressive glomerulosclerosis of diabetes.

In the Eastern Mediterranean Region, there has been a recent rapid increase in the prevalence of diabetes, particularly type 2. The prevalence rate in adults varies between 7% and 25% with an estimated 17 million people affected. Many countries in the Region are now reporting the onset of type 2 diabetes at an increasingly younger age, and in some countries type 2 is emerging in children. This might be related to the significant social and economic changes in the Region with rising rates of obesity, smoking and sedentary lifestyle [2].

Metabolic syndrome [59,60,61]

Metabolic syndrome refers to a constellation of cardiovascular risk factors related to hypertension, abdominal obesity, dyslipidaemia and insulin resistance. The National Cholesterol Education Program [62] defines the syndrome by the presence of three or more of the five risk factors given in Box 4. The prevalence of the condition is highly age dependent and is associated in men with a 4-fold increase in risk for fatal coronary artery disease and a 2-fold greater risk of cerebrovascular disease and all-cause mortality. Affected patients have a 5- to 9-fold increased risk of developing diabetes. The cornerstone of treatment is appropriate lifestyle changes but if blood pressure exceeds 140/90 mmHg pharmacological therapy is indicated. Associated impaired glucose tolerance, diabetes and lipid abnormalities are managed according to standard guidelines.

Box 4. Risk factors for the metabolic syndrome [3]

Waist circumference:	>102 cm for men, >88 cm for women
Blood pressure:	Systolic ≥130 mmHg and/or diastolic ≥85 mmHg
Fasting glucose:	≥110 mg/dL
Triglycerides:	≥150 mg/dL
HDL cholesterol:	<40 mg/dL in men, <50 mg/dL in women

HDL: high density lipoprotein

Obstructive sleep apnoea [63,64,65]

Obstructive sleep apnoea occurs in 2%–4% of the adult populations worldwide and >50% of affected individuals have hypertension. The index of suspicion should be high in any hypertensive patient whose body mass index exceeds 27 kg/m^2. Confirmation of diagnosis is accomplished by a formal sleep study. The impact of sleep apnoea on the cardiovascular system is probably related in large part to its association with elevated blood pressure. Episodes of apnoea with repeated oxygen desaturation have been shown to stimulate strong sympathetic nervous system discharges that directly elevate blood pressure. Other contributory factors for hypertension include the commonly associated obesity, impaired glucose tolerance and sleep deprivation. Other cardiovascular conditions associated with obstructive sleep apnoea include arrhythmias, myocardial ischaemia and failure and stroke.

Renal transplantation [3]

The prevalence of hypertension in patients receiving kidney allografts probably exceeds 65%. Hypertension is less common in other forms of transplantation. Nocturnal hypertension, a reversal of diurnal blood pressure rhythm, can present in renal transplant patients and they may need ambulatory blood pressure monitoring to evaluate overall blood pressure control. The mechanisms of hypertension in transplant patients are multifactorial and include vasoconstriction and structural vascular changes induced by calcineurin-inhibiting immunosuppression drugs (cyclosporine and tacrolimus), effect of steroid therapy, impairment of renal function that leads to salt and water retention and the occasional development of renal artery stenosis.

Perioperative hypertension [7,66,67]

Perioperative hypertension is defined as the presence of high blood pressure immediately before, during or after surgery that may require some attention to minimize risk to the patient. This situation may be encountered as a result of:

- previously unrecognized hypertension
- recognized but uncontrolled hypertension
- effect of stress and pain
- failure to take oral medications in the immediate post-surgical period.

Treatment of hypertension

Goals of therapy [3,5,68,69]

The ultimate goal in treatment of the hypertensive patient is to achieve the maximum reduction in the long-term total risk of cardiovascular morbidity and mortality. This requires:

- treatment of all reversible risk factors identified including smoking, dyslipidaemia and diabetes mellitus;
- appropriate management of associated clinical conditions such as congestive heart failure, coronary artery disease, peripheral vascular disease and transient ischaemic attacks;
- achieving office blood pressure values <130/80 mmHg for patients with diabetes mellitus or chronic renal disease. When home or ambulatory pressure measurements are used to evaluate the efficacy of treatment, daytime values around 10–15 mmHg lower for systolic blood pressure and 5–10 mmHg lower for diastolic blood pressure are the goal values.

Because most patients with hypertension, especially those aged ≥50 years, will reach the diastolic blood pressure goal once the systolic blood pressure is at goal, the primary focus should be on achieving systolic blood pressure goal.

Treating systolic and diastolic blood pressure to target is associated with a decrease in cardiovascular complications. This includes 35%–40% mean reduction in stroke incidence, 20%–25% mean reduction in myocardial infarction and >50% mean reduction in heart failure.

There are several strategies for achieving therapeutic goals: lifestyle modifications, pharmacological modifications and general strategies for hypertensive therapy. A simplified scheme for the treatment of hypertension is shown in Figure 1.

Lifestyle modifications

Adoption of healthy lifestyles by all individuals is critical in the prevention of high blood pressure and an indispensable part of the management of those with hypertension. Lifestyle modifications decrease blood pressure, enhance antihypertensive drug efficacy and decrease cardiovascular risk. Patients with prehypertension and no compelling indication (including heart failure, prior myocardial infarction or stroke, high coronary risk status, diabetes mellitus, chronic renal disease) respond well to lifestyle modifications and usually do not need drug therapy. For all other abnormal blood pressure categories, drug therapy is indicated if goal blood pressure is not achieved by lifestyle modification alone.
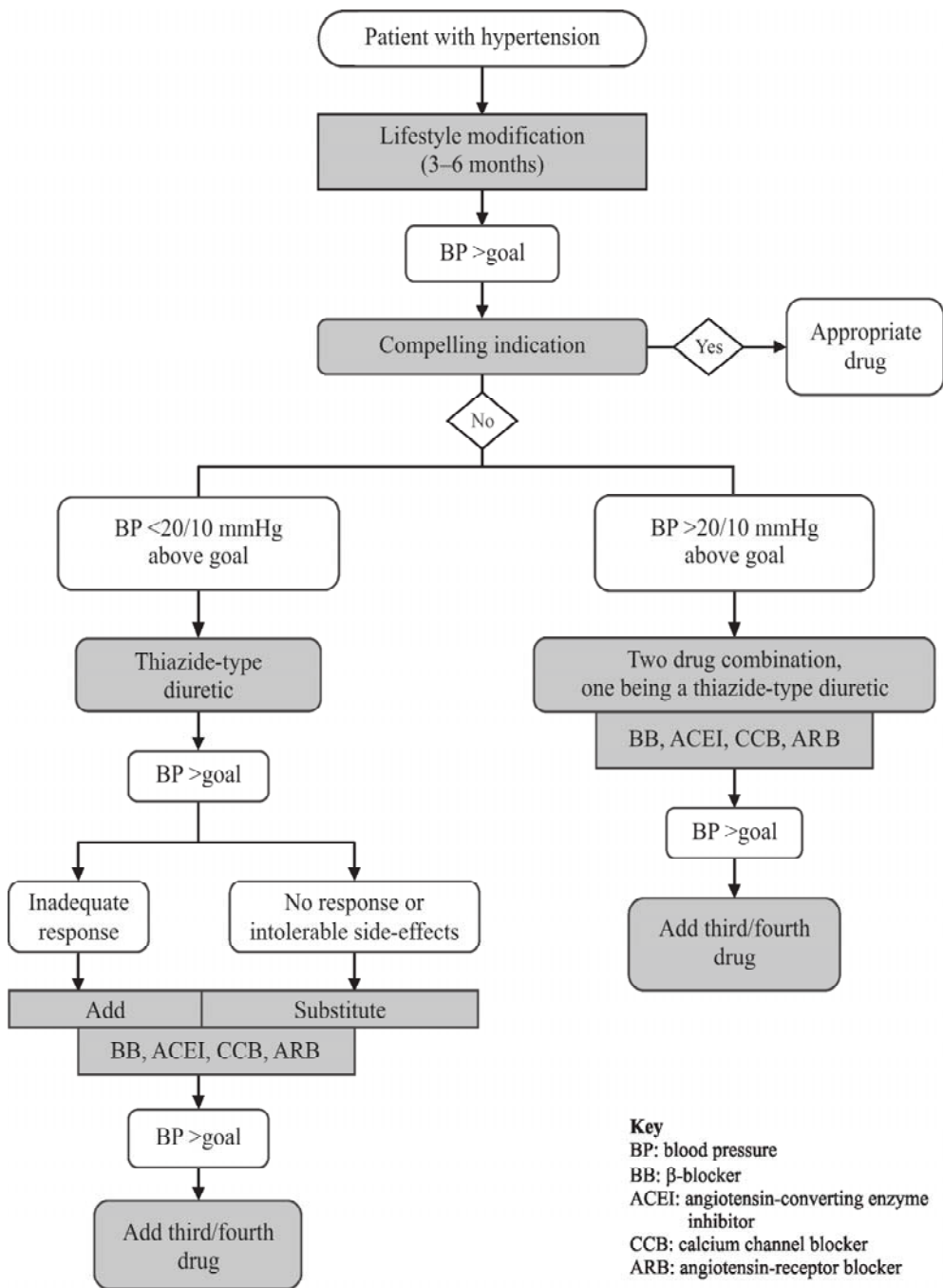
Figure 1. Treatment of hypertension

Table 6. Recommended lifestyle modifications

Modification	Recommendation	Approximate systolic BP reduction
Weight reduction	Maintain normal body weight	5–20 mmHg/10 kg
Adopt DASH eating plan	Consume a diet rich in vegetables, fruits, and low-fat dairy products with a reduced content of saturated and total fat	8–14 mm Hg
Dietary sodium sodium chloride	Reduce dietary sodium intake to no more than 2.4 g sodium or 6 g restriction	2–8 mmHg
Physical activity	Engage in regular aerobic physical activity at least 30 minutes daily, most days of the week	4–9 mmHg

BP: blood pressure

The lifestyle measures that should be considered in all patients are shown in Table 6. Combinations of two or more of them achieve better results.

Cessation of smoking [70,71,72]

This is probably the single most powerful lifestyle measure for the prevention of non-cardiovascular and cardiovascular diseases, including stroke and coronary heart disease. Although any independent chronic effect of smoking on blood pressure is small and smoking cessation does not lower blood pressure, total cardiovascular risk is greatly increased by smoking. In addition, smoking may interfere with the beneficial effects of some antihypertensive agents such as β-adrenergic blockers. When necessary, nicotine replacement or buspirone therapies should be considered since they appear to be safe in hypertension and to facilitate smoking cessation.

