

2003 European Society of Hypertension – European Society of Cardiology guidelines for the management of arterial hypertension*

Guidelines Committee**

Journal of Hypertension 2003, 21:1011–1053

Conflict of interest disclosures are given in the Appendix.

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Received 4 April 2003

Accepted 4 April 2003

Introduction and purpose

In preparing these guidelines the Committee established by the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) has aimed at offering the best available and most balanced information to all those involved in the management of arterial hypertension. The Committee is aware that it is easier to prepare guidelines on a medical condition in general than to deal with the individual patients with that condition requiring medical advice and intervention. Because of this awareness, the Committee has tried to avoid giving rigid rules that would constrain judgement on the management of individual patients differing in their personal, medical and cultural characteristics.

In the past, the European Society of Hypertension, together with the European Society of Cardiology, did not draw up specific guidelines on hypertension but chose to endorse guidelines prepared by the World Health Organization (WHO)/International Society of Hypertension (ISH) Liaison Committee [1,2], and to incorporate them, with some adaptation, into joint European recommendations for the prevention of coronary heart disease [3,4].

Since 1999, considerable new evidence on some of the important issues left open in the 1999 WHO/ISH guidelines has accumulated, requiring the present update of the guidelines. Moreover, the WHO/ISH guidelines are written for a global audience from countries that vary widely in the extent of their health care provision and the availability of resources. Europe is a much more homogeneous community, with populations enjoying greater longevity but suffering a higher incidence of chronic cardiovascular disease, often despite

well-developed health systems devoting high proportion of resources to disease prevention. With the preparation of these guidelines, the European Society of Hypertension and the European Society of Cardiology respond to the suggestion of the WHO/ISH guidelines that regional experts draw up recommendations specifically directed toward the management of patients in their own region [2]. Consequently these guidelines are also endorsed by the International Society of Hypertension.

These guidelines have been prepared on the basis of the best available evidence for all key recommendations, and with the principle that guidelines should be educational rather than merely prescriptive. The Committee members take the view that, although large randomized controlled trials and meta-analyses provide the strongest evidence about several aspects of therapy, scientific evidence is drawn from many sources, and where necessary all sources have been used. Therefore, the Committee has avoided rigid classification of its recommendations dependent upon the strength of available evidence. However, for readers preferring a more critical assessment of the evidence, these recommendations have been accompanied by relevant references, and those articles based on large randomized trials, meta-analyses or large observational studies have been clearly identified. Furthermore, for practitioners wishing to receive concise advice, these guidelines will be complemented by a brief set of Practice Recommendations.

The members of the Guidelines Committee, established by the ESH and ESC, have participated independently in the preparation of this document, drawing on their academic and clinical experience and utilizing an objective and critical examination of all available literature. Most have undertaken, and are undertaking, work in collaboration with industry and governmental

* Endorsed by the International Society of Hypertension

** Members of the Guidelines Committee and the Writing Committee are listed in the Appendix.

or private health providers (research studies, teaching conferences, consultation), but all believe such activities haven't influenced their judgement. The best guarantee of their independence is in the quality of their past and current scientific work. However, to ensure openness, their relations with industry, government and private health providers are listed in the Appendix at the end of these guidelines. Expenses for the Writing Committee and preparation of these guidelines were provided entirely by the European Society of Hypertension.

Box 1 Position statement: Purpose of guidelines

- The guidelines have been prepared by an Expert Committee appointed by the European Society of Hypertension and the European Society of Cardiology, and have been endorsed by the International Society of Hypertension.
- These have been prepared on the basis of the best available evidence on all issues deserving recommendations, and with the consideration that guidelines should have an educational purpose more than a prescriptive one.
- Although large randomized controlled trials and their meta-analyses provide the strongest evidence about several aspects of therapy, scientific evidence is drawn from many sources and, where necessary, all sources have been used.

Definition and classification of hypertension

Systolic, diastolic and pulse pressures as predictors

Historically more emphasis has been placed on diastolic than systolic blood pressure as a predictor of cerebrovascular and coronary heart disease. This was reflected in the design of the major randomized controlled trials of hypertension management which, almost universally, used diastolic blood pressure thresholds as inclusion criteria until the 1990s [5]. Subjects with isolated systolic hypertension were excluded by definition from such trials. Nevertheless, large compilations of observational data before [6] and since the 1990s [7] confirm that both systolic and diastolic blood pressures show a continuous graded independent relationship with risk of stroke and coronary events.

In the European context, the relationship between systolic blood pressure and relative risk of stroke is steeper than that for coronary events, which reflects the closer aetiological relationship with stroke. However, the attributable risk – that is excess deaths due to raised blood pressure – is greater for coronary events than for stroke, reflecting the higher incidence of heart disease in most of Europe. This notwithstanding, the

relative incidence of stroke is increasing in our ageing population, as shown in recent randomized controlled trials [8].

The apparently simple direct relationship between increasing systolic and diastolic blood pressures and cardiovascular risk is confounded by the fact that systolic blood pressure rises throughout the adult age range in European (as well as in many non-European) populations, whereas diastolic blood pressure peaks at about age 60 years in men and 70 years in women, and falls gradually thereafter [9]. These phenomena represent the results of some of the pathological processes that underlie 'hypertension' and cardiovascular diseases [10].

At least in elderly populations, these observations help to explain why a wide pulse pressure (systolic blood pressure minus diastolic blood pressure) has been shown in some observational studies to be a better predictor of adverse cardiovascular outcomes than either systolic or diastolic pressure individually, and to identify patients with systolic hypertension who are at specifically high risk. These studies [11–14] reported that for a given level of systolic blood pressure, diastolic blood pressure had an inverse association with cardiovascular risk. However, in the largest meta-analysis of observational data in almost 1 million patients from 61 studies (70% of which were in Europe) [7], both systolic and diastolic blood pressures were independently predictive of stroke and coronary mortality, and more so than pulse pressure. Even in this meta-analysis, however, the contribution of pulse pressure to cardiovascular risk increased after age 55 years.

In practice, given that we have randomized controlled trial data supporting the treatment of isolated systolic [15,16] and diastolic hypertension [5], we should continue to use both systolic blood pressure and diastolic blood pressure for guidance of treatment thresholds. For the purposes of classification and risk assessment (see Tables 1 and 2), while it could be argued that focusing on systolic blood pressure is sufficient, the use of both systolic and diastolic values to categorize blood pressure control levels, and thereby overall risk, remains a simple and pragmatic approach.

Classification of hypertension

The continuous relationship between the level of blood pressure and cardiovascular risk makes any numerical definition and classification of hypertension arbitrary. That offered by Rose [17] more than 30 years ago ('Hypertension should be defined in terms of a blood pressure level above which investigation and treatment do more good than harm') also indicates that any numerical definition must be a flexible one resulting

from evidence of risk and availability of effective and well-tolerated drugs.

In consequence, it would be appropriate to use a classification of blood pressure without the term 'hypertension'. However, this could be confusing and might detract attention from investigation of the mechanisms raising blood pressure and diminish the case for tight blood pressure control [18]. Therefore, the 1999 WHO/ISH classification [2] has been retained in Table 1, with the reservation that the real threshold for hypertension must be considered as flexible, being higher or lower based on the total cardiovascular risk profile of each individual. Accordingly, the definition of high normal blood pressure in Table 1 includes values that may be considered as 'high' (i.e. hypertension) in high-risk subjects, or acceptable in individuals at lower risk. As a result, the subgroup 'borderline' hypertension, present in the 1999 WHO/ISH guidelines [2], has not been retained.

Total cardiovascular risk

Historically, therapeutic intervention thresholds for the treatment of cardiovascular risk factors such as blood pressure, blood cholesterol and blood sugar have been based on variably arbitrary cutpoints of the individual risk factors. Because risk factors cluster in individuals [19,20] and there is a graded association between each risk factor and overall cardiovascular risk [21], the contemporary approach to treatment is to determine the threshold, at least for cholesterol and blood pressure reduction, based on the calculation of estimated coronary [3,4] or cardiovascular (coronary plus stroke) [22] risk over a defined, relatively short-term (e.g. 5- or 10-year) period.

Complex and computerized methods have been developed for estimating short-term risk. Most risk estimation systems are based on Framingham data [23]. Although this database has been shown to be reasonably applicable to some European populations [24], risk estimates require recalibration in other populations [25], due to important differences in the prevailing

incidence of coronary and stroke events. Estimates directly relevant to various European populations or patients specifically with hypertension are becoming increasingly available [26–32], and recently the SCORE project has provided tables that predict 10-year risk of fatal cardiovascular disease separately for higher-risk countries in northern Europe and lower-risk countries in southern Europe [33]. The main disadvantage associated with intervention thresholds based on relatively short-term absolute risk is that younger adults (particularly women) are unlikely to reach treatment thresholds despite being at high risk relative to their peers, though having more than one major risk factor. By contrast, most elderly men (e.g. >70 years) will often reach treatment thresholds while being at very little increased risk relative to their peers. The consequences are that most resources are concentrated on the oldest subjects, whose potential lifespan is relatively limited, despite intervention, while young subjects at high relative risk remain untreated, despite, in the absence of intervention, a greater predicted shortening of their otherwise much longer potential lifespan [34,35]. A simple approach to offset this lack of weighting for potential life years gained for the young at high relative risk, is to determine the threshold for intervention on the basis of estimated risk for the subject projected to the age of 60 [3,4]. Alternatively, intervention might be based on relative risk for subjects younger than 60 and on absolute risk level for older patients [26].

On this basis, a classification using stratification for total cardiovascular risk is suggested in Table 2. It is derived from the scheme included in the 1999 WHO/ISH guidelines [2], but extended to indicate the added risk in some group of subjects with 'normal' or 'high normal' blood pressure. The terms *low*, *moderate*, *high* and *very high added risk* are calibrated to indicate an approximate absolute 10-year risk of cardiovascular disease of <15%, 15–20%, 20–30% and >30%, respectively, according to Framingham criteria [23], or an approximate absolute risk of fatal cardiovascular disease <4%, 4–5%, 5–8%, and >8% according to the SCORE chart [33]. These categories can also be used as indicators of relative risks, thereby leaving doctors free to use one or the other approach without the constraint of arbitrary absolute thresholds based on a probable underestimation of treatment benefits [35,36]. The distinction between high and very high risk has been maintained, mostly in order to preserve a distinctive place for secondary prevention (patients with associated clinical conditions), although admittedly it does not influence management decisions significantly.

Table 3 indicates the most common risk factors, target organ damage, diabetes and associated clinical conditions which are used to stratify risk. This updates a

Table 1 Definitions and classification of blood pressure levels (mmHg)

Category	Systolic	Diastolic
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

When a patient's systolic and diastolic blood pressures fall into different categories, the higher category should apply. Isolated systolic hypertension can also be graded (grades 1, 2, 3) according to systolic blood pressure values in the ranges indicated, provided diastolic values are <90.

Table 2 Stratification of risk to quantify prognosis

Other risk factors and disease history	Blood pressure (mmHg)				
	Normal SBP 120–129 or DBP 80–84	High normal SBP 130–139 or DBP 85–89	Grade 1 SBP 140–159 or DBP 90–99	Grade 2 SBP 160–179 or DBP 100–109	Grade 3 SBP \geq 180 or DBP \geq 110
No other risk factors	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
1–2 risk factors	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
3 or more risk factors or TOD or diabetes	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
ACC	High added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk

ACC, associated clinical conditions; TOD, target organ damage; SBP, systolic blood pressure; DBP, diastolic blood pressure.

similar table in the 1999 WHO/ISH guidelines [2] in several major respects:

1. Obesity is defined as 'abdominal obesity', in order to give specific attention to an important sign of the metabolic syndrome [37].
2. Diabetes is listed as a separate criterion in order to underline its importance as a risk factor, at least twice as large as in absence of diabetes [33,38,39].
3. Microalbuminuria is categorized as a sign of target organ damage, but proteinuria as a sign of renal disease (associated clinical condition).
4. Slight elevation of serum creatinine concentration (107–133 $\mu\text{mol/l}$, 1.2–1.5 mg/dl) is taken as a sign of target organ damage, and concentrations $>133 \mu\text{mol/l}$ ($>1.5 \text{ mg/dl}$) as an associated clinical condition [39,40].
5. C-reactive protein has been added among risk factors (or markers) because of the mounting evidence that it is a predictor of cardiovascular events at least as strong as low-density lipoprotein (LDL)-cholesterol [41], and because of its association with the metabolic syndrome [42].
6. Generalized or focal narrowing of the retinal arteries is omitted from signs of target organ damage, since it is seen too frequently in subjects aged 50 years or older [43], but retinal haemorrhages, exudates and papilloedema are retained as associated clinical conditions.

The Committee is aware that the use of categorical tables rather than equations based on continuous variables may have limitations [44], and that cardiovascular risk evaluation is an inexact science [36]. Furthermore, the weight of target organ damage in determining calculation of overall risk will be heavily dependent on how carefully it is assessed [45]. This aspect will be discussed further in the section devoted to diagnosis.

Diagnostic evaluation

Diagnostic procedures are aimed at: (1) establishing blood pressure levels; (2) identifying secondary causes of hypertension; (3) evaluating the overall cardiovascular risk by searching for other risk factors, target organ damage and concomitant diseases or accompanying clinical conditions [46].

The diagnostic procedures comprise:

1. repeated blood pressure measurements;
2. medical history;
3. physical examination;
4. laboratory and instrumental investigations, some of which should be considered part of the routine approach in all subjects with high blood pressure, some which are recommended and may be used extensively (at least in the highly developed health systems of Europe), and some which are indicated only when suggested by some of the core examinations or the clinical course of the patient.