Weight reduction and physical exercise [73,74]

Weight reduction reduces blood pressure in overweight patients and has beneficial effects on associated risk factors such as insulin resistance, diabetes, hyperlipidaemia and LVH. Attainment of ideal body weight is by no means necessary to produce lower blood pressure. Blood pressure is lowered by 1.6/1.1 mmHg for every kilogram of weight loss. Many hypertensive patients have much more than 10 kg of excess adiposity and many of them would no longer be hypertensive if they lost even this amount of body fat. The blood pressure lowering effect of weight reduction may be enhanced by a simultaneous increase in physical exercise. Thus, sedentary patients should be advised to take up modest levels of aerobic exercise on a regular basis such as brisk walking for at least 30 minutes per day, most days of the week. However, isometric exercise such as heavy weight-lifting can have pressor effect and should be avoided. When hypertension is

poorly controlled, and always for severe hypertension, heavy physical exercise should be discouraged or postponed until appropriate drug treatment has been instituted and found to be effective.

Reduction of salt intake and other dietary changes [75,76,77]

Reducing dietary sodium intake to no more than 100 mEq/L (2.4 g sodium or 6 g sodium chloride) reduces the blood pressure by an average of 4–6 mmHg. Patients should be advised to avoid added salt, to avoid obviously salted food (particularly processed foods) and to eat more meals cooked directly from natural ingredients containing more potassium. Hypertensive patients should also be advised to eat more fruit and vegetables, to eat more fish and to reduce their intake of saturated fat and cholesterol. This is well achieved by adoption of the Dietary Approach to Stop Hypertension (DASH) eating plan. The DASH diet is rich in fruits, vegetables and low-fat dairy foods including whole grains, poultry, fish and nuts, and is reduced in fats, red meat, sweets and sugar-containing beverages. It contains reduced amounts of total and saturated fat and cholesterol, and increased amounts of potassium, calcium, magnesium, dietary fibre and protein. Fruits and vegetables, including nuts, are responsible for at least half of the total effect of the DASH diet. Moreover, the DASH diet is reasonably low in cost.

The combined effects on blood pressure of low sodium intake and the DASH diet are greater than the effects of either alone and are substantial [78].

Cessation of alcohol consumption [79,80]

There is a linear relationship between alcohol consumption, blood pressure levels and prevalence of hypertension in populations. High levels of alcohol consumption are associated with a high risk of stroke, particularly so for binge drinking. Additionally, alcohol attenuates the effects of antihypertensive drug therapy. Heavy drinkers may also experience a rise of blood pressure after acute alcohol withdrawal. Hypertensive patients who drink alcohol should be advised to stop drinking. If they insist on continuing to drink they should be advised, in any case, not to consume more than 30 ml of ethanol (the equivalent of two drinks per day) in men and no more than 15 ml of ethanol (one drink per day) in women and lighter-weight persons. (One drink is 360 ml of beer, 150 ml of wine and 45 ml of 80%-proof liquor).

Pharmacological therapy [81]

Initial drug therapy is determined by the presence or absence of compelling indications.

- In patients without compelling indications, drug therapy is usually initiated by a thiazide-type diuretic. Diuretics have been virtually unsurpassed in preventing the cardiovascular complications of hypertension. They enhance the antihypertensive

efficacy of multidrug regimens and are more affordable than other antihypertensive agents.

- In patients with compelling medications, initial drug selection is based on favourable outcome data (from clinical trials) for specific antihypertensive drugs in the treatment of special patient groups.

Compelling indications [7]

Although the main benefits of antihypertensive pharmacotherapy are due to lowering of blood pressure per se, largely independent of the drugs used, various clinical trials have supported the use of certain antihypertensive drug classes for special patient groups by demonstrating the benefits of such therapy on the associated condition.

This approach is illustrated by the antihypertensive drug selection in the following conditions [4,5,7].

Ischaemic heart disease [82]

- In patients with stable angina pectoris, the first drug of choice is usually a β-adrenergic blocker, alternatively long-acting calcium channel blockers (CCBs) can be used.
- In patients with unstable angina or myocardial infarction, initial drug therapy should be with β-adrenergic blockers and ACE inhibitors.
- In post-myocardial infarction patients, ACE inhibitors, β-adrenergic blockers and aldosterone antagonists are the most beneficial.

One caveat with respect to antihypertensive treatment in patients with ischaemic heart disease is the finding by some studies of an apparent increase in coronary risk at low levels of diastolic blood pressure (a J-shaped curve). In one study, lowering the diastolic blood pressure to below 55–60 mmHg was associated with an increase in cardiovascular events including myocardial infarction. No similar increase in coronary events has been observed with systolic blood pressure. Patients with occlusive coronary artery disease and/or LVH are put at risk of coronary events if diastolic blood pressure is low. Overall, however, many more events are prevented than caused if blood pressure is aggressively treated.

Heart failure [83]

- For patients with asymptomatic ventricular dysfunction, ACE inhibitors and β-adrenergic blockers are recommended.
- For patients with clinical heart failure, ACE inhibitors, β-adrenergic blockers, angiotensin receptor blockers (ARBs) and aldosterone blockers are recommended along with loop diuretics.

Blood pressure targets in heart failure have not been firmly established, but lowering systolic blood pressure is almost uniformly beneficial. In most successful trials, systolic

blood pressure was lowered to 110–130 mmHg. Very low blood pressures (e.g. systolic blood pressure <100 mmHg) may be advisable in some heart failure patients [84].

Diabetes mellitus [7,85,86,87]

- Combination of two or more drugs are usually needed to achieve the target blood pressure goal of <130/80 mmHg.
- Thiazide diuretics, β-adrenergic blockers, ACE inhibitors, ARBs and CCBs are beneficial in reducing cardiovascular disease and stroke incidence.
- ACE inhibitors or ARB-based treatments favourably affect the progression of diabetic nephropathy and reduce albuminuria. ARBs have been shown to reduce the progression to macroalbuminuria.

Chronic renal disease [7,88]

Patients with reduced excretory function (GFR <60 ml/minute per 1.73 m^2, serum creatinine >1.5 mg/dL in men or >1.4 mg/dL in women) and those with albuminuria (>300 mg/d) should receive aggressive blood pressure management to slow deterioration of renal function and prevent cardiovascular disease. They often need treatment with three or more drugs to reach target blood pressure values of <130/80 mmHg.

- ACE inhibitors and ARBs have favourable effects on the progression of diabetic and non-diabetic renal disease. A limited increase in serum creatinine of up to 35% above baseline is acceptable and not a reason to withhold treatment, unless hyperkalaemia develops.
- With advanced renal disease (GFR <30 ml/minute per 1.73 m^2, serum creatinine 2.5–3.0 mg/dL) increased doses of loop diuretics are usually needed in combination with other drug classes.

Cerebrovascular disease [7,86,89]

- In patients with recent ischaemic stroke whose systolic blood pressure is >220 mmHg or diastolic blood pressure is 120–140 mmHg, cautious reduction of blood pressure by about 10%–15% is suggested. This may be achieved by carefully monitored infusion of sodium nitroprusside.
- Systolic blood pressure >185 mmHg or diastolic pressures >110 mmHg are contraindications to the use of tissue plasminogen activator within the first 3 hours of an ischaemic stroke. Once a thrombolytic agent has been initiated, blood pressure should be monitored closely especially in the first 24 hours after infusion of treatment.
- Systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥105 mmHg usually necessitates therapy with intravenous agents to prevent intracerebral bleeding.

Tailoring drug therapy to the pathophysiology of the patient's hypertension [4,5]

Some investigators felt that greater success in treating hypertension could be achieved by basing therapy choice on the reason why the patient is hypertensive and matching that to the mechanisms of action of antihypertensive drugs. This approach, while more intellectually appealing, has major flaws.

- Attempts to profile patients either biochemically (e.g. using plasma renin activity) or haemodynamically (e.g. measuring cardiac output and peripheral vascular resistance) are too expensive and not precise enough to provide the information needed to predict the response to therapy.

- Many, if not all, antihypertensive drugs have more complex mechanisms of action than they were originally thought to have and work well in patient subgroups in which they were supposed to be ineffective. For example, thiazide diuretics not only reduce plasma volume but also are vasodilators after 4 weeks of therapy.

- It is simplistic to assume there is one overriding abnormality that is responsible for the patient's elevated blood pressure. In all likelihood more than one, if not many, of the systems that control blood pressure are dysfunctional simultaneously and single or combination drugs that reduce blood pressure do so by correcting more than one abnormality.

Therefore, the choice of drug therapy should be based primarily on evidence from clinical trials that document reduction of cardiovascular and/or renal events as well as the individual characteristics and comorbidities of each patient.

Concept of essential medicines [90,91,92]

Essential medicines are those that satisfy the priority health care needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness. Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amount, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford. The implementation of the concept of essential medicines is intended to be flexible and adaptable to many different situations; exactly which medicines are regarded as essential remains a national responsibility.

Most countries require that a pharmaceutical product be approved on the basis of efficacy, safety and quality before it can be prescribed. Medicines on such lists are selected after careful study of the medicine used to treat particular conditions and a comparison of the value they provide in relation to their cost.

The ideal antihypertensive drug

In choosing an antihypertensive agent, the following facts learned from the outcome of various therapeutic trials should be acknowledged.

- Overall, the antihypertensive efficacy varies little between various antihypertensive drugs. Virtually all drugs are designed to lower the blood pressure at least 10% in the majority of patients with mild to moderate hypertension. However, individual patients may vary considerably in their response to different drugs. Some of this variably can be accounted for by individual patient characteristics, including age and race [93].
- Antihypertensive agents may have favourable effects beyond their capability to lower blood pressure. Mounting evidence suggests that the superior cardio-renal protective properties of ACE inhibitors are related not only to their haemodynamic effects but also to their ability to modify indirectly the expression of genes in the heart, kidney and vasculature [94].
- Conversely, antihypertensive agents may have unfavourable effects on associated cardiovascular risk factors that could partly counteract the protective effect of blood pressure fall. In this sense drugs that ameliorate, or at least do not exacerbate, insulin resistance and dyslipidaemia should preferably be used [4].
- The presence of subclinical disease, as confirmed by surrogate or intermediate end points, may influence the choice of drugs. The detection of LVH or MA, for example, gives preference to drugs that block the renin angiotensin system [5].
- An ideal antihypertensive drug should fulfil the following requirements [5]:
    - be effective in reducing systemic blood pressure with prolonged duration of action to allow for once-daily dosing
    - to not induce adverse reaction or untoward metabolic effects
    - be able to facilitate the reversal of target organ damage.

At present, there is no single drug, or class of drugs, that possesses all these favourable effects but all classes have variable combinations of them.

Specifics about antihypertensive drugs

Antihypertensive drugs are generally be categorized into three groups:

- Diuretics.
- Adrenergic inhibitors that act centrally, peripherally or as receptor blockers.
- Vasodilators that act directly via calcium channel blockade, ACE inhibition or angiotensin receptor blockade.

Diuretics

Diuretics are now the most frequently prescribed antihypertensive drugs, following a period when their use declined in the early 1990s. This reflects recognition of their ability in lower doses to provide excellent protection against heart attacks, heart failure and stroke; a protection level equal to that seen with ACE inhibitors and CCBs [95].

In the short term, diuretics induce natriuresis and reduce blood volume, and hence the cardiac output. Hormonal and intrarenal counter-regulatory mechanisms, however, rapidly re-establish a steady state with sodium intake and excretion balanced within 3–9 days. With chronic use, plasma volume partially returns toward normal but at the same time peripheral vascular resistance decreases. The fall in peripheral vascular resistance may reflect the vasorelaxant effect seen in vitro [96].

In most published guidelines, thiazide-type diuretics are recommended as first-line therapy in the absence of conditions indicative of the selection of specific agents. They are particularly effective in volume-expanded (renin-suppressed) forms of hypertension. The presence of a polymorphism of the G-protein β3 subunit has been noted to be more common in this group of patients and may prove valuable in indicating better responders to thiazide diuretics [7].

The recommended daily dose of thiazide diuretics has been progressively falling from as high as 200 mg hydrochlorothiazide (or equivalent doses of other thiazides) in the early 1960s to as little as 6.25–12.8 mg today. Full antihypertensive effect of low doses may not, however, become evident except after 4 weeks. The antihypertensive effect of thiazides lasts beyond their diuretic effect, so once-daily hydrochlorothiazide reduces blood pressure for more than 24 hours. Loop diuretics, although more potent as natriuretics than thiazides, are less effective as antihypertensives. Their major use is in patients with renal insufficiency (GFR <50% of normal) and in patients receiving lithium therapy, as they block lithium absorption in the loop of Henle.

The need for diuretics may be lessened with ACE inhibitors and ARBs, which inhibit the renin-angiotensin-aldosterone mechanism and with CCBs which have some intrinsic natriuretic activity [97].

The metabolic side-effects of diuretics including hyperlipidaemia, insulin resistance and electrolyte disturbance are typically dose-dependent.

Adrenergic-inhibiting drugs

Antihypertensive agents can target almost all structures, neurons and receptors of the sympathetic nervous system starting from the brain-stem (where the α_2-adrenoreceptors and I1-imidazoline receptors are located) and going down to the sympathetic ganglia, postganglionic sympathetic neurons and finally the postsympathetic adrenergic receptors. Agents that act by blocking ganglia are no longer used [98].

Central agonists

These agents stimulate either the α_2-adrenoreceptors (methyldopa, guanfacine, guanabenz), the I_1-imidazoline receptors (rilmenidine, moxonidine) or both (clonidine). This inhibits sympathetic nerve activity and norepinephrine-mediated vasoconstriction. Since central α_2-agonists also stimulate the nucleus salivarium and nucleus coeruleus, dry mouth and sedation complicates their use. These side-effects are not shared by imidazoline receptor agonists.

The central α_2-agonists may be indicated when multidrug therapy is required for resistant cases: as a primary therapy for patients with sympathetically driven form of hypertension; for preoperative hypertension where an anaesthesia and analgesia-sparing properties of the drugs may prove beneficial; and as adjunctive therapy in systolic forms of heart failure.

Autoimmune side-effects are peculiar to α-methyldopa and include liver dysfunction and haemolytic anaemia. They result from inhibition of suppressor t-cells with resultant upregulation of antibody production by β-cells. Thus, α-methyldopa is favoured for treatment of hypertension during pregnancy in view of its time-honoured safety record in this condition [99].

Rebound hypertension, although occurring most frequently with clonidine, may occur as a part of the discontinuation syndromes that can complicate abrupt cessation of any antihypertensive drug therapy. These conditions likely reflect a rapid return of catecholamine secretion that has been suppressed during drug therapy. Patients who have been on a combination of a central-adrenergic agonist and a β-adrenergic blocker may be particularly susceptible if the central agonist is withdrawn while the β-blocker is continued [100].

Peripheral adrenergic inhibitors

These agents are rarely used nowadays. Reserpine is an inexpensive generic drug and thus has no constituency pushing for its use. Guanthedine has a steep dose–response relationship with prominent side-effects, including postural hypotension, fluid retention, diarrhoea and failure to ejaculate.

Selective α_1-adrenergic receptor blockers

Selective α_1- blockers have had a relatively small share of the overall market for antihypertensive drugs. However, the increasing awareness of their special ability to improve insulin sensitivity, lipid levels and to provide quick relief of symptoms of benign prostatic hypertrophy supports their more widespread use. However, the premature termination of the doxazosin arm of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) trial because of an increased incidence of heart failure will likely slow the increase in their use [85].

The selective effect of these agents on the postsynaptic α_1-receptors keeps the presynaptic α_2-receptors open, capable of binding neurotransmitters and thereby inhibiting the release of additional norepinephrine through a direct negative feedback inhibition. They relax the arterial and venous beds and, at least initially, may affect the visceral vascular bed more than the peripheral vascular bed. The subsequent pooling of blood in the viscera may explain the propensity to first-dose hypotension seen with the fast-acting prazosin hydrochloride. Terazosin and doxazosin are less lipid-soluble and have half or less of the affinity for α_1-receptors compared with prazosin, thus inducing slower and less profound initial fall of blood pressure particularly after standing [101]. Despite the ALLHAT termination of the doxazosin arm, the ALLHAT experience clearly indicates the need to use α-blockers in conjunction with a diuretic in those with LVH or other risk factors for heart failure. The place of α-blockers in multidrug treatment, in patients with insulin resistance, hypercholesterolaemia and those with benign prostatic hyperplasia cannot be deleted by the ALLHAT findings [4].

β-adrenergic receptor blockers

For many years, β-adrenergic blockers were the second most popular antihypertensive drugs after diuretics. In view of their proven ability to provide secondary cardioprotection after acute myocardial infarction, it was hoped that they would provide primary protection against initial coronary events as well. This hope, however, remains unfulfilled [102]. When compared with a diuretic in middle-aged patients, no significant difference between the two drugs in protecting against coronary mortality was noted in two large trials. Nevertheless, the benefits of β-adrenergic blockers in patients with either coronary artery disease or heart failure ensure that these drugs will continue to be widely used.

β-blockers decrease the cardiac output acutely by 15%–20% and this remains lowered chronically. On the other hand, the peripheral resistance usually rises acutely but falls toward (if not to) normal with time. Renin level falls promptly due to reduction in the processing of prorenin and active renin [18].

β-blockers have been proposed as initial monotherapy for most hypertensives particularly those with coexisting coronary artery disease, heart failure, migraine, tremor and stress-induced arrhythmias.

Various preparations have equal antihypertensive efficacy but some, particularly the lipophilic preparation, may not provide a full 24-hour lowering of blood pressure which can be particularly critical in protecting against early morning cardiovascular catastrophes. Most preparations have a flat dose response curve, but the combination with even a low dose of diuretic will enhance their efficacy [103].

To avoid the discontinuation syndrome, dosage should be cut by half every 2–3 days and the drug should be stopped after the third reduction.

Combined α- and β-adrenergic receptor blockers

Modification of the conventional β-blocker structure has provided agents with combined α- and β- blocking properties. The ratio of α- to β- blockade for carvidolol is 1:4. In high concentrations, it also blocks calcium entry and has antioxidant effects. For labetalol, the α- to β- blockade ratio is 1:10. The antihypertensive effect of these agents is mainly mediated by a fall in peripheral vascular resistance. Carvidolol has been shown to reduce the risk of death and hospitalization by cardiovascular causes in various degrees of heart failure. Labetalol has been used both orally and intravenously to treat hypertensive emergencies, acute aortic dissection, phaeochromocytoma, clonidine withdrawal and cocaine-related hypertensive crises.

The most common side-effect of these agents is orthostatic hypotension and the most serious is hepatotoxicity, which can progress slowly with minimal symptomatology [104].

Direct vasodilators

These agents enter the vascular smooth muscle cells to produce direct vasodilation unmediated by other mechanisms, such as inhibiting hormonal vasoconstriction, calcium entry or blocking α-adrenergic receptors. Minoxidil induces smooth muscle relaxation by opening cardiovascular ATP-sensitive potassium channels [105].

Coincidental to peripheral vasodilatation, the heart rate, stroke volume and cardiac output increase as a result of baroreceptors-mediated reflex increase in sympathetic discharge. This also increases renin release. Such compensatory response sharply limits the use of these drugs. They are chosen as third agents in multidrug treatment of severe hypertension, usually in combination with β-blockers and diuretics. Minoxidil is more potent than hydralazine and has become a mainstay in the therapy of severe hypertension associated with renal insufficiency.

The most important potential disadvantage of direct vasodilators is their failure when given alone to regress LVH because of their marked stimulation of sympathetic nervous activity [106].

Calcium channel blockers

Three types of CCB are now available: dihydropyridines, phenylalkylamines and benzothiazepines. They interact with the L-type voltage-gated plasma membrane channel to produce vasodilation [107]. They also restore nitric oxide availability, most probably by an antioxidant effect on endothelial cells. Additionally they relatively inhibit aldosterone production resulting in natriuresis. The increased excretion of sodium and water also probably reflects the unique ability of CCBs to maintain or increase effective renal blood flow and GFR, which has been attributed to their selective vasodilative action on renal afferent arterioles. However, a large body of experimental data suggest that increased

renal plasma flow and GFR may accelerate the progression of glomerulosclerosis by increasing intraglomerular blood pressure. Therefore, CCBs should only be added to ACE inhibitors if needed to control hypertension in patients with renal insufficiency [93].

CCBs are as effective as ACE inhibitors in inducing regression of LVH and improving diastolic function, probably by improving the impaired coronary reserve. The apparent greater effectiveness in the elderly may just reflect the higher systolic blood pressure in this group of patients, and the more pronounced efficacy of CCBs as the level of blood pressure increases. CCBs are also the drug of choice in treatment of cyclosporine related hypertension [108].