Blood pressure measurement

Blood pressure is characterized by large variations both within and between days [47]. Therefore, the diagnosis of hypertension should be based on multiple blood pressure measurements, taken on separate occasions. If blood pressure is only slightly elevated, repeated measurements should be obtained over several months, because there is often a regression to normal levels. If a patient has a more marked blood pressure elevation, evidence of hypertension-related organ damage or a high or very high cardiovascular risk profile, repeated measurements should be obtained over shorter periods of time, such as weeks or days. Blood pressure can be measured by the doctor or the nurse in the office or in the clinic (office or clinic blood pressure), by the patient at home, or automatically over a 24-h period. Blood pressure measurement procedures have been discussed extensively in a recent document of the

Table 3 Factors influencing prognosis

Risk factors for cardiovascular disease used for stratification	Target organ damage (TOD)	Diabetes mellitus	Associated clinical conditions (ACC)
<ul style="list-style-type: none"> • Levels of systolic and diastolic BP • Men > 55 years • Women > 65 years • Smoking • Dyslipidaemia (total cholesterol >6.5 mmol/l, >250 mg/dl* or LDL-cholesterol > 4.0 mmol/l, >155 mg/dl*, or HDL-cholesterol M < 1.0, W < 1.2 mmol/l, M < 40, W < 48 mg/dl) • Family history of premature cardiovascular disease (at age < 55 years M, < 65 years W) • Abdominal obesity (abdominal circumference M \geq 102 cm, W \geq 88 cm) • C-reactive protein \geq 1 mg/dl 	<ul style="list-style-type: none"> • Left ventricular hypertrophy (electrocardiogram: Sokolow-Lyons > 38 mm; Cornell > 2440 mm* ms; echocardiogram: LVMI M \geq 125, W \geq 110 g/m²) • Ultrasound evidence of arterial wall thickening (carotid IMT \geq 0.9 mm) or atherosclerotic plaque • Slight increase in serum creatinine (M 115–133, W 107–124 μmol/l; M 1.3–1.5, W 1.2–1.4 mg/dl) • Microalbuminuria (30–300 mg/24 h; albumin-creatinine ratio M \geq 22, W \geq 31 mg/g; M \geq 2.5, W \geq 3.5 mg/mmol) 	<ul style="list-style-type: none"> • Fasting plasma glucose 7.0 mmol/l (126 mg/dl) • Postprandial plasma glucose > 11.0 mmol/l (198 mg/dl) 	<ul style="list-style-type: none"> • Cerebrovascular disease: ischaemic stroke; cerebral haemorrhage; transient ischaemic attack • Heart disease: myocardial infarction; angina; coronary revascularization; congestive heart failure • Renal disease: diabetic nephropathy; renal impairment (serum creatinine M > 133, W > 124 μmol/l; M > 1.5, W > 1.4 mg/dl) • Proteinuria (>300 mg/24 h) • Peripheral vascular disease • Advanced retinopathy: haemorrhages or exudates, papilloedema

M, men; W, women; LDL, low-density lipoprotein; HDL, high-density lipoprotein; LVMI, left ventricular mass index; IMT, intima-media thickness. * Lower levels of total and LDL-cholesterol are known to delineate increased risk, but they were not used in the stratification

Working Group of the European Society of Hypertension [48]. These procedures can be summarized as follows.

Office or clinic blood pressure measurement

Blood pressure can be measured by a mercury sphygmomanometer with its various parts (rubber tubes, valves, quantity of mercury, etc.) kept in proper conditions. Other non-invasive devices (aneroid and auscultatory or oscillometric semiautomatic devices) can also be used and will, regrettably, become increasingly important because of the progressive restriction on mercury use in European countries. However, these devices should be validated according to standardized protocols [49] and their accuracy should be checked periodically by comparison with mercury sphygmomanometric values. Procedures for office blood pressure measurements are listed in Box 2.

Box 2 Procedures for blood pressure measurement

When measuring blood pressure, care should be taken to

- Allow the patients to sit for several minutes in a quiet room before beginning blood pressure measurements.
- Take at least two measurements spaced by 1–2 min, and additional measurements if the first two are quite different.
- Use a standard bladder (12–13 cm long and 35 cm wide) but have a larger and a smaller bladder available for fat and thin arms, respectively. Use the smaller bladder in children.
- Have the cuff at the heart level, whatever the position of the patient.
- Use phase I and V (disappearance) Korotkoff sounds to identify systolic and diastolic blood pressure, respectively.
- Measure blood pressure in both arms at first visit to detect possible differences due to peripheral vascular disease. In this instance, take the higher value as the reference one, when the auscultatory method is employed.
- Measure blood pressure 1 and 5 min after assumption of the standing position in elderly subjects, diabetic patients, and in other conditions in which orthostatic hypotension may be frequent or suspected.
- Measure heart rate by pulse palpation (30 s) after the second measurement in the sitting position.

Ambulatory blood pressure measurement

Several devices (mostly oscillometric) are available which permit the automatic monitoring of blood pres-

sure in patients allowed to conduct a near normal life. Such systems can provide information on blood pressure profiles over 24 h, as well as on average blood pressure values over 24 h or over more restricted periods, such as the day, the night and the morning [48]. This information should not be regarded as a substitute for information derived from conventional blood pressure measurements. However, it may be considered to provide additional clinical value, because cross-sectional and longitudinal studies have shown office blood pressure to have a limited relationship with 24-h pressure [50]. These studies have also shown that ambulatory blood pressure: (1) correlates with hypertensive target organ damage more closely than does office blood pressure [51–54]; (2) predicts, both in populations and in hypertensive patients, the cardiovascular risk over and above the prediction provided by office values [55–58]; and (3) measures more accurately than office blood pressure the extent of blood pressure reduction induced by treatment, because of the absence of a ‘white-coat’ [59] and placebo [60] effect, with higher reproducibility over time [61]. Although some of the above advantages can be obtained by increasing the number of office blood pressure measurements [62], 24-h ambulatory blood pressure monitoring before and during treatment can be recommended in some circumstances at the time of diagnosis and occasionally during treatment.

When measuring 24-h blood pressure [48], care should be taken to:

- 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;
- set the automatic readings at no more than 30 min intervals to obtain an adequate number of values, and have most hours represented if 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 on unusual events, and on duration and quality of night sleep. Although in the population, and in hypertensive patients, day and night blood pressures normally show a close correlation, there is evidence that subjects in whom nocturnal hypotension is blunted, and thus exhibit a relatively high night blood pressure, may have an unfavourable prognosis [63];
- obtain another ambulatory blood pressure monitoring if the first examination has less than 70% of the expected values because of a high number of artefacts;

Table 4 Blood pressure thresholds (mmHg) for definition of hypertension with different types of measurement

	SBP	DBP
Office or clinic	140	90
24-hour ambulatory	125	80
Home (self)	135	85

SBP, systolic blood pressure; DBP, diastolic blood pressure.

- remember that ambulatory blood pressure is usually several mmHg lower than office blood pressure [64–66]. As shown in Table 4, in the population, office values of 140/90 mmHg approximately correspond to 24-h average values 125/80 mmHg. Mean daytime and night-time values are several mmHg higher and, respectively, lower than 24-h means, but threshold values are more difficult to be established, as these are markedly influenced by behaviour during day or night.

Clinical decisions may be based on mean 24-h, day or night values, but preferably on 24-h means. Other information derivable from ambulatory blood pressure (e.g. blood pressure standard deviations, trough-to-peak ratio, smoothness index) is clinically promising but still only in the research phase.

Home blood pressure

Self-measurements of blood pressure at home cannot provide the extensive information on 24-h blood pressure values provided by ambulatory blood pressure monitoring. It can provide values on different days, however, in settings as close to daily life conditions as possible. When averaged over a period of a few days these values have been shown to share some of the advantages of ambulatory blood pressure, that is to have no white-coat effect and to be more reproducible and predictive of the presence and progression of organ damage than are office values [51,67]. Therefore, home blood pressure measurements for suitable periods (e.g. a few weeks) before and during treatment can also be recommended because this relatively cheap procedure may improve patient’s adherence to treatment [68].

When advising self-measurement of blood pressure at home [48] care should be taken to:

- advise only the use of validated devices; none of the presently available wrist devices for measurement of blood pressure have been validated satisfactorily; should any of these wrist devices become validated, the subject should be advised to keep the arm at heart level during measurement;
- recommend semi-automatic rather than mercury sphygmomanometric devices, to avoid the difficulty of patient instruction and the error from hearing problems in elderly individuals;

- instruct the patients to make measurement seated after several minutes of rest, and inform them that values may differ between measurements because of spontaneous blood pressure variability;
- avoid requesting an excessive number of measurements and ensure that some of these are made before drugs are taken to provide information on duration of the treatment effect;
- as for ambulatory blood pressure, note that normality values are lower for home compared with office pressures. Take 135/85 mmHg as the values for home blood pressure which correspond to 140/90 mmHg measured in the office or clinic (Table 4);
- give the patient clear instructions on the need to provide the doctor with proper documentation of the measured values and to avoid self-alterations of the treatment regimens.

Recently, the telephone transmission of self-measured blood pressures has been proposed to shorten treatment titration and improve blood pressure control, but the evidence is preliminary [69].

Box 3 Position statement: Blood pressure measurement

- Blood pressure values measured in the doctor's office or the clinic should commonly be used as reference.
- Twenty-four-hour ambulatory blood pressure monitoring may be considered of additional clinical value, when:
 - considerable variability of office blood pressure is found over the same or different visits;
 - high office blood pressure is measured in subjects otherwise at low global cardiovascular risk;
 - there is marked discrepancy between blood pressure values measured in the office and at home;
 - resistance to drug treatment is suspected;
 - research is involved.
- Self-measurement of blood pressure at home should be encouraged in order to:
 - provide more information for the doctor's decision;
 - improve patient's adherence to treatment regimens.
- Self-measurement of blood pressure at home should be discouraged whenever:
 - it causes patients anxiety;
 - it induces self-modification of the treatment regimen.
- Normal values are different for office, ambulatory and home blood pressure (see Table 4)

Systolic blood pressure measurements during physical exercise or laboratory stressors

Systolic blood pressure measurements during bicycle exercise (there has been no systematic study during treadmill exercise yet) have been proposed as more sensitive indicators of the degree of blood pressure elevation, the cardiovascular risk or the chance of normotensive individuals developing hypertension (diastolic blood pressure values during exercise may be inaccurate and are poorly reproducible). Although the cut-off exercise blood pressure dividing normotensive from hypertensive subjects has not been identified properly [70], the value of this approach in addition to conventional resting blood pressure is supported by large long-term studies [71,72]. A rise in exercise systolic blood pressure to >200 mmHg during the first 6 min of bicycle exercise predicts a doubling of cardiovascular death rate 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 does no longer carry independent prognostic power [73]. On the whole, systolic blood pressure measurement during exercise, though potentially valuable, is not recommended as a routine procedure in hypertensives.

Blood pressure values obtained during laboratory stressors have not been demonstrated conclusively to be useful predictors of outcome [74].

Isolated office or white-coat hypertension

In some patients office blood pressure is persistently elevated while daytime or 24-h blood pressure values are normal. This condition is widely known as '*white-coat hypertension*' [75], although a more descriptive and less mechanistic term '*isolated office (or clinic) hypertension*' is preferable because the office ambulatory blood pressure difference does not correlate with the office blood pressure elevation induced by the alert response to the doctor or the nurse, i.e. the true '*white-coat effect*' [76]. Regardless of the terminology, evidence is now available that isolated office hypertension is not infrequent (about 10% in the general population [77]) and that it accounts for a non-negligible proportion of individuals in whom hypertension is diagnosed. Also

Table 5 Isolated office (or clinic) hypertension (so-called 'white-coat hypertension')

Diagnosis	Office BP \geq 140/90 mmHg (at several visits); 24 h ambulatory BP < 125/80 mmHg
Investigation	Possible metabolic risk factors; possible target organ damage
Prescription	Lifestyle changes and close follow-up; drug treatment if evidence of target organ damage

BP, blood pressure

there is evidence that in individuals with isolated office hypertension, cardiovascular risk is less than in individuals with raised office and ambulatory blood pressures [77]. However, several, although 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 clinically [78].

As indicated in Table 5, physicians should diagnose isolated office hypertension whenever office blood pressure is $\geq 140/90$ mmHg at several visits while 24-h ambulatory blood pressure is $< 125/80$ mmHg. Diagnosis can also be based on home blood pressure values (average of several day readings $< 135/85$ mmHg). There should be a search for metabolic risk factors and target organ damage. Drug treatment should be instituted when there is evidence of organ damage or a high cardiovascular risk profile. Lifestyle changes and a close follow-up should be implemented in all patients with isolated office hypertension in whom the physicians elect not to start pharmacological treatment.

Though less frequent, a phenomenon that is the reverse of 'isolated office hypertension' may occur, viz. individuals with normal office blood pressure ($< 140/90$ mmHg) may have elevated ambulatory blood pressure values ('isolated ambulatory hypertension') [79]. These individuals have been shown to display a greater than normal prevalence of target organ damage [80].

Family and clinical history

A comprehensive family history (Box 4) should be obtained, with particular attention to hypertension, diabetes, dyslipidaemia, premature coronary heart disease, stroke or renal disease.

Clinical history should include:

1. duration and previous levels of high blood pressure;
2. symptoms suggestive of secondary causes of hypertension and intake of drugs or substances that can raise blood pressure, such as liquorice, cocaine, amphetamines, oral contraceptives, steroids, non-steroidal anti-inflammatory drugs, erythropoietin, and cyclosporins;
3. lifestyle factors, such as dietary intake of fat (animal fat in particular), salt and alcohol, smoking and physical activity, weight gain since early adult life;
4. past history or current symptoms of coronary disease, heart failure, cerebrovascular or peripheral vascular disease, renal disease, diabetes mellitus, gout, dyslipidaemia, bronchospasm or any other significant illnesses, and drugs used to treat those conditions;
5. previous antihypertensive therapy, its results and adverse effects; and
6. personal, family and environmental factors that may

Box 4 Guidelines for family and clinical history

1. Duration and previous level of high blood pressure.
2. Indications of secondary hypertension:
 - (a) family history of renal disease (polycystic kidney);
 - (b) renal disease, urinary tract infection, haematuria, analgesic abuse (parenchymal renal disease);
 - (c) drug/substance intake: oral contraceptives, liquorice, carbenoxolone, nasal drops, cocaine, amphetamines, steroids, non-steroidal anti-inflammatory drugs, erythropoietin, cyclosporin;
 - (d) episodes of sweating, headache, anxiety, palpitation (phaeochromocytoma);
 - (e) episodes of muscle weakness and tetany (aldosteronism).
3. Risk factors:
 - (a) family and personal history of hypertension and cardiovascular disease;
 - (b) family and personal history of hyperlipidaemia;
 - (c) family and personal history of diabetes mellitus;
 - (d) smoking habits;
 - (e) dietary habits;
 - (f) obesity; amount of physical exercise;
 - (g) personality.
4. Symptoms of organ damage:
 - (a) brain and eyes: headache, vertigo, impaired vision, transient ischaemic attacks, sensory or motor deficit;
 - (b) heart: palpitation, chest pain, shortness of breath, swollen ankles;
 - (c) kidney: thirst, polyuria, nocturia, haematuria;
 - (d) peripheral arteries: cold extremities, intermittent claudication.
5. Previous antihypertensive therapy:
 - (a) drugs used, efficacy and adverse effects.
6. Personal, family and environmental factors.

influence blood pressure, cardiovascular risk, as well as the course and outcome of therapy.