The currently available preparations seem comparable in their antihypertensive effect, but the short-acting dihydropyridines have been noted to increase the frequency of angina and mortality after acute myocardial infarction. They have also been shown to increase coronary events when used to treat hypertension, due to the induced abrupt fall in blood pressure and consequent sympathetic activation. Long-acting CCBs do not share these dangers. The slow onset and long duration of action of amlodipine provide continued effect even if daily doses are missed.

Because calcium entry is involved in so many cellular functions, concerns have been voiced about other potential adverse effects of CCBs. However, calcium metabolism seems to be little altered by these agents and initial reports of increased risks of cancer, bleeding and suicide have not been supported by subsequent data [109]. A unique advantage of these agents involves lack of interference of their antihypertensive effect by NSAIDs, a problem noted with most other classes of antihypertensive drugs [110].

Angiotensin-converting enzyme inhibitors

Three different classes of ACE inhibitors have been developed. They are classified by the ligand of the zinc ion of ACE: sulfhydryl, phosphoryl and carboxyl. The most obvious manner by which ACE inhibitors lower the blood pressure is by reducing the circulating level of angiotensin II, thereby removing the direct vasoconstriction induced by this peptide. At the same time, the activity of ACE within vessel walls and multiple tissues, including brain and heart, is inhibited to apparently variable degrees by different ACE inhibitors. However the role of tissue renin-angiotensin system remains uncertain. Some of the effects of ACE inhibitors may be mediated via inhibition of the breakdown of bradykinin, with an additional contribution from kinin stimulation of nitric oxide production. ACE inhibitors also blunt the expected increase in sympathetic activity seen after vasodilation. As a result, heart rate and cardiac output do not increase. Additionally, ACE inhibitors improve endothelial dysfunction and suppress endogenous endothelin secretion.

As a consequence of these multiple effects, ACE inhibition results in a damping of arterial wave reflection and increased aortic distensibility. These haemodynamic

improvements contribute to the reversal of hypertrophy both in the heart and in the vasculature, and may be quantitatively greater than with other antihypertensive agents [111].

ACE inhibitors are now included among drugs recommended for initial monotherapy of patients with a variety of comorbid conditions accompanying hypertension. Three places have been recognized where these agents promote special benefits beyond those produced by other agents: relief of heart failure; prevention of ventricular remodelling after myocardial infarction; and slowing glomerulosclerosis in diabetic, and other, nephropathies. Consequently, ACE inhibitors are recommended for initial therapy in hypertensives with such compelling indications. Evidence from a recent large trial has also led to the recommendation of ACE inhibitors for all patients at high risk for coronary heart disease, whether hypertensive or not [112].

Regardless of how ACE inhibitors lower the blood pressure, they do so in a manner that tends to protect the function of two organs: the heart and the kidneys. Renal protection may not be provided, however, for patients with the DD-ACE genotype that is associated with higher plasma ACE levels [113].

A dry, hacking, non-productive and sometimes intractable cough is the most frequent side-effect of ACE inhibitor therapy. Bronchospasm may be the second most frequent. A genetic polymorphism of bradykinin B2 receptor has been found in a high proportion of patients who have ACE inhibitor-related cough. Although the cough can be effectively treated with inhaled sodium cromoglycate and aspirin, the easiest way is to replace ACE inhibitors ARBs [114].

Angiotensin II receptor blockers

ARBs displace angiotensin II from its specific AT1 receptor, antagonizing all its effects and resulting in a fall in peripheral vascular resistance with little change in heart rate and cardiac output. No obvious good or bad effects of increased levels of angiotensin II have been noted [115].

The major difference between ARBs and ACE inhibitors is the absence of an increase in kinin levels. This increase may be responsible for some of the beneficial effects of ACE inhibitors and more probably is responsible for their side-effects, particularly cough. However, angioedema and ageusia have also been reported with ARBs.

All currently available ARBs have comparable antihypertensive efficacy and all are potentiated by the addition of a diuretic or ACE inhibitor (if both ARBs and ACE inhibitors are given in submaximal doses).

All current guidelines recommend ARBs only for those who should receive an ACE inhibitor but are intolerant to it, usually from cough. ARBs are effective in the presence of renal insufficiency and reduce the progression of renal damage in type 2 diabetes.

Significant regression of LVH has been seen, but the preliminary results indicating lower mortality with ARBs compared with ACE inhibitors were not confirmed when the same trial was expanded [116].

A comprehensive overview of the properties and effects of antihypertensive drugs is given in Tables 7 and 8.

Drugs under investigation [4]

A wide range of antihypertensive agents are still under investigation. The results of ongoing trials will determine which agents will become available for clinical use. They belong to the following categories:

- renin inhibitors
- vasopeptidase inhibitors
- dopamine-2 receptor agonist
- potassium channel openers
- endothelin receptor antagonists
- transcription modulating drugs
- antisense gene therapy.

Most drugs will be available in rate-controlled forms so that a single capsule or a patch may provide smooth control of blood pressure over many years.

General strategies for antihypertensive treatment

Choice of first drug

In selecting specific drug therapy, the initial choice is perhaps the most important decision made in the treatment process. The drug is likely to be effective in about half the patients and if no significant side-effects occur can be taken for many years.

Thiazide-type diuretics have become the basis of antihypertensive therapy in most outcome trials. They should be used as initial therapy, either alone or in combination with one of other classes, in most patients with hypertension [7]. Previously, β-blockers were recommended for initial therapy, but the failure to find primary protection against coronary artery disease weakened the argument for their use. In patients with compelling conditions that require specific classes of antihypertensive agents of proven efficacy in clinical trials, the appropriate agent is selected as initial therapy.

If the first choice does not lower blood pressure much or is associated with persistent side-effects, the drug should be stopped and one from another class should be tried. If the first drug did all that it can and still was not enough, addition of a second or (if needed) a third drug in a stepwise manner is logical. Patients with milder forms of hypertension will often need only one drug but in those with more severe hypertension drug combinations are often required [4].

Table 7. Preparations, mechanism of action and main features of antihypertensive drugs [4,5,7]

Drug	Dose mg/day	Doses /day	Mechanism of action	Special considerations
Diuretics				
Thiazides and related drugs			They initially lower BP by reducing plasma extracellular fluid volume and cardiac output. Within 6–8 weeks, these parameters return toward normal and the lower BP is related to fall in peripheral resistance	• Thiazides are more effective antihypertensives than loop diuretics, unless serum creatinine is ≥2.0 mg/ml or creatinine clearance ≤50 ml/min
• hydrochlorothiazide	12.5–25	1		• Without concomitant diuretics, antihypertensive drugs which do not block the RAA mechanism may cause sodium retention
• chlorothalidone	12.5–50	1		
• indapamide	2.5	1		• Weak diuretics may cause hyperkalaemia particularly when combined with ACE inhibitors, K-supplements or NSAIDS
Loop diuretics				
• furosemide	20–320	2		
• furosemide	20–320	2		
• bumetanide	0.5–5	2		
• ethacrynic acid	25–100	2		
• torsemide	5–20	1		
K-sparing diuretics				
• spironolactone	25–100	2–3		
• triamterene	50–100	2		
Fixed-dose combination				
• hydrochlorothiazide/ amiloride				
• hydprochlorothiazide/ triamterene				
Adrenergic inhibitors				
Acting within neurons				• Frequently cause orthostatic hypotension and sexual dysfunction
• reserpine	0.05–0.25	1	Depletes postganglionic adrenergic neurons of NE by inhibiting its reuptake in storage vesicles	
• guenfacine	0.5–2.0	1	Inhibits release of NE from adrenergic neurones	
Central α-agonists				• May cause inflammatory disorders in various organs commonly the liver.
• methyldopa	250–1500	2	α-methyl NE, derived from methyldopa stimulates central α-adrenergic receptors reducing sympathetic outflow	• Haemolytic anaemia rarely occurs
• clonidine	0.1–0.6	2	Same mechanism of action as methyldopa but also inhibits NE release from presynaptic α-neurones	• Central α-agonists have short half-life, so when discontinued, the inhibition of NE release disappears and rebound hypertension occurs
• clonidine TTS	0.1–0.3	once/ week		
α-adrenergic receptor antagonists			Selective antagonists of postsynaptic α-1 receptors Because presynaptic α- adrenergic receptors is left unblocked, the feedback inhibition of NE release is intact	• Inhibition of NE release may lead to first-dose hypotension
• prazocin	2–20	1–2		• Useful for prostatic hypertrophy
• doxazocin	2–16	1		• In older patients, doxazocin may increase the risks of stroke and heart failure
• terazocin	1–20	1		

Table 7. Preparations, mechanism of action and main features of antihypertensive drugs [4,5,7] (continued)

Drug	Dose mg/day /day	Doses /day	Mechanism of action	Special considerations
β-adrenergic receptor antagonists			They cause decrease in cardiac output, renin release and sympathetic discharge. Initially, vasoconstriction develops by overtime, vascular resistance is normalized	• The three most important differences in clinical use are cardioselectivity, ISA and lipid solubility
Cardioselective				• Cardioselectivity disappears when higher doses are given
• atenolol	25–100	1		• Cardioselectivity results in less metabolic side effects
• metoprolol	50–200	1–2		• ISA causes less decrease in heart rate, renin release and cardiac output and less metabolic side effects
Non-cardioselective				• Less lipid soluble agents do not enter the brain readily and thus cause less nervous side-effects
• propranolol	40–240	1–2		
• nadolol	20–240	1		
With intrinsic sympathetic activity (ISA)				
• acebutolol	200–1200	2		
• pindolol	10–60	2		
α-/β-blockers			Fall in BP results mainly from a decrease in peripheral resistance. α-/β blockade is 10:1 for labetalol and 4:1 for carvedilol	• β-blockers are well suited for younger and middle-aged hypertensives particularly in patients with myocardial ischaemia and high levels of stress. They may interfere with athletic performance.
• labetalol	200–800	2–3		
• carvedilol	3.75–25	2		
Direct vasodilators			Direct relaxation of smooth muscle cells	• Limited efficacy if given alone due to fluid retention and reflex sympathetic activation, so they should be
• hydralazine	50–200	2–4		with a diuretic and β-blocker
combined				• Hydralazine may cause lupus-like syndrome if dose >200 mg/day and in slow acetylators of the drug
• minoxidil	2.5–80	1		
Calcium antagonists			Block entry of calcium into smooth muscle cells Deltiazem and verapamil blunt increases in exercise heart rate	• May cause initial natriuresis, resulting in vasodilatation
Nondihydropyridines				• Effect is not blunted by NSAIDs
• verapamil	80–480	2–3		• Short acting agents may increase the risk of ischaemic heart disease
• verapamil SR	120–480	1–2		
• verapamil-covera HS	180–240	1 (bed-time)		
• diltiazem	90–360	3–4		
• diltiazem CD	180–360	1		
Dihydropyridines				• Liquid nifedipine reduces BP quickly but may precipitate cerebral and myocardial ischaemia
• nifedipine	30–120	3		
• nifedipine GTS	30–120	1		
• amlodipine	2.5–10	1		
• felodipine	5–20	1		
• isradipine	2.5–10	2		