Physical examination

In addition to blood pressure measurement, physical examination should search for evidence of additional risk factors (in particular abdominal obesity), for signs suggesting secondary hypertension, and for evidence of organ damage (Box 5).

Laboratory investigations

Laboratory investigations (Box 6) are directed at pro-

Box 5 Physical examination for secondary hypertension and organ damage

Signs suggesting secondary hypertension and organ damage

- Features of Cushing syndrome.
- Skin stigmata of neurofibromatosis (phaeochromocytoma).
- Palpation of enlarged kidneys (polycystic kidney).
- Auscultation of abdominal murmurs (renovascular hypertension).
- Auscultation of precordial or chest murmurs (aortic coarctation or aortic disease).
- Diminished and delayed femoral and reduced femoral blood pressure (aortic coarctation, aortic disease).

Signs of organ damage

- Brain: murmurs over neck arteries, motor or sensory defects.
- Retina: funduscopy abnormalities.
- Heart: location and characteristics of apical impulse, abnormal cardiac rhythms, ventricular gallop, pulmonary rales, dependent oedema.
- Peripheral arteries: absence, reduction, or asymmetry of pulses, cold extremities, ischaemic skin lesions.

viding evidence of additional risk factors, searching for secondary hypertension and assessing absence or presence of target organ damage. The minimum laboratory investigations needed are a matter of debate. However, it is agreed that investigations should progress from the most simple to the more complicated. The younger the patient, the higher the blood pressure and the faster the development of hypertension, the more detailed the diagnostic work-up will be.

In the rather uniform European context, where cardiovascular diseases are the primary cause of morbidity and mortality, routine laboratory investigations should include: blood chemistry for glucose (preferably fasting), total cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides, urate, creatinine, sodium, potassium, haemoglobin and haematocrit; urinalysis (dipstick test complemented by urine sediment examination); and an electrocardiogram. Whenever fasting plasma glucose is ≥ 6.1 mmol/l (110 mg/dl), post-prandial blood glucose should also be measured or a glucose tolerance test performed [81,82]. A fasting plasma glucose of 7.0 mmol/l (126 mg/dl) or a 2-h post-prandial plasma glucose of 11 mmol/l (198 mg/dl) are now considered threshold values for diabetes mellitus [81,82]. Because of evidence supporting C-reactive protein use in primary prevention [41], its measurement by the now widely available high-sensitivity assays is recom-

Box 6 Laboratory investigations

Routine tests

- Plasma glucose (preferably fasting)
- Serum total cholesterol
- Serum high-density lipoprotein (HDL)-cholesterol
- Fasting serum triglycerides
- Serum uric acid
- Serum creatinine
- Serum potassium
- Haemoglobin and haematocrit
- Urinalysis (dipstick test complemented by urinary sediment examination)
- Electrocardiogram

Recommended tests

- Echocardiogram
- Carotid (and femoral) ultrasound
- C-reactive protein
- Microalbuminuria (essential test in diabetics)
- Quantitative proteinuria (if dipstick test 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; computer-assisted tomography (CAT); brain magnetic resonance imaging

mended, particularly in hypertensive patients with the metabolic syndrome [42].

Searching for target organ damage

Due to the importance of target organ damage in determining the overall cardiovascular risk of the hypertensive patient (see Tables 2 and 3), evidence of organ involvement should be sought carefully. Recent studies have shown that without ultrasound cardiovascular investigations for left ventricular hypertrophy and vascular (carotid) wall thickening or plaque, up to 50% of hypertensive subjects may be mistakenly classified as at low or moderate added risk, whereas presence of cardiac or vascular damage places them within a higher risk group [45]. Echocardiography and vascular ultrasonography can therefore be considered as recommended tests, particularly in patients in whom target organ damage is not discovered by routine investigations including an electrocardiogram. Likewise, searching for microalbuminuria is recommended, because of the mounting evidence that it may be a sensitive marker of organ damage, not only in diabetes but also in hypertension.

Because of the importance of organ damage, not only in

diagnosing cardiovascular risk but also in the follow-up of patients, as well as in using additional endpoints for assessing treatment outcomes, methods for evaluating organ damage are mentioned in greater detail below.

Heart

Electrocardiography should be part of all routine assessment of subjects with high blood pressure to detect ischaemia, conduction defects and arrhythmias. Its sensitivity in detecting left ventricular hypertrophy is low but, none the less, positivity of the Sokolow–Lyons index ($SV_1 + RV_{5-6} > 38$ mm) or of the Cornell modified index (> 2440 mm*ms) has been shown to be an independent predictor of cardiovascular events [83]. The Cornell voltage QRS duration product has been used successfully in detecting patients with left ventricular hypertrophy to be included in an intervention trial [84]. Electrocardiography can be used also to detect patterns of ventricular overload ('strain'), known to indicate more severe risk [83]. Echocardiography is undoubtedly much more sensitive than electrocardiography in diagnosing left ventricular hypertrophy [85] and predicting cardiovascular risk [86]. The availability of echocardiography has increased in Europe, and when treatment decisions are uncertain an echocardiographic examination may help in more precisely classifying the overall risk of the hypertensive patient and in directing therapy [45]. The evaluation should include measurements of interventricular septum and posterior wall thicknesses and of end diastolic left ventricular diameter, with calculation of left ventricular mass according to available formulae [87]. Although the relation between left ventricular mass index and cardiovascular risk is continuous, the threshold of 125 g/m² for men, and 110 g/m² for women, is most widely used for conservative estimates of left ventricular hypertrophy. Classification into concentric or eccentric hypertrophy, and concentric remodelling by using the wall to radius ratio (values >0.45 define concentric patterns) have been shown also to have risk-predicting value [88]. Ultrasound methods for quantitatively evaluating the fibrosis component accompanying hypertrophy (echoreflexivity [89], back scattering [90]) have been described, but, at present, are of research interest only. In addition, echocardiography provides a means of assessing left ventricular systolic function including midwall fractional shortening, which has been proposed as a reliable predictor of cardiovascular events [91,92]. Furthermore, left ventricular diastolic distensibility (so-called diastolic function) can also be assessed by Doppler measurement of the ratio between the E and A waves of transmitral blood flow (and, more precisely, by adding measurement of early diastolic relaxation time and evaluating patterns of pulmonary vein outflow into the left atrium) [93]. There is current interest in whether patterns of so-called 'diastolic dysfunction' can predict onset of dyspnoea and impaired effort tolerance

without evidence of systolic dysfunction, frequently occurring in hypertension and in the elderly (so-called 'diastolic heart failure') [92]. Finally, echocardiography can provide evidence of left ventricular wall contraction defects due to ischaemia or previous infarction, and of systolic dysfunction. Other diagnostic cardiac procedures, such as nuclear magnetic resonance, cardiac scintigraphy, exercise testing and coronary angiography are reserved for specific indications (diagnosis of coronary artery disease, cardiomyopathy, etc.). An X-ray of the thorax may often represent a useful additional diagnostic procedure, when information on large intrathoracic arteries or the pulmonary circulation is required.

Blood vessels

Ultrasound examination of the carotid arteries with measurement of the intima–media complex thickness and detection of plaques [94] has repeatedly been shown to predict occurrence of both stroke and myocardial infarction [95–100]. A recent survey indicates that it can usefully complement echocardiography in precise risk stratification of hypertensive patients [45]. The relation between carotid artery intima–media thickness and cardiovascular events is continuous, but a threshold ≥ 0.9 mm can be taken as a conservative estimate of significant alteration.

The increasing interest in systolic blood pressure and pulse pressure as predictors of cardiovascular events [101] (see above), stimulated by trial evidence of the beneficial effects of lowering blood pressure in the elderly and in isolated systolic hypertension, has stimulated the development of techniques for measuring large artery compliance. A large body of important pathophysiological, pharmacological and therapeutic information has accumulated [102,103]. Two of these techniques have further been developed for possible use as diagnostic procedures, namely the pulse wave velocity measurement [104] and the augmentation index measurement device (Sphygmocor) [10,105]. 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, may be predictive of outcomes [104,106] and may be differently affected by different antihypertensive drugs. However, both techniques need to be tested further in prospective trials in order to establish their predictive value.

Finally, there has been widespread interest in endothelial dysfunction or damage as an early marker of cardiovascular damage [107,108]. Although these investigations have also caused considerable advances in our understanding of hypertension and its consequences, evidence that isolated endothelial dysfunction has a predictive value in hypertension is still rather scanty

[109]. Furthermore, the techniques used so far for investigating endothelial responsiveness to various stimuli are either invasive or too laborious and time consuming for use in the clinical evaluation of the hypertensive patient. However, current studies on circulating markers of endothelial activity, dysfunction or damage (NO and its metabolites, endothelins, cytokines, adhesion molecules, endothelins, etc.) may soon provide simpler tests of endothelial dysfunction and damage to be investigated prospectively and possibly used clinically [110], as is already occurring with C-reactive protein [41].

Kidney

The diagnosis of hypertension-induced renal damage is based on the finding of an elevated value of serum creatinine, of a decreased (measured or estimated) creatinine clearance, or the detection of an elevated urinary excretion of albumin below (microalbuminuria) or above (macroalbuminuria) the limit of the usual laboratory methods to detect proteinuria. The presence of mild renal insufficiency has been defined recently as serum creatinine values equal to or above 133 $\mu\text{mol/l}$ (1.5 mg/dl) in men and 124 $\mu\text{mol/l}$ (1.4 mg/dl) in women [111,112], or by the finding of estimated creatinine clearance values below 60–70 ml/min [40]. An estimate of creatinine clearance in the absence of 24-h urine collection can be obtained based on prediction equations corrected for age, gender and body size [112]. 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 a serum urate level in excess of 416 $\mu\text{mol/l}$ (7 mg/dl)] is frequently seen in untreated hypertensives and has also been shown to correlate with the existence of nephrosclerosis [113].

While an elevated serum creatinine concentration points to a reduced rate of glomerular filtration, an increased rate of albumin or protein excretion points to a derangement in the glomerular filtration barrier [114]. Microalbuminuria has been shown to predict the development of overt diabetic nephropathy in both type 1 and type 2 diabetics [115], while the presence of proteinuria generally indicates the existence of established renal parenchymatous damage [114]. In non-diabetic hypertensive patients microalbuminuria, even below the current threshold values [116], has been shown to predict cardiovascular events [117–119], and a continuous relation between urinary albumin excretion and cardiovascular, as well as non-cardiovascular, mortality has recently been found in a general population study [120].

The finding of a deranged renal function in a hypertensive patient, expressed by any of the above para-

eters, is frequent and constitutes a very potent predictor of future cardiovascular events and death [39,40,121,122]. Therefore, it is recommended that serum creatinine (and possibly also estimated creatinine clearance calculated on the basis of age, gender and body size) [112], serum urate and urinary protein (by dipstick) be measured in all hypertensive patients. Microalbuminuria should be measured in all diabetic patients and, whenever possible, in non-diabetic hypertensives (dipstick-negative patients) by a validated laboratory method on urine samples collected during the night, and preferably related to creatinine excretion (age-adjusted albumin to creatinine ratio) [115,123].

Funduscopy

In contrast to the 1930s, when the Keith Wagener and Baker classification of hypertensive eye ground changes in four grades [124] was formulated, nowadays most hypertensive patients present early, and haemorrhages, exudates (grade 3) and papilloedema (grade 4) are very rarely observed. Grades 1 and 2 arteriolar changes are often noted, but no evidence is available that these have a significant prognostic value. A recent evaluation of 800 hypertensive patients attending a hypertension outpatient clinic [43] showed that the prevalence of grades 1 and 2 retinal changes was as high as 78% (in contrast to prevalences of 43% for carotid plaques, 22% for left ventricular hypertrophy and 14% for microalbuminuria). Therefore, it is doubtful whether grades 1 and 2 retinal changes can be used as evidence of target organ damage to stratify global cardiovascular risk, whereas grades 3 and 4 are certainly markers of severe hypertensive complications. More selective methods for investigating ocular damage in hypertension are being developed, but remain research applications [125].

Brain

In patients who have suffered a stroke, imaging techniques nowadays allow improved diagnosis of the existence, nature and location of a lesion [126]. Cranial computed tomography (CT) is the standard procedure for diagnosis of a stroke but, except for prompt recognition of an intracranial haemorrhage, CT is progressively being replaced by magnetic resonance imaging (MRI) techniques. Diffusion-weighted MRI can identify ischaemic injury within minutes of arterial occlusion. Furthermore MRI, particularly in fluid-attenuated inversion recovery (FLAIR) sequences, is much superior to CT in identifying silent brain infarctions, the large majority of which are small and deep (so-called lacunar infarcts). In two population-based studies, the Cardiovascular Health Study [127] and the Atherosclerosis Risk in Community Study [128], MRI investigation detected silent brain infarcts larger than 3 mm in diameter in 28 and 11% of the subjects, respectively. Despite the clinical relevance of these observations, the limited availability, the time-consuming nature and

the cost of MRI do not yet allow its widespread use in the diagnostic evaluation of elderly hypertensives, but more liberal application may be acceptable in all hypertensives reporting neural disturbances, and particularly memory loss. Finally, as cognition disturbances in the elderly are, at least in part, hypertension-related [129,130], suitable cognition evaluation tests should more often be used in the clinical assessment of the elderly hypertensive.