Table 7. Preparations, mechanism of action and main features of antihypertensive drugs [4,5,7] (concluded)

Drug	Dose mg/day	Doses /day	Mechanism of action	Special considerations
ACE inhibitors			Block conversion of angiotensin I to angiotensin II, thus removing the effects of the latter as a vasoconstrictor and as a stimulant of aldosterone synthesis. They also inhibit break-down of bradykinin, increase levels of vasodilatory prostaglandins, decrease levels of endothelins, and inhibit RAA system within the heart and other tissues	• First dose may precipitate dramatic fall in BP but full effect may not appear for 7–10 days • Effect is potentiated by diuretics • May cause hyperkalaemia in patients with renal failure, hypoaldosteronism and those receiving K-sparing diuretics or NSAIDS. • May cause acute renal failure in patients with bilateral renal artery stenosis, renal artery stenosis of a solitary kidney, creatinine >3 mg/dl or severe heart failure • Particularly effective in patients with diabetic vasculopathy, heart failure or systolic dysfunction after myocardial infarction
• captopril	12.5–100	2–3		
• enalapril	2.5–40	1–2		
• fusinopril	10–40	1		
• lisinopril	5–40	1		
• perindopril	1–16	1–2		
• ramipril	1.25–20	1		
• trandolapril	1–4	1		
Angiotensin II receptor blockers			Block the angiotensin-II receptors	Recommended only if ACE inhibitors cannot be tolerated because of cough or angioedema
• losartan	25–100	1–2		
• valsartan	80–320	1		
• candesartan	8–32	1		
• irbesartan	150–300	1		

RAA: renin angiotensin aldosterone
NSAIDs: non-steroidal anti-inflammatory agents
NE: norephinephrine
ISA: intrinsic sympathomimetic activity
ACE: angiotensin-converting enzyme

Table 8. Main side-effects of antihypertensive drugs [4]

Drug	Main side-effects
Diuretics	
Thiazides and related drugs	Hypokalaemia, hypomagnesaemia, hyperuricaemia, hyperlipidaemia, hypercalcaemia, hyperglycaemia and insulin resistance, impotence
Loop diuretics	As thiazides, but hypocalcaemia and ototoxcity may occur
K-sparing diuretics	Hyperkalaemia
Adrenergic inhibitors	
Acting within neurons	
• reserpine	Nasal congestion, lethargy, sexual dysfunction, depression
• guanethidine	Postural hypotension
Central α-agonists	
• methyldopa	Sedation, dry mouth, impotence, galactorrhea, positive ANA test, haemolytic anaemia, inflammatory disorders in various organs (commonly the liver)
• clonidine	As methyldopa but no immune or inflammatory side effects, withdrawal syndrome (hypertension, tachycardia, sweating, restlessness)
α-adrenergic receptor antagonists	First-dose hypotension, dizziness, weakness, fatigue, headache, sedation, dry mouth, impotence
β-adrenergic receptor	Bradycardia, fatigue, insomnia, bizarre dreams, antagonists depression, sexual dysfunction, hypertriglyceridoemia, decreased HDL, aggravation of bronchospasm, peripheral vascular disease and heart failure
α-/β-blockers	Nausea, fatigue, postural hypotension, headache, hepatotoxicity
Direct vasodilators	
hydralazine	Tachycardia, flushing, headache, angina, lupus-like syndrome
minoxidil	Hirsutism, pericardial effusion, ascites
Calcium antagonists	
deltiazem	First-degree AV block, bradycardia, worsening of systolic function
verapamil	Constipation, 1st-degree AV block, bradycardia
dihydropyridines	Ankle oedema, flushing, tachycardia, gingival hypertrophy
ACE inhibitors	Cough, taste disturbances, rash, hyperkalaemia, angioedema, proteinuria, leukopenia
ARBs	Hyperkalaemia, renal dysfunction, angioedema (rare)

ACE: angiotensin-converting enzyme   ARB: angiotensin-II receptor blockers
ANA: antinuclear antibody   HDL: high lipid density
AV: atrioventricular

When blood pressure is >20/10 mmHg above the goal, consideration should be given to initiate therapy with two drugs either as separate prescriptions or in fixed combinations. The initiation of drug therapy with more than one drug may increase the likelihood of achieving blood pressure goal in a more timely fashion, but particular caution is advised in patients at risk for orthostatic hypotension such as those with diabetes, autonomic dysfunction and some older persons.

Choice of subsequent drugs

The key in the addition of second, third or more drugs is to combine agents with different mechanisms of action. Combination of low doses of two or more agents from different classes has been shown to provide additional antihypertensive efficacy and to minimize the likelihood of dose-dependent side-effects. A low dose of diuretics can potentiate the effect of antihypertensive agents without producing adverse metabolic effects. Low-dose combination of an ACE inhibitor and non-dihydropyridine may reduce proteinuria more than either drug alone. In diabetics with nephropathy, a combination of an ACE inhibitor and CCB is better than either alone [5,7].

Start low and go slow [3,4,5]

Attempting to control hypertension rapidly and completely often leads to undue fatigue, weakness and postural dizziness due to the development of cerebral ischaemia. To allow for autoregulation of blood flow to maintain perfusion to vital organs when pressure is lowered, the decline in pressure should be relatively small and gradual. More precipitous reductions in pressure, as frequently occur with larger starting doses, may induce considerable hypoperfusion that results in symptoms that are at least bothersome (fatigue, impotence) and may be potentially hazardous (postural hypotension, coronary ischaemia).

Once daily dosing [3,4,5]

Single daily dosing should be feasible with virtually all patients. This improves adherence to therapy and avoids potentially inducing too great a peak effect and inadequate trough effect at the end of the dosing interval. Medications should be taken as early in the morning as possible, at 04:00 or 05:00 if the patient awakens at that time, to blunt the abrupt rise in blood pressure that occurs on awakening in the morning. If short-acting medications are taken at bedtime to ensure coverage in the early morning, ischaemia to vital organs might be induced by the combination of the maximal effect of the drug within 3–6 hours after intake and the usual nocturnal decline in blood pressure.

A chronobiological approach to antihypertensive therapy has become available. These drug-delivery systems release active drug for 18–20 hours beginning between 02:00 and 04:00, leaving the patient with no active drug in the circulation from about 22:00 to 02:00. This avoids exaggerating the nocturnal fall in blood pressure and provides adequate active drug as the blood pressure rises on awakening and during the peak time of cardiovascular events (06:00 to 12.00).

Cost as a factor [7,117]

The cost of the medications may pose an obstacle to controlling hypertension. The cost per tablet varies considerably among various antihypertensive agents. However, the cost of the tablet may not be the major cost of prescribing the medications. Hypokalaemia from diuretics and hyperlipidaemia induced by β-blockers must be corrected and this adds considerably to the cost of prescribing these drugs. Prescription of the least expensive agent should not be discounted, particularly as inexpensive agents have been tested and shown to reduce mortality as well as more expensive agents.

Reduction and discontinuation of therapy [118,119]

Once antihypertensive drug therapy is initiated, most patients should return for follow-up and adjustment of medications, at approximately monthly intervals, until blood pressure goal is reached. More frequent visits will be necessary for patients with stage 2 hypertension or with complicating comorbid conditions. Serum potassium and creatinine should be monitored at least 1–2 times per year. After blood pressure is at goal and is stable, follow-up visits can usually be at 3–6 month intervals. Comorbidities such as heart failure, associated diseases such as diabetes, and the need for laboratory tests influence the frequency of visits.

Once a good response has occurred and has been maintained for a year or longer, medications may be reduced or discontinued. Features that make withdrawal more likely to succeed include: lower blood pressure levels before and after therapy; fewer and lower doses of medications needed for control; and the patient's willingness to follow lifestyle modifications. It is more sensible in well-controlled patients to first decrease the dose of the drug used and, if this succeeds, withdrawal may be attempted with continued surveillance of blood pressure.

Additional considerations in antihypertensive drug choices [5,7]

Antihypertensive drugs can have favourable or unfavourable effects on other comorbidities.

Potential favourable effects

- Thiazide diuretics are useful in slowing demineralization in osteoporosis.
- β-adrenergic blockers can be useful in the treatment of atrial tachyarrhythmias/ fibrillation, migraine, thyrotoxicosis, essential tremor, or perioperative hypertension.
- CCBs may be useful in Raynaud syndrome and certain arrhythmias.
- α-blockers may be useful in prostatitsm.

Potential unfavourable effects

- Thiazide diuretics should be used cautiously in patients who have gout or who have a history of significant hyponatraemia.

- β-adrenergic blockers should generally be avoided in individuals who have asthma, reactive airways disease, or second-or third-degree heart block.
- ACE inhibitors should not be used in individuals with a history of angioedema.
- Aldosterone antagonists and potassium-sparing diuretics can cause hyperkalaemia and should generally be avoided in patients who have serum potassium values >5.0 mEq/L while not taking medication.

Therapy considerations in special groups and circumstances

Pregnant women [43,120]

Women with stage 1 hypertension are low risk for cardiovascular complications during pregnancy and are candidates for lifestyle modification therapy only. However, aerobic exercise should be restricted to avoid inadequate placental blood flow and weight reduction should not be attempted even in obese pregnant women. Women with target organ damage or a prior requirement for multiple antihypertensive agents should continue on antihypertensive medications as needed to control blood pressure. In all cases, treatment should be reinstituted once blood pressure reaches 160 mmHg systolic or 100 mmHg diastolic. Aggressive treatment of severe chronic hypertension in the first trimester is critical as fetal loss rates of 50% and significant maternal mortality have been reported in these patients.

Treatment of pre-eclampsia includes hospitalization for bed rest, control of blood pressure, seizure prophylaxis in the presence of signs of impending eclampsia and timely delivery. Regardless of gestational age, delivery should be strongly considered when there are signs of fetal distress or intrauterine growth retardation or signs of maternal problems including severe hypertension, haemolysis, elevated liver enzymes, low platelet count, deteriorating renal function, visual disturbance, headache or epigastric pain.