Screening for secondary forms of hypertension

A specific cause of blood pressure elevation can be identified in a minority (from less than 5 to 10%) of adult patients with hypertension. Simple screening for secondary forms of hypertension can be obtained from clinical history, physical examination and routine laboratory investigations (Boxes 4–6). Furthermore, a secondary form of hypertension is suggested by a severe blood pressure elevation, sudden onset of hypertension and blood pressure responding poorly to drug therapy. In these cases, specific diagnostic procedures may become necessary, as outlined below.

Renal parenchymal hypertension

Renal parenchymal disease is the most common cause of secondary hypertension. The finding of bilateral upper abdominal masses at physical examination is consistent with polycystic kidney disease and should lead to an abdominal ultrasound examination. Renal ultrasound has now almost completely replaced intravenous urography in the anatomical exploration of the kidney. While the latter requires the injection of potentially nephrotoxic contrast medium, ultrasound is non-invasive and provides all the necessary anatomic data about kidney size and shape, cortical thickness, urinary tract obstruction and renal masses [131]. Assessing the presence of protein, erythrocytes and leucocytes in the urine, as well as measuring serum creatinine concentration, are the appropriate functional screening tests for renal parenchymal disease [132,133]. These tests should be performed in all patients with hypertension. Renal parenchymal disease may be excluded if urinalysis and serum creatinine concentration are normal on repeated determinations. The presence of erythrocytes and leucocytes should be confirmed by microscopic examination of the urine. If the screening tests for renal parenchymal hypertension are positive, a detailed work-up for kidney disease should ensue.

Renovascular hypertension

Renovascular hypertension is the second most common cause of secondary hypertension. In about 75% of the patients, the renal artery stenosis is caused by atherosclerosis (particularly in the elderly population). Fibromuscular dysplasia accounts for up to 25% of total cases (and is the most common variety in young adults). Signs of renal artery stenosis are an abdominal bruit

with lateralization, hypokalaemia, polyglobulia, and progressive decline in renal function. However, these signs are not present in many patients with renovascular hypertension. An abdominal bruit, for instance, is heard in only about 40% of the patients with renal artery stenosis. Determination of the longitudinal diameter of the kidney using ultrasound can be used as a screening procedure. However, a difference of more than 1.5 cm in length between the two kidneys – which is usually considered as being diagnostic for renal artery stenosis – is only found in about 60–70% of the patients with renovascular hypertension. Colour Doppler sonography with calculation of peak systolic velocity and resistance indices in the renal artery is able to detect stenoses of the renal artery, particularly those localized close to the origin of the vessel [134]. In experienced hands, the technique has high sensitivity and specificity, but the procedure is highly observer-dependent [135]. There is evidence that investigations of the renal vasculature by breath-hold three-dimensional, gadolinium-enhanced magnetic resonance angiography may become the diagnostic procedure of choice for renovascular hypertension in the future [136]. Some authors report that the sensitivity of this method is over 95% [137]. Another imaging procedure with similar sensitivity is spiral computed tomography, which requires the application of iodine-containing contrast media and the use of relatively high X-ray doses. Once there is a strong suspicion of renal artery stenosis, intra-arterial digital subtraction angiography should be performed for confirmation. This invasive procedure is still the gold standard for the detection of renal artery stenosis. The determination of the renal vein renin ratio requires catheterization of both renal veins and simultaneous sampling from each renal vein and from the inferior vena cava. Despite some claims to the contrary, this test has not achieved acceptable sensitivity or specificity and cannot be recommended as a screening procedure. There are more data supporting its value to assess the functional significance of a renal artery stenosis noted on arteriography, but the matter is still controversial [127].

Phaeochromocytoma

Phaeochromocytoma is a very rare form of secondary hypertension. The determination of catecholamines (noradrenaline and adrenaline) as well as of metanephrines in several 24-h urine samples is a reliable method for detection of the disease. The sensitivity of the method is well above 95%. In most patients with phaeochromocytoma, the excretion of noradrenaline, adrenaline, normetanephrine and metanephrine is so elevated that no further confirmation is required [138]. If the urinary excretion of catecholamines and their metabolites is only marginally increased, or normal, despite a strong clinical suspicion of phaeochromocytoma, the glucagon stimulation test can be applied. This

test requires the measurement of catecholamines in plasma and should be performed after the patient has been effectively treated with an α -blocker. This pre-treatment prevents marked blood pressure rises after the injection of glucagon. The clonidine suppression test also requires the determination of plasma catecholamines. This test is used to identify patients with essential hypertension with increased activity of the sympathetic nervous system causing slight elevations of the excretion of catecholamines and their metabolites in urine [139]. Once the diagnosis of pheochromocytoma has been established, localization of the tumour is necessary. As pheochromocytomas are often big and localized in or in close proximity of the adrenal glands, they are often detected by ultrasound. A more sensitive imaging procedure is computer tomography. The metaiodobenzylguanidine (MIBG) scan is useful in localizing extra-adrenal pheochromocytomas and metastases of the 10% of pheochromocytomas that are malignant.

Primary aldosteronism

The determination of serum potassium levels is considered to be a screening test for the disease. However, only about 80% of the patients have hypokalaemia in an early phase [140], and some authorities maintain that hypokalaemia may even be absent in severe cases [141]. Particularly in patients with bilateral adrenal hyperplasia, serum potassium levels may be normal or only slightly decreased [142]. The diagnosis is confirmed [after withdrawal of drugs influencing renin, such as β -blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor antagonists and diuretics] by a low plasma renin activity (< 1 ng/ml per hour) and elevated plasma aldosterone levels. A plasma aldosterone (ng/dl):plasma renin activity (ng/ml per hour) >50 is highly suggestive of primary aldosteronism [142]. The diagnosis of primary aldosteronism is confirmed by the fludrocortisone suppression test: in the presence of primary aldosteronism 4-day administration of fludrocortisone further suppresses plasma renin activity without suppressing plasma aldosterone below a threshold value (5 ng/dl) [143]. Imaging procedures such as computer tomography and magnetic resonance imaging are used to localize an aldosterone-producing tumour, but adrenal morphology correlates poorly with function, and adrenal venous sampling, although invasive and difficult to perform, is considered by some investigators as a more reliable procedure [141,144].

Cushing's syndrome

Hypertension is a very common finding in Cushing's syndrome, affecting about 80% of such patients. The syndrome is often suggested by the typical body habitus of the patient. The determination of 24-h urinary cortisol excretion is the most practical and reliable index of cortisol secretion, and a value exceeding 110 nmol (40 μ g) is highly suggestive of the syn-

drome. The diagnosis is confirmed by the 2-day, low-dose dexamethasone suppression test (0.5 mg every 6 h for eight doses) or the overnight dexamethasone suppression test (1 mg at 2300 h). In the 2-day test, urinary cortisol excretion higher than 27 nmol (10 μ g) per day on day two indicates Cushing's syndrome. The same is true if plasma cortisol concentration is greater than 140 nmol/l (5 μ g/dl) at 0800 h in the overnight test. A normal result in either of the two suppression tests excludes the possibility of Cushing's syndrome [145]. Further tests and imaging procedures have to be used to differentiate the various forms of the syndrome [146].

Coarctation of the aorta

Coarctation of the aorta is a rare form of hypertension in children and young adults. The diagnosis is usually evident from physical examination. A midsystolic murmur, which may become continuous with time, is heard over the anterior part of the chest and also over the back. The femoral pulse is delayed relative to the radial pulse. Hypertension is found in the upper extremities concomitantly with low or unmeasurable pressures in the legs.

Drug-induced hypertension

Substances or drugs that can raise blood pressure include: liquorice, oral contraceptives, steroids, non-steroidal anti-inflammatory drugs, cocaine and amphetamines, erythropoietin, cyclosporins. The patient should be asked specifically at the time clinical history is taken, and the use of drugs that can raise blood pressure, when necessary, should be monitored carefully.

Genetic analysis

Genetic analysis has not yet a clear role to play in the routine assessment of people with hypertension. Although there is often a family history of high blood pressure in hypertensive patients, suggesting that inheritance contributes to the pathogenesis of this disorder, the most common form of hypertension – essential hypertension – has a highly heterogeneous character, which points to a multifactorial aetiology and polygenic abnormalities [147,148]. Variants in some genes might render an individual more or less sensitive to a given factor in the environment [149] or to drugs [150]. A number of mutations in the genes encoding for major blood pressure controlling systems (such as angiotensin-converting enzyme, angiotensinogen, angiotensin II receptor, α -adducin and the amiloride-sensitive epithelial sodium channel [ENaC]) have been recognized in humans, but their exact role in the pathogenesis of essential hypertension is still unclear [147,148]. The search for candidate gene mutations in the individual hypertensive is therefore not useful at present. In rarer monogenic forms of inherited hypertension, genetic analysis can be useful to confirm or

exclude specific diagnoses. Monogenic forms of hypertension are the Liddle's syndrome, caused by activating mutations of the ENaC [151]; the apparent mineralocorticoid excess syndrome due to inactivating mutations in the gene coding for the enzyme 11 β -hydroxysteroid dehydrogenase type 2 (the enzyme which converts cortisol to cortisone), leading to an enhanced stimulation of the mineralocorticoid receptor by cortisol [152]; and the glucocorticoid remediable aldosteronism, which results from the presence in the adrenal zona glomerulosa of a hybrid gene encoding both aldosterone synthase and 11 β -hydroxylase and, because the 11 β -hydroxylase activity depends on ACTH, from enhanced aldosterone synthesis [153].

Therapeutic approach

When to initiate antihypertensive treatment

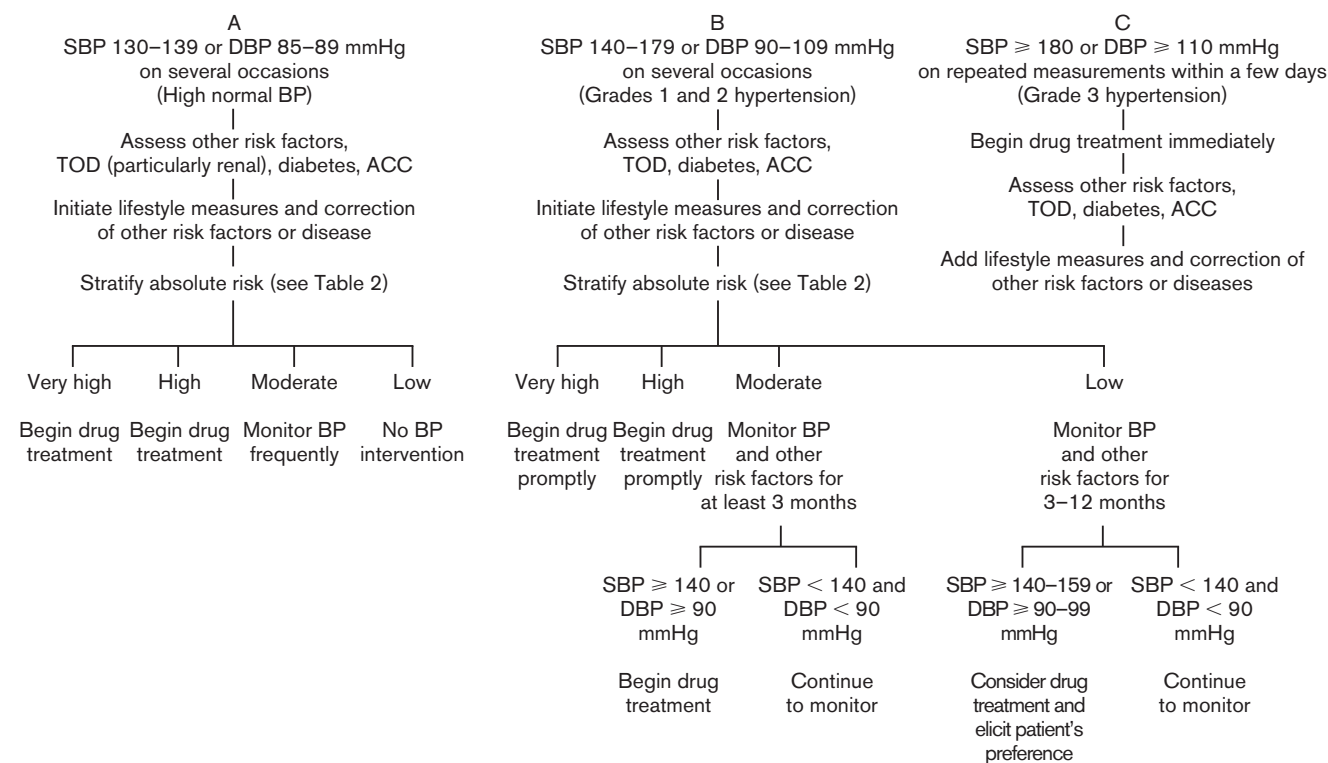
Guidelines for initiating antihypertensive treatment are based on two criteria: (1) the total level of cardiovascular risk, as indicated in Table 2; and (2) the level of systolic and diastolic blood pressure (Table 1). The total level of cardiovascular risk is the main indication for intervention, but lower or higher blood pressure values are also less or more stringent indicators for

blood-pressure-lowering intervention. With respect to previous guidelines of the European Societies [3,4] or the WHO/ISH [2], the recommendations summarized in Figure 1 are no longer limited to patients with grades 1 and 2 hypertension, but also extend to subjects with high normal blood pressure. They also describe in greater detail how to deal with patients with grade 3 hypertension.

Consideration of subjects with systolic blood pressure 130–139 mmHg and diastolic blood pressure 85–89 mmHg for possible initiation of antihypertensive treatment is based on the following recent evidence:

1. The PROGRESS study [154] has shown that patients with previous stroke or transient ischaemic attack and blood pressures < 140/90 mmHg, if left untreated (placebo), have an incidence of cardiovascular events of about 17% in 4 years (very high risk according to the guidelines), and their risk is decreased by 24% by blood pressure lowering.
2. Similar observations have been made in the HOPE study [155] for 'normotensive' patients with high coronary risk.

Fig. 1



Initiation of antihypertensive treatment. Decision based on initial blood pressure levels (A, B, C) and total risk level. BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; TOD, target organ damage; ACC, associated clinical conditions.