Antihypertensive drug selection in pregnancy [121,122]

For treatment of chronic hypertension in pregnancy methyldopa is preferred as first-line therapy, based on reports of stable uteroplacental blood flow and fetal haemodynamics and absence of long-term adverse affects on development of children. However, labetalol is now increasingly preferred to methyldopa because of reduced side-effects. β-adrenergic blockers are generally safe but there are reports of intrauterine growth retardation with use of atenolol. Diuretics should not be used as first-line agents but otherwise are probably safe. ACE inhibitors and angiotensin II receptor antagonists are contraindicated in pregnancy because of repeated fetal renal effects and death.

In pre-eclampsia when delivery is imminent (in <48 hours) parenteral antihypertensive agents are practical and effective. Intravenous hydralazine is the first choice and labetalol

is a second-line agent. Rarely, sodium nitroprusside is needed for resistant cases with due attention to the development of fetal cyanide poisoning if drug infusion is needed for >4 hours.

Children and adolescents [45]

Secondary causes of hypertension should be carefully searched for in children and adolescents. Lifestyle modifications are strongly recommended, with pharmacological therapy instituted only for higher levels of blood pressure (above the 99th percentile) or if there is insufficient response to lifestyle modifications. Choices of antihypertensive drugs are similar in children and adults, but effective doses for children are often smaller and should be adjusted carefully. The use of anabolic steroids should, however, be strongly discouraged. Vigorous interventions should be considered for other coexisting modifiable risk factors (e.g. smoking).

The elderly [4,5,7,46,123,124]

Older patients (>60 years) with systolic/diastolic or isolated systolic hypertension benefit from antihypertensive treatment in terms of reduced cardiovascular morbidity and mortality. In subjects aged ≥ 80 years, fatal and non-fatal cardiovascular events but not total mortality are reduced by antihypertensive therapy. Use of specific drug classes is largely similar to that recommended in the general population. Combination therapy with two or more drugs is generally needed to achieve optimal blood pressure control, particularly as it is often difficult to lower systolic blood pressure to <140 mmHg. In routine practice if the systolic goal is achieved, the diastolic goal will almost always be reached as well. Blood pressure measurement should be performed in the erect posture to exclude patients with marked postural hypotension from treatment and to evaluate postural effect of treatment. Many elderly patients will have other risk factors, target organ damage and associated cardiovascular conditions to which the choice of first drug should be tailored.

Patients with diabetes mellitus [51,52,53,54,55]

Clinical trials have demonstrated benefit in the treatment of hypertension in both type 1 and type 2 diabetes. The majority of diabetics will require two or more drugs to achieve the target level of 130/80 mmHg or lower. Thiazide-type diuretics are beneficial, either alone or as a part of a combined regimen. Of potential concern is the tendency for thiazide-type diuretics to worsen hyperglycaemia, but this effect is minor and does not produce more cardiovascular events compared with the other drug classes. ACE inhibitors may be used alone for lowering blood pressure but are much more effective when combined with a thiazide-type diuretic or other antihypertensive drugs. Both ACE inhibitors and ARBs are recommended for use in type 2 diabetes with chronic renal disease because these agents delay the deterioration in GFR and the worsening

of albuminuria. β-adrenergic blockers (especially $β_1$-selective agents) are beneficial in diabetics as part of multidrug therapy but their value as monotherapy is less clear. A β-adrenergic blocker is indicated in diabetics with ischaemic heart disease but may be less effective in preventing stroke than an ARB. CCBs may be useful in diabetics, particularly as part of combination therapy to control blood pressure.

Overweight and obesity [125,126]

The prevalence of overweight (body mass index 25.0–29.9) and obesity (body mass index >30) is escalating in the Eastern Mediterranean Region. The emphasis for weight management should be on avoidance of excess total energy intake and a regular pattern of physical activity. Adoption of the well-studied low-sodium DASH eating plan promotes weight loss, reduces blood pressure in both hypertensive and prehypertensive individuals and reduces low-density lipoprotein (LDL) cholesterol. Weight loss ≥2.25 kg is associated with reduction in cardiovascular risk of about 40%. Increased physical activity when combined with a reduction in calories is essential to weight loss success. The recommendation is to engage in regular physical activity at least 30 minutes daily, most days of the week. The cardiovascular benefits of slow walking appear to be comparable to those of walking more quickly, suggesting that the most important predictor of benefit is the walking time not the speed.

Obstructive sleep apnoea [127,128]

In addition to weight loss, improvements in the quality of sleep in obstructive sleep apnoea patients can occur as a result of a variety of posturing measures during sleep, particularly sleeping on one's side. Treatment with continuous positive airway pressure can be useful in lowering blood pressure and may also improve myocardial ischaemia and failure. No specific class of antihypertensive drugs has yet been demonstrated to be superior for blood pressure lowering in these patients. The role of oral prosthesis and surgical approaches remain to be fully defined.

Renal transplantation [3]

Since hypertension correlates with deterioration in graft function, blood pressure should be lowered to ≤130/80 mmHg. No particular class of antihypertensives can be considered to be superior to any other, but combination drugs are necessary in almost all patients. Serum creatinine and potassium should be monitored for 1–2 weeks following initiation or escalation in therapy with ACE inhibitors or angiotensin-receptor blockers (ARBs). Increase in serum creatinine >1 mg/dL should raise the question of renal artery stenosis.

Perioperative hypertension

Preoperative assessment for elective surgery should include blood pressure measurement in the outpatient clinic. Uncontrolled hypertensive patients should undergo

further assessment and management. Controlled hypertensives should continue on their treatment even on the day of the surgery. Delaying surgery in some uncontrolled patients may be beneficial if there is evidence of target organ damage, secondary hypertension and sudden onset of hypertension.

Asymptomatic hypertension should not be corrected rapidly as cerebral infarction in the watershed areas and blindness may complicate a sudden rapid fall in blood pressure. In particular, sublingual nifedipine capsules should not be used for treatment of acute hypertension as they may cause a sudden unpredictable fall in blood pressure and the drug is not evenly absorbed from the buccal mucosa. The blood pressure reduction should be achieved gradually unless there is concomitant hypertensive emergency such as hypertensive encephalopathy or heart failure requiring rapid intervention. For elective surgery, effective blood pressure control can be achieved over several days to weeks of outpatient treatment. In urgent situations, rapidly acting parenteral agents such as sodium nitroprusside, nicardipine hydrochloride and labetalol can be utilized to attain effective control rapidly.

Preoperative medication with anxiolytics may be necessary to minimize the exaggerated blood pressure response to operative stress. During induction of anaesthesia, laryngoscopy and intubation, the circulatory response should be kept minimum. Adequate anaesthetic techniques to inhibit the transmission of afferent nociceptors in response to surgical stimuli or to suppress the systemic response to them are essential to minimize sympathetic tone. Acute venous dilatation during induction or surgery may cause profound hypotension particularly in hypertensive patients and this may lead to acute renal failure, myocardial ischaemia or stroke. This can be counteracted by transient head-tilt of the patient, adequate fluid replacement and methoxamine hydrochloride.

During the operation, acute rise of blood pressure >20% is considered as an emergency. Possible underlying causes such as inadequate anaesthesia, cross-clamping of major arteries or manipulation of large vessels may require prompt intervention including the use of antihypertensive medications. Intravenous infusion of sodium nitroprusside, nicardipine and labetalol can be effective. Nitroglycerin is often an agent of choice in patients with ischaemic heart disease. During certain surgical procedures, the blood pressure may have to be maintained within a specific range in order to avoid perioperative complications especially in cardiovascular surgery and neurosurgery.

Postoperatively, hypertension may occur with an incidence varying from 3% to 20% after neck surgery to 34% after myocardial revascularization. Pathogenically, it can be attributed to pain, bladder distension, hypoxoemia, hypercapnoea or sympathetic

stimulation. Additionally, oral antihypertensive medications may not be possible to administer. To avoid hypertension and tachycardia, adequate analgesia and correction of other important reversible causes are important prior to antihypertensive therapy. The later should be instituted if necessary to avoid complications such as myocardial infarction, stroke and bleeding. Periodic dosing with intravenous enalaprilate or transdermal clonidine hydrochloride may be useful.

In the management of perioperative hypertension, it is important to monitor renal function and, in situations where blood pressure fluctuates, to monitor for evidence of cardiac and cerebrovascular ischaemia.

Hypertension with left ventricular hypertrophy [7,16,129]

Regression of LVH occurs with aggressive blood pressure management including weight loss, sodium restriction and treatment with all classes of antihypertensive agents except the direct vasodilators, hydralazine and minoxidil. The most consistent reduction in LV mass is achieved with ACE inhibitors, the least reduction occurs with β-adrenergic blockers and intermediate benefits occur with diuretics and CCBs.

Hypertension with peripheral arterial disease [130,131]

Any class of antihypertensive drug can be used in most patients with peripheral arterial disease. If Raynaud syndrome is present, CCBs can be used. β-adrenergic blockers have very little effect on walking distance or calf blood flow in patients with intermittent claudication. Thus, β-adrenergic blockers can be used in patients with peripheral arterial disease especially if needed for treatment of ischaemic heart disease or heart failure [7]. Other risk factors should be managed aggressively and aspirin should be used.

Hypertension with dyslipidaemia [59,132,133]

In large doses, thiazide diuretics and related compounds such as chlorthalidone raise total cholesterol and LDL by at least 5%–10% transiently and triglycerides by 15%–30%. They may lower HDL by 2%–4%. With the doses currently recommended (up to 25 mg/day of hydrochlorothiazide) there are little, if any, alterations in these parameters. β-blockers that do not have intrinsic sympathomimetic activity lower HDL by 10% and raise triglycerides by 20%. β-blockers with intrinsic sympathomimetic activity, α-/β-blocker, ACE inhibitors, calcium antagonists and ARBs are lipid-neutral. Direct vasodilators raise HDL and lower triglycerides and peripheral α-blockers reduce total cholesterol and LDL by 8%–10%, triglycerides by 15% and HDL by 10%–15%.

Erectile dysfunction and hypertension [134,135]

Whereas hypertension per se may be associated with erectile dysfunction, the use of various antihypertensive medications may increase the incidence in part because blood pressure lowering may cause reduction of penile blood flow. One study revealed,

however, no difference in incidence of sexual dysfunction between CCBs, ACE inhibitors, hydrochlorothiazide or β-adrenergic blockers when compared with placebo. Because of the low risk of erectile dysfunction among men who are physically active, not obese and who are non-smokers, lifestyle modification should be encouraged to forestall its occurrence. If erectile dysfunction appears after institution of antihypertensive drug therapy, the offending agent should be discontinued and treatment restarted with another agent. Sildenafil or other phosphodiesterase-5 inhibitors may be prescribed without a significant likelihood of adverse reaction in those with concomitant antihypertensive therapy, so long as nitrates are avoided.