3. The ABCD-Normotensive trial [156] has shown that type 2 diabetic patients with blood pressures < 140/90 mmHg may also benefit by more aggressive blood pressure lowering, at least for stroke prevention and progression of proteinuria.
4. The Framingham Heart Study [157] has shown that male subjects with high normal blood pressure have a 10-year cardiovascular disease incidence of 10%, i.e. in the range that these guidelines classify as low added risk.

Because the evidence of blood-pressure-lowering benefits in patients with high normal blood pressures is so far limited to subjects with stroke [154], coronary artery disease [155] and diabetes [156], antihypertensive treatment within this blood pressure range can only be recommended for patients at least at high risk. Close monitoring of blood pressure and no blood pressure intervention is recommended for patients at moderate or low total risk, who are considered to benefit mostly from lifestyle measures and correction of other risk factors (e.g. smoking).

In patients with grade 1 and 2 hypertension, previous guidelines [2] are reconfirmed, with the recommendation to check blood pressure values on several occasions, initiate lifestyle measures and stratify absolute risk. Antihypertensive drug treatment should be initiated promptly in subjects classified as at high or very high risk, whereas in subjects at moderate or low added risk blood pressure, as well as other cardiovascular risk factors, should be monitored for extended periods (at least 3 months) with only non-pharmacological treatment. If after extended observation, systolic values ≥ 140 or diastolic values ≥ 90 mmHg persist, antihypertensive drug treatment should be initiated in patients at moderate risk, and considered in patients at lower risk (whose blood pressure by definition, is in the grade 1 range, see Table 2). In the latter group of patients, rather than using a higher blood pressure threshold (systolic ≥ 150 or diastolic ≥ 95 mmHg) for intervention [2–4], it is suggested that patient preferences and/or resource issues influence treatment decisions. Lowering blood pressure in grade 1 and 2 hypertensives at low or moderate added risk is less cost effective immediately, but the patient should be informed that several trials of antihypertensive therapy, particularly the HDFP [158] and the HOT study [159], have shown that, despite intensive blood pressure lowering, residual cardiovascular risk remains higher in patients with initial higher cardiovascular risk than in patients with initial moderate risk. This suggests that some of the major cardiovascular changes may be difficult to reverse, and that restricting antihypertensive therapy to patients at high or very high risk, although cost saving for health providers, may be less than optimal for the patient.

Figure 1 also includes recommendations about initiation of treatment in patients with grade 3 hypertension. In these subjects confirmation of elevated blood pressure values should be obtained within a few days, and treatment instituted quickly, without the preliminary need of establishing the absolute risk (high even in absence of other risk factors). Complete assessment of other risk factors, target organ damage or associated disease can be carried out after treatment has been started, and lifestyle measures can be recommended at the same time as initiation of drug therapy.

Goals of treatment

The primary goal of 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 the reversible risk factors identified, including smoking, dyslipidaemia or diabetes, and the appropriate management of associated clinical conditions, as well as treatment of the raised blood pressure *per se*.

For target blood pressure, more evidence is available for diastolic than for systolic blood pressure. Randomized trials comparing less with more intensive treatment are few (HOT [160], UKPDS [161], ABCD-HT [162], ABCD-NT [156]), and most are limited to diabetic patients, so that the meta-analysis of these trials, although suggesting greater benefits of more intensive blood pressure lowering [163], does not indicate whether this also applies to non-diabetic individuals. The only trial not exclusively involving diabetics is the HOT study [160], which, because of the small diastolic blood pressure differences achieved (2 mmHg) between adjacent blood pressure target groups (randomized to ≤ 90 , ≤ 85 or ≤ 80 mmHg), was unable to detect significant differences in the risk of cardiovascular events (except for myocardial infarction) between these blood pressure target groups. However, the results of the HOT study have confirmed that there is no increase in cardiovascular risk in the patients randomized to the lowest target group (mean achieved diastolic blood pressure values 81 mmHg). Although subgroup analyses have obvious limitations, a recent subgroup analysis of the HOT study [164] suggests that a J-shaped curve may exist for current smokers only. Once smokers were excluded, reduction of diastolic blood pressure to an average of 82 rather than 85 mmHg significantly reduced major cardiovascular events not only in diabetics, but in patients at high/very high risk (50% of HOT study patients), as well as in patients with previous ischaemic heart disease, in patients older than 65 years and in women. In patients with a history of stroke or transient ischaemic attack the PROGRESS trial [154] showed cardiovascular mortality and morbidity benefits by reducing diastolic blood pressure to 79 mmHg (active treatment group)

rather than 83 mmHg (placebo group), and in patients with coronary disease the HOPE study [155] also made similar observations, although the role of blood pressure reduction in this trial has been debated.

For systolic blood pressure, most of the trials have been unable to achieve average values below 140 mmHg [165]. However, in the subgroup analysis of the HOT study that showed benefits of reducing diastolic values to 82 rather than 85 mmHg, achieved systolic blood pressure averaged between 142–145 and 145–148 mmHg, respectively [164]. In PROGRESS [154] benefits were shown for systolic blood pressure values of 132 versus 141 mmHg, and in HOPE [155] of 140 versus 142 mmHg. Finally, if the slightly greater reduction in strokes recently reported in the ALLHAT study by using chlorthalidone versus doxazosin [166], or chlorthalidone versus lisinopril [167] are mostly due to systolic blood pressure differences, the ALLHAT data suggest that systolic values of 134 mmHg may be safer than values of 136 mmHg.

In diabetic patients, a recent review of more- or less-intensive blood-pressure-lowering trials [168] has shown that a reduction of cardiovascular morbidity in more intensively treated diabetics was associated with systolic/diastolic blood pressure values of 144/82 mmHg in UKPDS [161], 144/81 mmHg in HOT [160,164] and 140/77 mmHg in MICROHOPE [169]. Therefore, diastolic values between 77 and 82 mmHg could be achieved and were shown to be beneficial. However, in most positive trials systolic values remained higher than 140 mmHg. Only the two ABCD studies were able to achieve low blood pressure values (132/78 mmHg in ABCD-HT, [162], and 128/75 mmHg in ABCD-NT, [156]), but in both studies benefits of more intensive treatment on cardiovascular disease are not impressive (significant reduction only in total mortality in ABCD-HT [162], and in stroke in ABCD-NT [156]). Finally, a prospective observational study within the UKPDS programme [170] has found a significant relation between follow-up systolic blood pressure and incidence of macro- and microvascular complications in diabetic patients, with a continuous increment of complications for values > 120 mmHg.

In patients with non-diabetic renal disease, data about the effects of more- or less-intensive blood pressure lowering on cardiovascular events are scant: the HOT study was unable to find any significant reduction in cardiovascular events in the subset of patients with plasma creatinine > 115 $\mu\text{mol/l}$ (>1.3 mg/dl) [164] or >133 $\mu\text{mol/l}$ (>1.5 mg/dl) [40] when subjected to more- versus less-intensive blood pressure lowering (139/82 versus 143/85 mmHg). However, none of these trials suggests an increased cardiovascular risk at the lowest blood pressure achieved.

In conclusion, on the basis of current evidence from trials, it can be recommended that blood pressure, both systolic and diastolic, be lowered intensively to at least below 140/90 mmHg and to lower values if tolerated, in all hypertensive patients, and to below 130/80 mmHg in diabetics (see below). The goal to be achieved, as well as the achievable goal, may depend on the pre-existing blood pressure level, particularly systolic values, and systolic values below 140 mmHg may be difficult to achieve, particularly in the elderly. The blood pressure goals indicated should not be taken as less rigorous than those in previous guidelines [2], but as a more flexible recommendation, rendering doctors more directly responsible for decision making in individual cases.

When home or ambulatory blood pressure measurements are used to evaluate the efficacy of treatment, it must be remembered that values provided by these methods (compared with office measurement) are on average at least 5–15 mmHg lower for systolic and 5–10 mmHg lower for diastolic blood pressure, although these differences are normally greater when office blood pressure is high, and tend to become smaller at lower office blood pressure values, such as those recommended as treatment goals [65].

Box 7 Position statement: Goals of treatment

- The primary goal of treatment of the patient with high blood pressure is to achieve the maximum reduction in the long-term total risk of cardiovascular morbidity and mortality. This requires treatment of all the reversible risk factors identified, including smoking, dyslipidaemia or diabetes, and the appropriate management of associated clinical conditions, as well as treatment of the raised blood pressure *per se*.
- On the basis of current evidence from trials, it can be recommended that blood pressure, both systolic and diastolic, be intensively lowered at least below 140/90 mmHg and to definitely lower values, if tolerated, in all hypertensive patients, and below 130/80 mmHg in diabetics, keeping in mind, however, that systolic values below 140 mmHg may be difficult to achieve, particularly in the elderly.

Lifestyle changes

Lifestyle measures should be instituted whenever appropriate in all patients, including subjects with high normal blood pressure and patients who require drug treatment. The purpose is to lower blood pressure and

to control other risk factors and clinical conditions present. The lifestyle measures that are widely agreed to lower blood pressure or cardiovascular risk, and that should be considered in all patients, are: (1) smoking cessation; (2) weight reduction; (3) reduction of excessive alcohol intake; (4) physical exercise; (5) reduction of salt intake; and (6) increase in fruit and vegetable intake and decrease in saturated and total fat intake. Healthy eating should always be promoted. However, lifestyle measures have not been shown to prevent cardiovascular complications in hypertensive patients, and should never delay unnecessarily the initiation of drug treatment, especially in patients at higher levels of risk, or detract from compliance with drug treatment.

Smoking cessation

Smoking cessation is probably the single most powerful lifestyle measure for the prevention of non-cardiovascular and cardiovascular diseases, including stroke and coronary heart disease [171]. Those who quit before middle age typically have a life expectancy that is not different to that of lifelong non-smokers. Although any independent chronic effect of smoking on blood pressure is small [172] and smoking cessation does not lower blood pressure [173], total cardiovascular risk is greatly increased by smoking [171]. Therefore, hypertensives who smoke should be counselled on smoking cessation. In addition, data suggest that smoking may interfere with the beneficial effects of some antihypertensive agents, such as β -blockers [174,175], or may prevent the benefits of more intensive blood pressure lowering [164]. Where necessary, nicotine replacement [176,177] or bupropion therapy [177,178] should be considered since they appear to be safe in hypertension and to facilitate smoking cessation.

Moderation of alcohol consumption

There is a linear relationship between alcohol consumption, blood pressure levels and the prevalence of hypertension in populations [179]. Beyond that, high levels of alcohol consumption are associated with a high risk of stroke [180]; this is particularly so for binge drinking. Alcohol attenuates the effects of antihypertensive drug therapy, but this effect is at least partially reversible within 1–2 weeks by moderation of drinking by around 80% [181]. Heavier drinkers (five or more standard drinks per day) may experience a rise in blood pressure after acute alcohol withdrawal, and are more likely to be diagnosed as hypertensive at the beginning of the week if they have a weekend drinking pattern. Accordingly, hypertensive patients who drink alcohol should be advised to limit their consumption to no more than 20–30 g ethanol/day for men, and no more than 10–20 g ethanol/day for women. They should be warned against the increased risk of stroke associated with binge drinking.

Weight reduction and physical exercise

Excess body fat predisposes to raised blood pressure and hypertension [182]. Weight reduction reduces blood pressure in overweight patients and has beneficial effects on associated risk factors such as insulin resistance, diabetes, hyperlipidaemia and left ventricular hypertrophy. The blood-pressure-lowering effect of weight reduction may be enhanced by a simultaneous increase in physical exercise [183], by alcohol moderation in overweight drinkers [184] and by reduction in sodium intake [185]. Physical fitness is a rather strong predictor of cardiovascular mortality independent of blood pressure and other risk factors [186]. Thus, sedentary patients should be advised to take up modest levels of aerobic exercise on a regular basis, such as walking, jogging or swimming for 30–45 min, three to four times a week [187]. The extent of the pretraining evaluation will depend on the extent of the exercise programme and on the patient's symptoms, signs, overall cardiovascular risk and associated clinical conditions. Even mild exercise may lower systolic blood pressure by about 4–8 mmHg [188–190]. However, isometric exercise such as heavy weight-lifting can have a pressor effect and should be avoided. If hypertension is poorly controlled, and always in severe hypertension, heavy physical exercise should be discouraged or postponed until appropriate drug treatment has been instituted and found to be effective.

Box 8 Position statement: Lifestyle changes

- Lifestyle measures should be instituted whenever appropriate in all patients, including subjects with high normal blood pressure and patients who require drug treatment. The purpose is to lower blood pressure and to control other risk factors and clinical conditions present.
- The lifestyle measures that are widely agreed to lower blood pressure or cardiovascular risk, and that should be considered, are:
 - smoking cessation;
 - weight reduction;
 - reduction of excessive alcohol intake;
 - physical exercise;
 - reduction of salt intake;
 - increase in fruit and vegetable intake and decrease in saturated and total fat intake.

Reduction of high salt intake and other dietary changes

Epidemiological studies suggest that dietary salt intake is a contributor to blood pressure elevation and to the prevalence of hypertension [191]. The effect appears to be enhanced by a low dietary intake of potassium-

containing foods. Randomized controlled trials in hypertensive patients indicate that reducing sodium intake by 80–100 mmol (4.7–5.8 g) per day from an initial intake of around 180 mmol (10.5 g) per day will reduce blood pressure by an average of 4–6 mmHg [192] or even more if combined with other dietary counselling [193], and enhance the blood-pressure-lowering effect of medication. 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. Counselling by trained dietitians may be useful. Hypertensive patients should also be advised to eat more fruit and vegetables [194], to eat more fish [195] and to reduce their intake of saturated fat and cholesterol. The recent DASH study has shown that such diet may influence other cardiovascular risk factors beneficially and lower blood pressure [196].

Pharmacological therapy

Introduction

Recommendations about pharmacological therapy are preceded by analysis of the available evidence (as provided by large randomized trials based on fatal and non-fatal events) of the benefits obtained by antihypertensive therapy and of the comparative benefits obtained by the various classes of agents. This is the strongest type of evidence available. However, it is commonly recognized that event-based randomized therapeutic trials have some limitations. These include the special selection criteria of the subjects randomized; the frequent selection of high-risk patients in order to increase the power of the trial, so that the vast majority of uncomplicated and lower risk hypertensives are rarely represented. The therapeutic programmes used often diverge from usual therapeutic practice; stringent follow-up procedures enforce patients' compliance well beyond that obtained in common medical practice. Perhaps the most important limitation is the necessarily short duration of a controlled trial (in most cases 4–5 years), whereas additional life expectancy, and hence expectancy of therapeutic duration, for a middle-aged hypertensive is 20–30 years [34,197]. Long-term therapeutic benefits, and long-term differences between benefits of various drug classes may also be evaluated by using intermediate endpoints (i.e. subclinical organ damage changes). These evaluations do not provide the same weight of evidence as 'hard' endpoints, such as fatal and non-fatal myocardial infarction or stroke, and cardiovascular or all-cause mortality, but several of the recent event-based trials have also used 'softer' endpoints, such as congestive heart failure (certainly clinically relevant, but often based on subjective diagnosis), hospitalization, angina pectoris and coronary revascularization (the latter highly subjected to local clinical habits and facilities), etc. Admittedly, evidence that regression or retardation of subclinical organ damage is

associated with a reduction of cardiovascular events is largely indirect, but a large body of evidence is available that some of these alterations have predictive value of subsequent fatal and non-fatal events (see above). Therefore, evidence from the major randomized studies on intermediate endpoints has been summarized. Treatment-induced alterations of metabolic parameters, such as serum LDL- or HDL-cholesterol, serum potassium, glucose tolerance, induction or worsening of the metabolic syndrome or diabetes, although they can hardly be expected to increase cardiovascular event incidence during the short term of a trial, may have an impact during the longer course of the patient's life, and for this reason they are taken into account when assessing total cardiovascular risk.

Box 9 Position statement: Values and limitations of event-based clinical randomized trials

Values

- Randomization is the safest procedure to avoid bias.
- Large number of patients guarantees power to detect differences in primary endpoint.
- Most events used as endpoints are well-defined events of clinical relevance.

Limitations

- Selection of patients (most often patients at elevated cardiovascular risk): extrapolation to patients at a different risk level is doubtful.
- Most trials are not powered for secondary endpoints.
- Therapeutic programmes in trials often diverge from those followed in clinical practice.
- Compliance of patients in trials is much higher than in clinical practice.
- Controlled randomized trials last for 4–5 years, whereas life expectation in middle-aged hypertensives is of 20–30 years.

Trials based on mortality and morbidity endpoints comparing active treatment with placebo

Most of these outcome trials have been subjected to meta-analyses, either to arrive at more precise and generalizable conclusions, or to answer questions on subgroups, which could not be addressed in individual studies [198]. Table 6 summarizes the results of meta-analyses of trials performed in mostly systolic–diastolic hypertension [5,199] and in elderly patients with isolated systolic hypertension [200]. Antihypertensive

Table 6 Relative risk reduction of fatal events and combined fatal and non-fatal events in patients on active antihypertensive treatment versus placebo or no treatment

	Systolic–diastolic hypertension		Isolated systolic hypertension	
	Risk reduction	<i>P</i>	Risk reduction	<i>P</i>
Mortality				
all cause	–14%	<0.01	–13%	0.02
cardiovascular	–21%	<0.001	–18%	0.01
non-cardiovascular	–1%	NS		NS
Fatal and non-fatal events				
stroke	–42%	<0.001	–30%	<0.001
coronary	–14%	<0.01	–23%	<0.001

treatment resulted in significant and similar reductions of cardiovascular and all-cause mortality in both types of hypertension. With regard to cause-specific mortality, Collins *et al.* [5] observed a significant reduction in fatal stroke (–45%; $P < 0.001$), but not in fatal coronary heart disease (–11%; NS). This could be related to age because coronary mortality was significantly reduced by 26% ($P < 0.01$) in a meta-analysis on elderly with systolic–diastolic hypertension [201]. Fatal and non-fatal strokes combined, and all coronary events, were significantly reduced in the two types of hypertension. The Blood Pressure Lowering Treatment Trialists collaboration [163] performed separate meta-analyses of placebo-controlled trials in which active treatment was initiated by a calcium antagonist or by an ACE inhibitor, and showed that the reductions in cardiovascular endpoints were similar to those found in the trials in which active treatment was based on diuretics or β -blockers.

Risk for cardiovascular events, particularly coronary heart disease, differs greatly between men and women. It is unclear from individual intervention trials whether the effect of antihypertensive treatment in reducing cardiovascular risk depends on gender. This issue was explored by the INDANA working group, based on a meta-analysis of individual patient data from seven randomized controlled trials [202]. The total number of individuals was 40 777, of whom 49% were men. In men, odds ratios favouring treatment were statistically significant for all-cause (–12%; $P = 0.01$), stroke (–43%; $P < 0.001$) and coronary mortality (–17%; $P < 0.01$) and all fatal and non-fatal cardiovascular events (–22%, $P = 0.001$), strokes (–34%; $P < 0.001$) and coronary events (–18%; $P < 0.001$). In women, whose event rates were, in general, lower than in men, odds ratios favouring treatment were statistically significant for fatal strokes (–29%; $P < 0.05$) and for combined fatal and non-fatal cardiovascular events (–26%; $P = 0.001$) and strokes (–38%; $P < 0.001$), but not for other outcomes. However, the risk ratios between the treated and control groups did not differ between men and women, regardless of outcome, and there were no significant interactions between treatments effect and gender, so that the proportional reduction of the cardio-

vascular risk appears to be similar in women and in men.

Additional information has more recently been provided by other trials, not yet included in the previously mentioned meta-analysis. In SCOPE [203] 4973 older hypertensive patients were randomized to the angiotensin II antagonist, candesartan, or placebo. Since antihypertensive treatment other than study drugs could be given to all patients for better blood pressure control, the study ended as a comparison between candesartan and a control group receiving other antihypertensive drugs. The blood pressure reduction was slightly better in the candesartan group (3.2/1.6 mmHg), in which the incidence of the primary composite endpoint (stroke, myocardial infarction, cardiovascular death) tended to be somewhat lower (–11%; $P = 0.19$), and the secondary endpoint of non-fatal stroke was significantly reduced (–28%, $P = 0.04$). Other placebo-controlled trials addressed the effect of the angiotensin receptor antagonists losartan [204] and irbesartan [205,206] in patients with diabetes type 2 and nephropathy. All studies concluded that the drug treatment was renoprotective (see below) but that there was no evidence of benefit in secondary cardiovascular endpoints (for the evaluation of which, however, these trials had insufficient power). It can be concluded from these recent placebo-controlled trials that blood pressure lowering by angiotensin II antagonists can also be beneficial, particularly in stroke prevention, and, in patients with diabetic nephropathy, in slowing progression of renal disease.

Trials based on mortality and morbidity endpoints comparing treatments initiated by different drug classes

During the past 5 years many controlled randomized trials have compared antihypertensive regimens initiated with different classes of antihypertensive agents, most often comparing older (diuretics and β -blockers) with newer agents (calcium antagonists, ACE inhibitors, angiotensin receptor antagonists, α -blockers), and occasionally comparing newer drug classes. Nine trials [100,167,207–213], with 67 435 randomized patients, comparing calcium antagonists with older drugs have been reviewed recently by Staessen and Wang [214].

For none of the outcomes considered in this analysis, including all-cause and cardiovascular mortality, all cardiovascular events, stroke, myocardial infarction and heart failure, did the *P*-values for heterogeneity reach statistical significance ($0.11 \leq P \leq 0.95$). The pooled odds ratios expressing the possible benefit of calcium antagonists over old drugs were close to unity and non-significant for total mortality (0.98, 95% confidence interval 0.92–1.03, $P = 0.42$), cardiovascular mortality (1.03, 95% confidence interval 0.95–1.11, $P = 0.51$), all cardiovascular events (1.03, 95% confidence interval 0.99–1.08, $P = 0.15$) and myocardial infarction (1.02, 95% confidence interval 0.95–1.10, $P = 0.61$). Calcium antagonists provided slightly better protection against fatal and non-fatal stroke than old drugs. For the nine trials combined, the odds ratio for stroke was 0.92 (95% confidence interval 0.84–1.01, $P = 0.07$). It reached formal significance (0.90, 95% confidence interval 0.82–0.98, $P = 0.02$) when CONVINCENCE [213], a large trial based on verapamil, was excluded. For heart failure, calcium antagonists appeared to provide less protection than conventional therapy, regardless of whether (1.33, 95% confidence interval 1.22–1.44, $P < 0.0001$) or not (1.33, 95% confidence interval 1.22–1.46, $P < 0.0001$) CONVINCENCE was incorporated in the pooled estimates.

Staessen and Wang [214] have also reviewed five trials with 46 553 randomized patients comparing ACE inhibitors with old drugs [167,209,215–217]. The pooled odds ratios expressing the possible benefit of ACE inhibitors over conventional therapy were close to unity and non-significant for total mortality (1.00, 95% confidence interval 0.94–1.06, $P = 0.88$), cardiovascular mortality (1.02, 95% confidence interval 0.94–1.11, $P = 0.62$), all cardiovascular events (1.03, 95% confidence interval 0.94–1.12, $P = 0.59$), myocardial infarction (0.97, 95% confidence interval 0.90–1.04, $P = 0.39$) and heart failure (1.04, 95% confidence interval 0.89–1.22, $P = 0.64$). Compared with old drugs, ACE inhibitors provided slightly less protection against stroke, with a pooled odds ratio of 1.10 (95% confidence interval 1.01–1.20, $P = 0.03$). For all-cause and cardiovascular mortality, stroke and myocardial infarction, *P*-values for heterogeneity among the trials of ACE inhibitors were non-significant ($0.16 \leq P \leq 0.88$). In contrast, for all cardiovascular events ($P = 0.006$) and heart failure ($P = 0.04$) heterogeneity was significant due to the ALLHAT [167] findings. Compared with chlorthalidone, ALLHAT patients allocated lisinopril had a greater risk of stroke (1.15, 95% confidence interval 1.02–1.30, $P = 0.02$), heart failure (1.19, 95% confidence interval 1.07–1.31, $P < 0.001$), and hence combined cardiovascular disease (1.10, 95% confidence interval 1.05–1.16 $P < 0.001$) [167]. Similar findings were reported previously for the comparison of the α -blocker doxazosin with chlorthalidone, an ALLHAT arm that was interrupted prematurely [166].

Although ALLHAT [167] stands out as the largest double-blind trial undertaken in hypertensive patients, interpretation of its results is difficult for several reasons, which may account for the heterogeneity of ALLHAT results with respect with those of the other trials:

1. In ALLHAT, 90% of the patients at randomization were already on antihypertensive treatment, most often diuretics; thus, ALLHAT tested continuing a diuretic versus switching drug classes. Patients on diuretics with latent or compensated heart failure were deprived of their therapy when they were not randomized to chlorthalidone.
2. The achieved systolic pressure was higher on doxazosin (+2.0 mmHg), amlodipine (+1.1 mmHg) and lisinopril (2.3 mmHg, and 4 mmHg in African Americans) than on chlorthalidone. Presumably, these factors explain why the Kaplan–Meier curves started to diverge immediately after randomization for heart failure and approximately 6 months later also for stroke.
3. The sympatholytic agents used for step-up treatment (atenolol, clonidine and/or reserpine at the physician's discretion) led to a somewhat artificial treatment regimen, which does not reflect modern clinical practice, is not usually recommended and is known to potentiate the blood pressure response to diuretics much more than to ACE inhibitors or α -blockers.
4. ALLHAT did not include systematic end-point evaluation, which may have particularly affected evaluation of 'softer' endpoints, such as congestive heart failure.

These limitations notwithstanding, ALLHAT [166, 167], either alone or in combination with the other trials, supports the conclusion that the benefits of antihypertensive therapy depend largely on blood pressure lowering, thus confirming the preliminary findings of the interim meta-analysis of the Blood Pressure Lowering Treatment Trialists' Collaboration [163] and the opinion expressed in the 1999 WHO/ISH guidelines [2]. These conclusions are further confirmed by the recent results of the INVEST study (presented at the American College of Cardiology meeting, Chicago, 2003), which has compared the calcium antagonist verapamil often combined with an ACE inhibitor (trandolapril) to a β -blocker often combined with a diuretic, in hypertensive patients with coronary heart disease, without showing any significant differences in either primary (all cause death, non-fatal myocardial infarction and stroke) or secondary outcomes.

Two recent trials have studied the new class of angiotensin receptor antagonists. The LIFE trial [218]

has compared losartan with the β -blocker atenolol in hypertensive patients with left ventricular hypertrophy for an average of 4.8 years, and found a significant ($P = 0.021$) 13% reduction in major cardiovascular events, mostly due to a significant ($P = 0.001$) 25% reduction in stroke. There were no blood pressure differences between the treatment groups. The SCOPE trial [203] was initiated as a comparison of elderly patients receiving candesartan or placebo, but since, for ethical reasons, 85% of the placebo-initiated patients received antihypertensive therapy (mostly diuretics, β -blockers or calcium antagonists) the study is a comparison of antihypertensive treatment with or without candesartan. After 3.7 years of treatment there was a non-significant 11% reduction in major cardiovascular events, and a significant ($P = 0.04$) 28% reduction in non-fatal strokes among candesartan-treated patients, with an achieved blood pressure slightly lower (3.2/1.6 mmHg) in the candesartan group.