Orthostatic hypotension [136,137]

Orthostatic hypotension is present when there is a supine-to-standing blood pressure decrease >20 mmHg systolic or >10 mmHg diastolic. Normally, standing is accompanied by a small decrease in systolic blood pressure and a small increase in diastolic blood pressure when compared with supine values. The causes of orthostatic hypotension include severe volume depletion, baroreceptor dysfunction, autonomic insufficiency (e.g. in diabetes) and certain venodilator antihypertensive drugs especially α-blockers and α-/β-blockers. Diuretics and nitrates further aggravate orthostatic hypotension.

Orthostatic hypotension is a common barrier to intensive blood pressure control and there is a strong correlation between its severity and premature death, as well as increased numbers of falls and fractures. In presence of orthostatic hypotension, drug therapy should be adjusted by slow-dose titration, volume depletion should be avoided and appropriate warnings given to patients.

Resistant hypertension [4,138,139]

Resistant hypertension is defined as the failure to reach goal blood pressure in patients who are adhering to an adequate and appropriate triple-drug regimen that includes a diuretic, with all three drugs prescribed in near maximal doses. For older patients with isolated systolic hypertension, resistance is defined as failure of adequate triple-drug regimen to reduce systolic blood pressure to below 160 mmHg.

The various causes of resistance to therapy are shown in Box 5. The most common is volume overload, owing either to inadequate diuretic or to excessive dietary sodium intake. Larger doses or more potent diuretics often bring resistant hypertension under control. NSAIDs interfere with the action of virtually all antihypertensive drugs except calcium antagonists and possibly ARBs.

Resistance can usually be overcome by adequate doses of a diuretic, calcium antagonists and ACE inhibitors, with minoxidil reserved for those who still remain refractory.

Box 5. Causes of resistant hypertension

Improper blood pressure measurement

Volume overload and pseudotolerance
- Excess sodium intake
- Volume retention from kidney disease
- Inadequate diuretic therapy

Drug-induced or other cause
- Non-adherence
- Inadequate doses
- Inappropriate combinations
- Non-steroidal anti-inflammatory drugs; cyclooxygenase 2 inhibitors
- Cocaine, amphetamines, other illicit drugs
- Sympathomimetics (decongestants, anorectics)
- Oral contraceptives
- Adrenal steroids
- Cyclosporine and tacrolimus
- Erythropoitetin
- Liquorice (including some chewing tobacco)
- Selected over-the-counter dietary supplements and medicines (e.g. ephedra, ma haung, bitter orange)

Associated conditions
- obesity
- excessive alcohol intake

Identifiable causes of hypertension

Therapy for hypertensive crises

Hypertensive emergencies [40,41]

- Patients presenting with a hypertensive emergency should be started promptly on effective parentral therapy, often sodium nitroprusside 0.5 µg/kg per minute, in an intensive care unit. Blood pressure should be reduced about 25% gradually over 2–3 hours. Oral antihypertensive therapy (often with an immediate-release calcium antagonist) can be instituted after 6–12 hours of parental therapy. Evaluation for secondary causes of hypertension may be considered after transfer from the intensive care unit.
- In a haemorrhagic stroke, hypertension probably should not be treated pharmacologically except when the mean arterial pressure is >130 mmHg. Even then it should be controlled slowly into an intermediate range (e.g. 160/100 mmHg). Previously hypertensive patients should be managed even less aggressively.

Table 9. Suggested therapy in various types of hypertensive crisis

Type of crisis	Drug of choice	BP target and other goals
Neurological		
Hypertensive encephalopathy	nitroprusside	25% reduction in mean BP over 2–3 hours
Intracranial haemorrhage or stroke in evolution	nitroprusside	0–25% reduction in BP over 6–12 hours
Subarachnoid haemorrhage	nimodipine	Up to 25% reduction in mean previously hypertensives. 130–160 mmHg SBP in normotensives
Cardiac		
Ischaemia/infarction	nitroglycerin or nicardipine	Reduction in ischaemia
Heart failure	nitroprusside or nitroglycerin	Improvement in failure
Aortic dissection	β-blocker + nitroprusside	120 mmHg SBP in 30 minutes
Renal		
Haematuria or acute renal impairment	fenoldopam	0–25% reduction in mean BP over 1–12 hours
Catecholamine excess states		
Phaeochromocytoma	phentolamine	To control symptoms
Drug withdrawal	drug reinstitution	Typically one dose is necessary
Pregnancy-related		
Eclampsia	magnesium sulfate, methyldopa, hydralazine	Typically <90 mmHg but often lower

BP: blood pressure   SBP: systolic blood pressure

- In acute subarachnoid haemorrhage, hypertension should also be only treated when the mean arterial pressure exceeds 120 mmHg. A short-acting intravenous drug (e.g. nitroprusside) is typically recommended since it can be discontinued quickly and the patients can be given fluids to restore the previous blood pressure level if the neurological status worsens. Alternatively, nimodipine may be the drug of choice for most neurological crises because of its antihypertensive and anti-ischaemic effects.
- Hypertensive crises involving cardiac ischaemia/infarction or pulmonary oedema are managed with either nitroglycerin or nitroprusside, although typically a combination of drugs (including an ACE inhibitor where there is heart failure) is used in these settings. Efforts to preserve myocardium and open the obstructed coronary artery (by thrombolysis, angioplasty or surgery) are also indicated.
- Patients with aortic dissection are managed by a β-blocker added to the intravenous vasodilator and the goal systolic blood pressure is typically 100–120 mmHg.

Table 10. Parenteral drugs used for treatment of hypertensive emergency

Drug	Dosage	Onset of action	Adverse effects
Vasodilators			
nitroprusside	0.25–10 µg/kg per min IV infusion	Instantaneous	Nausea, vomiting, twitching, thiocyanate toxicity
nitroglycerin	5–100 µg/min IV infusion	2–5 min	Tachycardia, flushing, headache, methaemoglobinoemia
nicardipine	5–15 mg/h IV	5–10 min	Tachycardia, headache, flushing, local phlebitis
hydralazine	10–20 mg IV or 10–50 mg IM	10–20 min 20–30 min	Tachycardia, flushing, headache, aggravation of angina
enalapril	1.25–5 mg every 6 hours	15 min	Abrupt fall in BP in high renin states. Variable response
fenoldopam	0.1–0.3 µg/kg per min	<5 min	Tachycardia, headache, flushing
Adrenergic inhibitors			
phentolamine	5–15 mg IV	1–2 min	Tachycardia, flushing
esmolol	500 µg/kg per min for 4 min then 150–300 µg/kg per min IV infusion	1–2 min	Hypotension
labetalol	20–80 mg IV bolus every 10 min, then 2 mg/min IV infusion	5–10 min	Vomiting, scalp tingling, burning throat, postural hypotension

BP: blood pressure   IV: intravenous

- Hypertensive crises involving the kidney are best managed with fenoldopam, which is preferred to nicardipine or nitroprusside because of its specific renal vasodilating effect and lack of toxic metabolites. Blood pressure should be reduced by about 10% during the first hour and a further 10%–15% during the next 1–3 hours. The need for acute dialysis is often precipitated by blood pressure reduction.

- Hypertensive crises resulting from catecholamine excess states (phaeochromocytoma, monoamine oxidase inhibitors, cocaine, etc.) are best managed with an intravenous α-blocker (phentolamine) with the β-blocker added later if necessary. Many patients with severe hypertension caused by sudden withdrawal of antihypertensive agents (e.g. clonidine) are easily managed by reinstituting such therapy.

- Hypertensive crises during pregnancy are managed with magnesium sulfate, methyldopa and hydralazine. Oral labetalol and nifedipine are second-choice drugs.

Tables 9 and 10 give an overview of therapies that can be used in the event of a hypertensive crisis or emergency.

Hypertensive urgencies [4,5,7,140]

These conditions require less aggressive management and nearly always with combinations of oral antihypertensive agents without admission to the hospital. Furosemide, propranolol, captopril, labetalol and several other short-acting antihypertensive drugs have been used for this problem. Liquid nifedipine administered orally or sublingually has been reported to cause precipitous hypotension, stroke, myocardial infarction and death, and so should be avoided. The most important aspect of managing a hypertensive urgency is to assure compliance with antihypertensive therapy during long-term follow-up. These patients should be carefully evaluated and monitored for hypertension-induced heart and kidney damage and for secondary causes of hypertension.

Problems with adherence to management [7,141,142]

Adherence/compliance with hypertension management is a major obstacle to achieving adequate control of high blood pressure in the population. Each step in management is associated with significant numbers of patients being lost from medical care.

Patients have great difficulty adhering to lifestyle modifications prescribed for hypertension. The measures recommended are often very difficult for the patient and their family to accept. Dietary and activity habits most often undergo dramatic changes. These changes require the development of new skills such as reading food labels, knowledge of healthy cooking methods, time management and making appropriate food choices outside the home.

Several factors affect the persistence with pharmacological therapy including the choice of the initial antihypertensive agent, the discomfort of side-effects and poor tolerability of an agent, as well as the number of times a patient has their drug regimen changed.

Strategies to improve adherence and therefore blood pressure control must involve the patient, the provider and the health care system. They should include the following interventions:

- patient education about hypertension and the importance of treatment;
- description of the potential complications of uncontrolled hypertension;
- scheduling a follow-up appointment during the office visit and reconfirmation by telephone;
- presenting the drug regimen least likely to result in adverse effects;
- choosing the least costly regimen likely to be effective;
- prescribing once-a-day regimen, if feasible;
- simplifying drug regimen by using a fixed-dose-combination product;
- tracking attendance;

- setting a blood pressure goal for the patient;
- providing feedback about progress toward the goal;
- having patients monitor their blood pressure at home;
- enquiring about difficulties with the prescribed regimen;
- discussing new treatment strategies with the patient and involving them in the decision process.

All health care providers including nurses, nutritionists, educators and psychologists are needed to improve patient adherence to lifestyle interventions as well as to treatment recommendations. Patients also need motivation, support and follow-up as they attempt to learn new skills and change their daily habits. The resources to make all these changes possible require commitment by health care organizations and systems, as well as by patients and providers.