Randomized trials based on intermediate endpoints

Left ventricular hypertrophy. Many studies have tested the effects of various antihypertensive agents on hypertension-associated left ventricular hypertrophy, mostly evaluated by left ventricular mass on the echocardiogram, but only a few of them have followed strict-enough criteria to provide reliable information. Consequently, meta-analyses cannot provide indisputable evidence [219,220]. As studies in hypertensive patients with left ventricular hypertrophy cannot be placebo controlled but must compare active treatments, large number of patients must be included in order to have sufficient power to detect small between-treatment differences, and special precautions must be taken in order to prevent regression to the mean and reading bias if the sequence of scans is not blinded. The very few studies adhering to these strict criteria do not yet provide uncontroversial answers: the LIVE study [221] concludes for superiority of the diuretic indapamide over the ACE inhibitor enalapril after 12 months but not after 6 months; the ELVERA [222], PRESERVE [223] and FOAM studies [224] have shown equal regression with ACE inhibitors (lisinopril, enalapril and fosinopril, respectively) and with calcium antagonists (amlodipine, nifedipine and amlodipine, respectively); the CATCH study [225] has demonstrated equal regression with the angiotensin receptor antagonist, candesartan, and the ACE inhibitor, enalapril; and the ELSA study [226] has reported equal regression after 1 and 4 years with the calcium antagonist lacidipine and the β -blocker atenolol. A series of comparisons of different angiotensin receptor antagonists with the β -blocker atenolol have shown a significantly greater regression with angiotensin antagonists [227–229]. The beneficial effect of left ventricular hypertrophy regression has been documented by the observation that it is accompanied by an improvement of systolic function [230]. The large and long-term (5

years) LIFE Study [218] is particularly relevant, since, in line with Framingham [231] and HOPE data [232], the greater regression of electrocardiographically determined left ventricular hypertrophy with losartan was accompanied by a reduced incidence of cardiovascular events. The same findings were obtained in a LIFE substudy in which left ventricular hypertrophy was determined by echocardiography [233], thus confirming previous evidence from smaller series of patients [234,235]. It is interesting that in another recent study comparing losartan with atenolol (REGAAL [229]), although the difference between treatment-induced reductions in left ventricular mass index fell short of statistical significance, concentrations of natriuretic peptides were decreased by losartan and increased by atenolol, suggesting opposite effects on left ventricular compliance. Future studies should investigate treatment-induced effects on indices of collagen content or fibrosis of the ventricular wall, rather than on its mass only.

Arterial wall and atherosclerosis. Several randomized trials have compared the long-term (2–4 years) effects of different antihypertensive regimens on carotid artery wall intima–media thickness. There is uniform evidence of the beneficial action of calcium antagonists on this endpoint. A placebo-controlled study showed the superiority of amlodipine over placebo [236]; three studies have shown the superiority of calcium antagonist (isradipine [207], verapamil [98], nifedipine [237]) over diuretic therapy; and one study the superiority of the calcium antagonist, lacidipine, over the β -blocker, atenolol [100]. The latter study (ELSA [100]) was able to show a greater effect of lacidipine not only in slowing progression of intima–media thickness in the common carotid bifurcation, but also in plaque progression and regression. Until recently the evidence concerning ACE inhibitors appeared to be conflicting: one placebo-controlled trial showed no effect of ramipril on common carotid intima–media thickness [238], whereas another showed a significant slowing of intima–media thickness progression measured at the carotid bifurcation and internal carotid, as well as in the common carotid [239]. More recently, the results of the PHYL-LIS study have reconciled the observations of the two previous studies by reporting that the ACE inhibitor fosinopril prevents the progression of carotid intima–media thickness seen in patients treated with hydrochlorothiazide, but the effect is largely limited to the bifurcation, with no or minor changes in the common carotid wall [240].

Renal function. The most abundant evidence concerns renal function in diabetic patients. This has recently been reviewed [168]. In brief, the analysis of trials of more or less intensive blood pressure lowering, or of the addition of active versus placebo therapy, has shown

that, in diabetic patients with advanced nephropathy, progression of renal dysfunction can be slowed by adding an angiotensin receptor antagonist (losartan [204], or irbesartan [205]) rather than placebo (and a consequent difference of 3–4 mmHg in systolic blood pressure). Consistent effects of more intensive blood pressure lowering were found on urinary protein excretion, both overt proteinuria and microalbuminuria. According to this recent review [168], of the six trials in diabetic patients comparing treatments initiated by different agents, four (one of an ACE inhibitor versus a β -blocker [215]; one of a calcium antagonist versus a diuretic [212]; and two of an ACE inhibitor versus a calcium antagonist [156,241]) did not show a difference in the renal protective effect of the comparator drugs, whereas one indicated the angiotensin antagonist irbesartan to be superior to the calcium antagonist amlodipine in retarding development of renal failure [205], and the other indicated that the angiotensin antagonist losartan reduced incidence of new overt proteinuria better than the β -blocker atenolol [242]. The recent results of ALLHAT, a trial including 36% of patients with diabetes, was unable to detect differences in renal function (but data on proteinuria and microalbuminuria are not available) in the very large number of patients randomized to chlorthalidone, amlodipine or lisinopril, possibly as a consequence of the very good blood pressure control (134–136/75 mmHg) achieved in all groups [167].

In patients with non-diabetic renal disease, a recent meta-analysis of 11 randomized trials, comparing anti-hypertensive regimens including or excluding an ACE inhibitor [243], indicated a significantly slower progression in patients achieving blood pressure of 139/85 mmHg rather than 144/87 mmHg. However, it is not clear whether the benefit should be ascribed to ACE inhibition, as suggested by the authors [243], or to the lower blood pressure achieved. The recently completed AASK trial [244] failed to find any further reduction in the progress of renal dysfunction in African-American hypertensives with nephrosclerosis by reducing blood pressure to 128/78 rather than 141/85 mmHg, but ACE inhibitors were shown to be somewhat more effective than β -blockers [244] or calcium antagonists [245] in slowing the decline in glomerular filtration rate. Therefore, it appears that in patients with non-diabetic renal disease the use of an ACE inhibitor may be more important than aggressive blood pressure lowering, whereas in diabetic patients aggressive control of blood pressure may be as equally important as blockade of the renin–angiotensin system. Nonetheless, it appears prudent to lower blood pressure intensively in patients with non-diabetic renal disease also.

New onset diabetes. Trials that have monitored new onset diabetes during the treatment follow-up have

shown a lower incidence of new diabetes when an ACE inhibitor was used rather than placebo [155], when a calcium antagonist was used rather than a thiazide diuretic [212], when an ACE inhibitor was used rather than diuretics or β -blockers [216] and when an angiotensin receptor antagonist was used rather than a β -blocker [218,246] or usual therapy [203]. ALLHAT [167] has also reported lower incidences of new diabetes in patients randomized to amlodipine or lisinopril compared with those randomized to chlorthalidone.

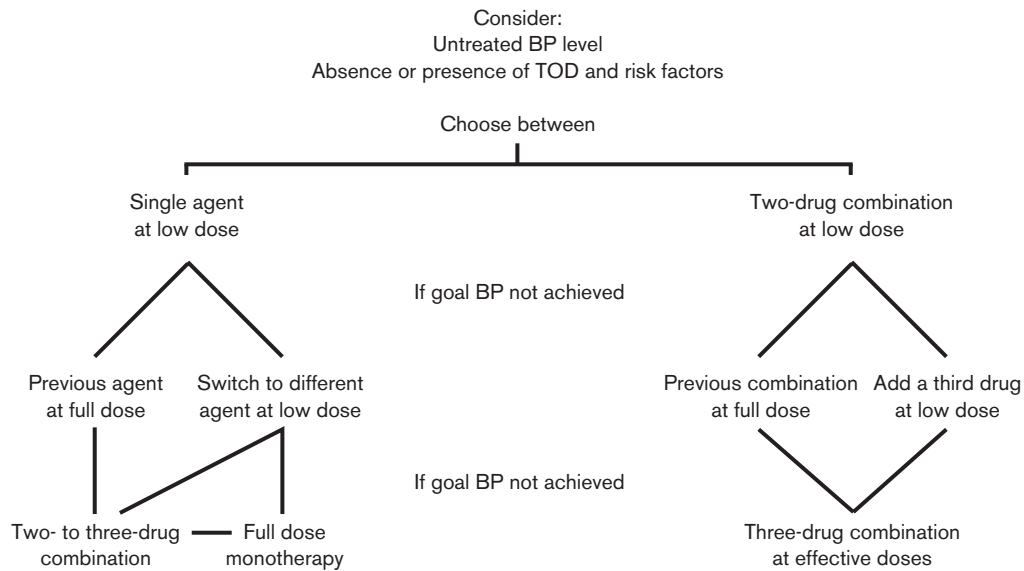
Therapeutic strategies

Principles of drug treatment: monotherapy versus combination therapy. In most, if not all, hypertensive patients, therapy should be started gradually, and target blood pressure values achieved progressively through several weeks. To reach such target blood pressures, it is likely that a large proportion of patients will require combination therapy with more than one agent. The proportion of patients requiring combination therapy will depend on baseline blood pressure values. In grade 1 hypertensives, monotherapy is likely to be successful more frequently. In ALLHAT, which recruited grade 1 and 2 hypertensives mostly on monotherapy, about 60% of the patients remained on monotherapy [167]. In the HOT study [160], which recruited grade 2 and 3 hypertensives after washout from previous medication, monotherapy was successful in only 25–40% of patients, according to the target diastolic blood pressure. In trials of diabetic patients the vast majority of patients were on at least two drugs, and in two recent trials on diabetic nephropathy [204,205] an average of 2.5 and 3.0 non-study drugs were required in addition to the angiotensin receptor antagonist used as study drug.

According to the baseline blood pressure and the presence or absence of complications, it appears reasonable to initiate therapy either with a low dose of a single agent or with a low dose combination of two agents (Fig. 2). Initiation of treatment by combination therapy was effectively tested in the VA study at the beginning of the antihypertensive treatment trial era [247,248] and recently in the PROGRESS study [154]. If low-dose monotherapy is chosen and blood pressure control is not achieved, the next step is to switch to a low dose of a different agent, or to increase the dose of the first compound chosen (with a greater possibility of causing adverse effects) or to move to combination therapy. If therapy has been initiated by a low-dose combination, a higher dose combination can subsequently be used or a low dose of a third compound added.

The advantage of starting with low dose monotherapy and, if the initial compound is not well tolerated, switching to another agent is that of being able to find the drug to which any individual patient best responds

Fig. 2



Choice between monotherapy and combination therapy. BP, blood pressure; TOD, target organ damage.

(both in terms of efficacy and tolerability); but unless pharmacogenomics provides help in the future, the procedure is laborious and frustrating for both doctors and patients, and may lead to low compliance.

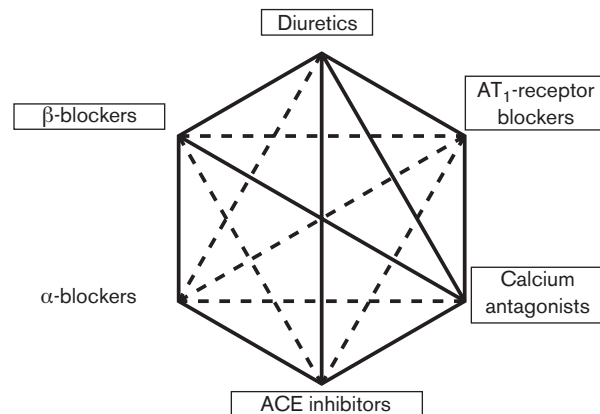
An obvious disadvantage of initiating with two drugs, even if at a low dose, is that of potentially exposing the patient to an unnecessary agent, but the advantages are that: (1) by using two drugs with different mechanisms of action, it is more likely that blood pressure and its complications are controlled; (2) by using combinations, both the first and second drugs can be given in the low

dose range that is more likely to be free of side-effects; (3) fixed low-dose combinations are available in Europe as well as in other parts of the world, allowing the administration of two agents within a single tablet, thus optimizing compliance.

The following two-drug combinations have been found to be effective and well tolerated (Fig. 3):

- diuretic and β -blocker;

Fig. 3



Possible combinations of different classes of antihypertensive agents. The most rational combinations are represented as thick lines. ACE, angiotensin-converting enzyme. The frames indicate classes of antihypertensive agents proven to be beneficial in controlled interventional trials.

Box 10 Position statement: Monotherapy versus combination therapy

- In most, if not all, hypertensive patients, therapy should be started gradually, and target blood pressure values achieved progressively through several weeks.
- To reach target blood pressure, it is likely that a large proportion of patients will require combination therapy with more than one agent.
- According to the baseline blood pressure and the presence or absence of complications, it appears reasonable to initiate therapy either with a low dose of a single agent or with a low-dose combination of two agents.
- There are advantages and disadvantages with either approach.

- diuretic and ACE inhibitor or angiotensin receptor antagonist;
- calcium antagonist (dihydropyridine) and β -blocker;
- calcium antagonist and ACE inhibitor or angiotensin receptor antagonist;
- calcium antagonist and diuretic;
- α -blocker and β -blocker;
- other combinations (e.g. with central agents, including α_2 -adrenoreceptor agonists and imidazoline I₂ receptor modulators, or between ACE inhibitors and angiotensin receptor antagonists) can be used if necessary, and three or four drugs may be required in many cases.

The use of long-acting drugs or preparations providing 24-h efficacy on a once-daily basis is recommended. The advantages of such medications include improvement in adherence to therapy and minimization of blood pressure variability, thus possibly providing greater protection against the risk of major cardiovascular events and the development of target-organ damage [249,250].

Particular attention should be given to adverse events, even purely subjective disturbances, because they may be an important cause of non-compliance. The patients should always be asked about adverse effects, and dose or drug changes made accordingly. Some adverse effects have a similar incidence for all compounds of the same class (e.g. cough for ACE inhibitors), whereas for other adverse events there may be compounds within the same drug class less prone to induce them (e.g. among β -blockers less fatigue or Raynaud's phenomenon with vasodilating compounds; among calcium antagonists no constipation with dihydropyridines, no tachycardia with verapamil and diltiazem).

Choice of antihypertensive drugs. The large number of randomized trials, both those comparing active treatment versus placebo and those comparing active treatment regimens based on different compounds (see above), clearly confirm the conclusions of the previous guidelines of the European societies [3,4] and of the WHO/ISH [2], that the main benefits of antihypertensive therapy are due to lowering of blood pressure *per se*, largely independently of the drugs used to lower blood pressure.