Prevention of hypertension

General prevention [7,43]

In the Eastern Mediterranean Region, the prevalence of hypertension in adults is estimated at approximately one in four, or 125 million persons. Each year, there are several million new cases of hypertension and more of prehypertension [2]. International guidelines, such as those of the WHO Expert Committee on Hypertension Control [142] and the National High Blood Pressure Education Program [39], have stressed the importance of primary prevention of hypertension. The goal of such an intervention would include preventing the blood pressure rise observed with ageing, lowering overall blood pressure levels in the population and addressing other modifiable risk factors in an effort to decrease cardiovascular morbidity and mortality. A population-based programme to slightly lower overall blood pressure levels and prevent the rise of blood pressure associated with ageing would have an effect on cardiovascular disease equal to or greater than that of treating patients with established hypertension.

Epidemiological and clinical studies uniformly indicate that obesity, sedentary lifestyle and intake of salt and alcohol are all associated with increased risk of developing hypertension. In order to decrease the incidence of hypertension in the general population the following lifestyle modifications are necessary:

- weight control
- increased physical activity
- limiting dietary sodium to ≤2.4 per day (equivalent to 6 g of sodium chloride)
- abstention from alcohol
- increased dietary potassium.

Adopting the DASH eating plan, which is a diet rich in fruits, vegetables and low-fat dairy products and low in saturated and total fat and cholesterol, is more important than just altering individual micronutrients such as sodium [77,78,79].

Prehypertensives are at higher risk of developing hypertension and cardiovascular disease than those with normal blood pressure and are therefore excellent targets for primary prevention. Individuals with a family history of hypertension and those with a predisposition to develop obesity or diabetes are also excellent candidates for programmes to reduce weight, salt intake, alcohol use and improve dietary habits while increasing exercise. These recommendations help promote health in all persons but are especially important in those with other risk factors for hypertension-associated conditions, such as coronary artery disease.

Studies concerning awareness, treatment and control of high blood pressure as well as the continued prevalence of hypertension suggest that primary prevention is not being effectively practised. Barriers to prevention include:

- cultural norms;
- insufficient attention to health education by health care practitioners;
- lack of reimbursement for health education services;
- lack of access to places to engage in physical activity;
- larger servings of food in restaurants;
- lack of availability of healthy food choices in many schools, worksites and restaurants;
- lack of exercise programmes in schools;
- large amounts of sodium added to foods by the food industry and restaurants;
- the higher cost of food products that are low in sodium and calories.

Overcoming the barriers will require a multipronged approach directed not only to high-risk populations but also to communities, schools, worksites and the food industry [39]. The recent recommendations that the food industry reduce sodium in the food supply by 50% over the next decade is the type of approach that, if implemented, would reduce high blood pressure in the population [3,144,145]. An equally important area of concern is the need for improvement in provider and patient communication. The lifestyle changes used to help prevent hypertension are very difficult for many people, especially those at highest risk who often must give up many long-term habits. Recommendations for dietary and activity changes by a provider have little chance of being followed if their importance and potential benefits are not communicated to the patient. Such communication is dependent on the provider's confidence in his/her ability to teach patients the necessary skills to follow recommendations and the amount of time available for preventive services. Health care organizations may help remedy this problem by providing training, personnel and support to address patient education and counselling.

Community approach to prevention of primary hypertension

Introduction

Integrated community-based intervention programmes are comprehensive packages in which different kinds of activities are combined to produce synergetic effect. The community approach to hypertension prevention has a high degree of generalization and cost-effectiveness [146,147], is able to diffuse information successfully, and has potential

for influencing environmental and institutional policies that have a bearing on health status of the population. Close collaboration between those implementing the community approach and national health authorities is important to sustain primary prevention and for influencing policy development in regard to health.

The objective of the Eastern Mediterranean Approach to Noncommunicable Diseases (EMAN) for primary hypertension prevention is to reduce the major risk factors for cardiovascular diseases and their social and economic determinants through community-based programmes aiming at integrated prevention and control and development of standards of care and cost-effective case management.

Role of primary prevention of hypertension in primary health care settings

A variety of lifestyle modifications have been shown to lower blood pressure and to reduce the prevalence of hypertension. These include reduction of dietary sodium intake, weight loss in people who are overweight, physical activity, increased dietary potassium intake and a diet with increased fresh fruit and vegetables and reduced saturated fat intake.

As part of the community approach to primary prevention of hypertension, primary health care professionals should measure blood pressure regularly in all persons above 40 years of age, even if they are normotensive, at least once every 2 years and advise patients with mild hypertension on lifestyle modifications, such as increasing physical exercise, and reducing salt and saturated fat intake. Hypertension, hyperlipidaemia, hyperglycaemia, obesity and smoking are interlinked risks for ill health. The risk of coronary heart disease multiplies with additional cardiovascular risk factors. Reducing salt intake from 12 g per day to 3 g per day reduces strokes by 33% and coronary heart disease by 25%.

Although antihypertensive drug therapy represents one of the major success stories in the prevention of cardiovascular disease, the pharmacological approach to management has limitations if used in isolation. Population studies, as well as randomized controlled trials, show that environmental factors are major determinants of hypertension. The most important of these factors are: excess body fat and obesity, a sedentary lifestyle, alcohol consumption, tobacco use and other dietary factors. Patients can achieve significant reductions in blood pressure by making appropriate changes to their lifestyle. Family doctors should be able to provide effective advice that complements any necessary therapy.

Cost–effectiveness of the community approach to primary prevention of hypertension

The cost of applying the community approach to primary prevention of hypertension includes the costs of any medicines prescribed, of screening tests, of follow-up, of treating side-effects, of ineffective treatment and of alleviating concomitant disorders. The cost–effectiveness of the approach lies in the application of standard and proven treatment policies based on the use of the most effective drugs, such as those recommended by WHO in its model list of essential medicines. The list comprises drugs with the least side-effects, simple regimens, generics from reliable sources and drugs with favourable effects on concomitant disorders. It includes recommended antihypertensive medicines (see Annex 2).

Other factors that contribute to cost–effectiveness include starting treatment early in the course of the disease, the low cost of approved essential medicines, post-marketing surveillance and using tender systems rather than direct purchase. False savings result from purchasing low quality drugs from companies that do not meet WHO standards of Good Manufacturing Practice.

Implementation of the community approach at national level

Countries of the Eastern Mediterranean Region need to prioritize hypertension on the national agenda by stressing that it is a serious, prevalent and costly national public health problem. Its true epidemiological and economic burden should be determined in every country. Countries need to design national strategies to confront hypertension as part of an integrated approach to prevention and care of noncommunicable diseases. This will address hypertension jointly with other major related and preventable risk factors. At the same time it is necessary to support health care systems to develop: cost-effective services for primary prevention and control of hypertension in primary health care settings; public education to increase community awareness about hypertension; and a strategy to integrate nutrition, physical activity and cessation of smoking into the community approach to primary prevention and care of hypertension.

References

Key to references

CT: controlled trial
GL: guideline/experts' opinion
MA: meta-analysis
OS: observational study
RT: randomized trial
RV: review
X: cross sectional survey
C: clinical intervention (non-randomized)

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Annex 1
Regional consultation on hypertension prevention and control
Abu Dhabi, United Arab Emirates, 20–22 December 2003

The following recommendations were made at the Regional Consultation on Hypertension Prevention and Control, Abu Dhabi, United Arab Emirates, 20–22 December 2003 [2].

Member States

1. Prioritize hypertension on the national agenda by stressing that it is a serious, prevalent and costly national public health problem whose true epidemiological and economic burden should be determined in every country.

2. Design national strategies to confront hypertension as part of an integrated approach to noncommunicable diseases prevention and care. This will address hypertension jointly with other major related and preventable risk factors.

3. Support health care systems to provide and develop the following:
   - cost-effective services for primary prevention and control of hypertension in primary health care;
   - public education to increase community awareness about hypertension;
   - actions for putting nutrition and physical activity along with smoking cessations as priority programmes for hypertension prevention and care.

4. Enhance health care systems to develop health services for chronic noncommunicable disease conditions. This will require evolution of health care from an acute model towards a coordinated, comprehensive system of care.

5. Increase training to deliver patient education at primary health care level through collaboration with the Regional Office for the Eastern Mediterranean and university hospital-based services.

Regional Office

6. Continue monitoring patient education activities in Member States and facilitate networking between countries.

7. Establish regional training courses for noncommunicable disease educators and in particular for cardiovascular disease educators.

8. Establish regional guidelines for nutrition, obesity and other healthy lifestyle measures.

9. Establish regional guidelines on hypertension prevention and care within the following framework:

    •   adapted from internationally approved guidelines for the requirements and specifics of the Region;

    •   simple, flexible, updateable, recognizing the priority of using inexpensive, but at the same time cost-effective drugs, and acknowledging the role of compelling indications and the pharmacokinetic principles that govern drug addition and substitution;

    •   based on a population approach and can be easily taught to the general practitioner, nurses and pharmacists after a reasonable period of training

    •   implemented through national training activities, lecturing, seminar holding and by using them in poster systems, hand-held cards and medication inserts.

The guidelines should not replace the prudent judgment of the physician or the pivotal role of the physician in promoting motivation and adherence to therapy among patients.

The participants in the consultation were as follows.

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Annex 2

WHO list of essential antihypertension medicines[1]

□ atenolol	tablet, 50 mg, 100 mg
□ enalapril	tablet, 2.5 mg
hydralazine[a]	tablet 25 mg, 50 mg (hydrochloride)
	powder for injection, 20 mg (hydrochloride) in ampoule
□ hydrochlorothiazide	scored tablet, 25 mg
methyldopa[b]	tablet, 250 mg
□ nifedipine[c]	sustained-release formulations, tablet 10 mg

Complementary list medicine
sodium nitroprusside   powder for infusion, 50 mg in ampoule

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[a] Hydralazine is listed for use in the acute management of severe pregnancy-induced hypertension only. Its use in the treatment of essential hypertension is not recommended in view of the availability of more evidence of efficacy and safety of other medicines.

[b] Methyldopa is listed for use in management of pregnancy-induced hypertension only. Its use in the treatment of essential hypertension is not recommended in view of the availability of further evidence of the efficacy and safety of other medicines.

[c] The public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion in the Model List will be reviewed at the next meeting of the Expert Committee.

□ Recommended example within a pharmaceutical class.

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[1] The 13th WHO model list of essential medicines. In: *The selection and use of essential medicines. Report of the WHO Expert Committee, 2003*. Geneva, World Health Organization, 2004 (WHO Technical Report Series No. 920), pages 54-100.