However, there is also evidence that specific drug classes may differ in some effect or in special groups of patients. For example, angiotensin receptor antagonists appear more effective in preventing stroke than β -blockers [218] or usual therapy [203], particularly in patients with left ventricular hypertrophy [219] or the elderly [203]; thiazide diuretics, either alone or in combination, may be more useful than some other agents in preventing congestive heart failure [212,167];

ACE inhibitors and angiotensin receptor antagonists have been shown to retard progress of renal deterioration in diabetic and non-diabetic nephropathy [204–206,243–245]; angiotensin receptor antagonists seem more effective than β -blockers in regressing left ventricular hypertrophy [218,227–229]; calcium antagonists have been shown to be more effective than diuretics [98,207,237] or β -blockers [100], and ACE inhibitors more effective than a diuretic [240] in slowing progression of carotid atherosclerosis. Finally, drugs are not equal in terms of adverse disturbances, particularly in individual patients, and the patient's preference is a prerequisite for compliance and the success of therapy.

Therefore, it can be concluded that the major classes of antihypertensive agents: diuretics, β -blockers, calcium antagonists, ACE inhibitors and angiotensin receptor antagonists, are suitable for the initiation and maintenance of antihypertensive therapy. Although the interruption of the only trial testing an α -blocker (the doxazosin arm of the ALLHAT trial [166]) has been criticized, evidence favouring the use of α -blockers is more scanty than evidence of the benefits of other antihypertensive agents, but α -blockers too can be

Box 11 Position statement: Choice of antihypertensive drugs

- The main benefits of antihypertensive therapy are due to lowering of blood pressure *per se*.
- There is also evidence that specific drug classes may differ in some effect, or in special groups of patients.
- Drugs are not equal in terms of adverse disturbances, particularly in individual patients.
- The major classes of antihypertensive agents – diuretics, β -blockers, calcium antagonists, ACE inhibitors, angiotensin receptor antagonists – are suitable for the initiation and maintenance of therapy.
- Emphasis on identifying the first class of drugs to be used is probably outdated by the need to use two or more drugs in combination in order to achieve goal blood pressure.
- Within the array of available evidence, the choice of drugs will be influenced by many factors, including:
 - previous experience of the patient with antihypertensive agents;
 - cost of drugs;
 - risk profile, presence or absence of target organ damage, clinical cardiovascular or renal disease or diabetes;
 - patient's preference.

considered, particularly for combination therapy. Central agents, α_2 -adrenoreceptors agonists and modulators of imidazoline I_2 receptors, may also be helpful in combination therapy. Emphasis on identifying the first class of drugs to be used is probably outdated by the awareness that two or more drugs in combination are necessary in the majority of patients, particularly those with higher initial blood pressures or target organ damage or associated diseases, in order to achieve goal blood pressure.

Within the array of available agents, the choice of drugs will be influenced by many factors, including:

1. The previous, favourable or unfavourable, experience of the individual patient with a given class of compounds.
2. The cost of drugs, either to the individual patient or to the health provider, although cost considerations should not predominate over efficacy and tolerability in any individual patient.

3. The cardiovascular risk profile of the individual patient.
4. The presence of target organ damage, of clinical cardiovascular disease, renal disease and diabetes.
5. The presence of other coexisting disorders that may either favour or limit the use of particular classes of antihypertensive drugs.
6. The possibility of interactions with drugs used for other conditions present in the patient.

The physician should tailor the choice of drugs to the individual patient, after taking all these factors, together with patient preference, into account. Indications and contraindications of specific drug classes are listed in Table 7, and therapeutic approaches to be preferred in special conditions are discussed in the next section.

Therapeutic approaches in special conditions

Elderly

There is little doubt from randomized controlled trials

Table 7 Indications and contraindications for the major classes of antihypertensive drugs

Class	Conditions favouring the use	Contraindications	
		Compelling	Possible
Diuretics (thiazides)	Congestive heart failure; elderly hypertensives; isolated systolic hypertension; hypertensives of African origin	Gout	Pregnancy
Diuretics (loop)	Renal insufficiency; congestive heart failure		
Diuretics (anti-aldosterone)	Congestive heart failure; post-myocardial infarction	Renal failure; hyperkalaemia	
β -Blockers	Angina pectoris; post-myocardial infarction; congestive heart failure (up-titration); pregnancy; tachyarrhythmias	Asthma; chronic obstructive pulmonary disease; A-V block (grade 2 or 3)	Peripheral vascular disease; glucose intolerance; athletes and physically active patients
Calcium antagonists (dihydropyridines)	Elderly patients; isolated systolic hypertension; angina pectoris; peripheral vascular disease; carotid atherosclerosis; pregnancy		Tachyarrhythmias; congestive heart failure
Calcium antagonists (verapamil, diltiazem)	Angina pectoris; carotid atherosclerosis; supraventricular tachycardia	A-V block (grade 2 or 3); congestive heart failure	
Angiotensin-converting enzyme (ACE) inhibitors	Congestive heart failure; LV dysfunction; post-myocardial infarction; non-diabetic nephropathy; type 1 diabetic nephropathy; proteinuria	Pregnancy; hyperkalaemia; bilateral renal artery stenosis	
Angiotensin II receptor antagonists (AT_1 -blockers)	Type 2 diabetic nephropathy; diabetic microalbuminuria; proteinuria; left ventricular hypertrophy; ACE-inhibitor cough	Pregnancy; hyperkalaemia; bilateral renal artery stenosis	
α -Blockers	Prostatic hyperplasia (BPH); hyperlipidaemia	Orthostatic hypotension	Congestive heart failure

A-V, atrioventricular; LV, left ventricular.

**Box 12 Position statement:
Antihypertensive therapy in the elderly**

- There is little doubt from randomized controlled trials that older patients with systolic–diastolic or with isolated systolic hypertension benefit from antihypertensive treatment in terms of reduced cardiovascular morbidity and mortality.
- Initiation of antihypertensive treatment in elderly patients should follow the general guidelines, but should be particularly gradual, especially in frail individuals.
- Blood pressure measurement should also be performed in the erect posture, to exclude patients with marked postural hypotension from treatment and to evaluate postural effects of treatment.
- Many elderly patients will have other risk factors, target organ damage and associated cardiovascular conditions, to which the choice of the first drug should be tailored.
- Many elderly patients need two or more drugs to control blood pressure, particularly since it is often difficult to lower systolic blood pressure to below 140 mmHg.
- In subjects aged 80 years and over, a recent meta-analysis concluded that fatal and non-fatal cardiovascular events, but not mortality, are reduced by antihypertensive therapy.

that older patients benefit from antihypertensive treatment in terms of reduced cardiovascular morbidity and mortality, irrespective of whether they have systolic–diastolic hypertension or isolated systolic hypertension [199,200]. Whereas trials in the elderly usually include patients who are at least 60 years old, a recent meta-analysis concluded that fatal and non-fatal cardiovascular events combined were significantly reduced in participants in randomized, controlled trials of antihypertensive drug treatment aged 80 years and over, but all-cause mortality was not reduced [251]. The larger randomized controlled trials of antihypertensive treatment versus placebo or no treatment in elderly patients with systolic–diastolic hypertension used a diuretic or a β -blocker as first-line therapy [201]. In trials of isolated systolic hypertension, first-line drugs comprised a diuretic [14] or a dihydropyridine calcium-channel blocker [15]. Treatment was initiated with the latter drug class in two less orthodox Chinese trials, one in systolic–diastolic hypertension [252] and the other in isolated systolic hypertension [253]. In all these trials, active therapy was superior to placebo or no treatment. Other drug classes have only been used in trials in which ‘newer’ drugs were compared with ‘older’ drugs. The STOP-2 trial [209] found that the incidence of cardiovascular events was similar in elderly hypertensives

randomized to a calcium antagonist, an ACE inhibitor, or to conventional treatment with a diuretic and/or a β -blocker, and ALLHAT [167] showed that a diuretic, a calcium antagonist and an ACE inhibitor influenced cardiovascular events to the same extent in patients older than 65 years. The LIFE trial [218] showed that, in 55- to 80-year-old hypertensive patients with evidence of left ventricular hypertrophy, the angiotensin receptor antagonist losartan was more effective in reducing cardiovascular events, particularly stroke, than the β -blocker atenolol; and this was also true for patients with isolated systolic hypertension [254]. SCOPE [203] showed a reduction in non-fatal strokes in hypertensive patients aged 70 years or older treated with an antihypertensive regimen containing the angiotensin receptor antagonist candesartan, in comparison with patients receiving an antihypertensive treatment without candesartan. Therefore, it appears that benefit has been shown in older patients for at least one representative agent of several drug classes, i.e. diuretics, β -blockers, calcium antagonists, converting enzyme inhibitors and angiotensin receptor antagonists.

Initiation of antihypertensive treatment in elderly patients should follow the general guidelines. Many patients will have other risk factors, target organ damage and associated cardiovascular conditions, to which the choice of the first drug should be tailored. Furthermore, many patients will need two or more drugs to control blood pressure, particularly since it is often difficult to lower systolic pressure to below 140 mmHg [165,255]. The optimal diastolic blood pressure is less clear. In an important *post-hoc* analysis, the SHEP investigators assessed the role of the on-treatment diastolic blood pressure in patients with isolated systolic hypertension [256]. They concluded that an achieved diastolic pressure of less than 70 mmHg, and especially below 60 mmHg, identifies a high-risk group that has a poorer outcome. These patients may have been overtreated. Further studies are needed to determine how far diastolic blood pressure can be lowered in elderly patients with isolated systolic hypertension and uncontrolled systolic blood pressure on therapy.

Diabetes mellitus

The prevalence of hypertension is increased in patients with diabetes mellitus [257]. The main forms of hyperglycaemic disorders consist of type 1 diabetes (B-cell destruction, usually leading to absolute insulin deficiency) and type 2 diabetes (ranging from predominantly insulin resistance with relative insulin deficiency to predominantly insulin secretory defect with insulin resistance) [258]. Type 2 diabetes is by far the most common form, occurring about 10–20 times as often as type 1 [259]. Hypertensive patients frequently exhibit a condition known as ‘metabolic syndrome’, associating insulin resistance (with the concomitant hyperinsulinae-

mia), central obesity and characteristic dyslipidaemia (high plasma triglycerides and low high-density lipoprotein cholesterol) [37,260]. These patients are prone to develop type 2 diabetes [261].

In type 1 diabetes, hypertension often reflects the onset of diabetic nephropathy [262] whereas a large fraction of hypertensive patients still have normoalbuminuria at the time of diagnosis of type 2 diabetes [263]. The prevalence of hypertension (defined as a blood pressure $\geq 140/90$ mmHg) in patients with type 2 diabetes and normoalbuminuria is very high (71%), and increases even further, to 90% in the presence of microalbuminuria [264]. The coexistence of hypertension and diabetes mellitus (either of type 1 or 2) substantially increases the risk of macrovascular complications, including stroke, coronary heart disease, congestive heart failure and peripheral vascular disease, and is responsible for an excessive cardiovascular mortality [262,265]. The presence of microalbuminuria is both an early

marker of renal damage and an indicator of increased cardiovascular risk [266,267]. Also there is evidence that hypertension accelerates the development of diabetic retinopathy [268]. The level of blood pressure achieved during treatment influences greatly the outcome of diabetic patients. In patients with diabetic nephropathy, the rate of progression of renal disease is in a continuous relationship with blood pressure down to levels of 130 mmHg systolic and 70 mmHg diastolic [269,270]. Aggressive treatment of hypertension protects patients with type 2 diabetes against cardiovascular events. As mentioned above, the primary goal of antihypertensive treatment in diabetics should be to lower blood pressure below 130/80 mmHg whenever possible, the optimal blood pressure being the lowest one that remains tolerated.

Weight gain is a critical factor in the progression to type 2 diabetes [271]. A key component of management is to avoid overweight by all the means indicated above, particularly by calorie restriction and a decrease in sodium intake, as a strong relationship exists between obesity, hypertension, sodium sensitivity and insulin resistance [272].

No major trial has been performed to assess the effect of blood pressure lowering on cardiovascular morbidity and mortality in hypertensive patients with type 1 diabetes. However, there is good evidence that β -blocker- and diuretic-based antihypertensive therapy delays the progression of nephropathy in these patients [273]. In albuminuric patients with type 1 diabetes, the best protection against renal function deterioration is provided by ACE inhibition [274]. It remains unknown whether angiotensin II receptor antagonists are equally effective in this indication.

In type 2 diabetes, the effects of antihypertensive drugs on cardiovascular complications have been compared in several controlled randomized trials, that have been reviewed recently [168]. Evidence for the superiority or inferiority of different drug classes is still vague and contradictory. Unfortunately, most of the comparisons have been made in relatively small studies, or substudies of larger trials, each without adequate power of testing for the relatively small differences to be expected. Superiority of ACE inhibitors in preventing the aggregate of major cardiovascular events is limited to two trials, one against diuretics/ β -blockers [216], the other against a calcium antagonist [162], or in analyses of cause-specific events for which the trial power was even less. ALLHAT [167] has also failed to find differences in cardiovascular outcomes in the large number of type 2 diabetics included in that trial randomized to a diuretic, a calcium antagonist or an ACE inhibitor. Recent evidence with angiotensin II receptor antagonists has shown a significant reduction

**Box 13 Position statement:
Antihypertensive therapy in diabetics**

- Non-pharmacological measures (particularly weight loss and reduction in salt intake) should be encouraged in all patients with type 2 diabetes, independently of the existing blood pressure. These measures may suffice to normalize blood pressure in patients with high normal or grade 1 hypertension, and can be expected to facilitate blood pressure control by antihypertensive agents.
- The goal blood pressure to aim at during behavioural or pharmacological therapy is below 130/80 mmHg.
- To reach this goal, most often combination therapy will be required.
- It is recommended that all effective and well-tolerated antihypertensive agents are used, generally in combination.
- Available evidence indicates that renoprotection benefits from the regular inclusion in these combinations of an ACE inhibitor in type 1 diabetes and of an angiotensin receptor antagonist in type 2 diabetes.
- In type 2 diabetic patients with high normal blood pressure, who may sometimes achieve blood pressure goal by monotherapy, the first drug to be tested should be a blocker of the renin-angiotensin system.
- The finding of microalbuminuria in type 1 or 2 diabetics is an indication for antihypertensive treatment, especially by a blocker of the renin-angiotensin system, irrespective of the blood pressure values.

of cardiovascular events, cardiovascular death and total mortality in diabetics when losartan was compared with atenolol [242]. If renal endpoints are also considered (see above), the benefits of angiotensin II receptor antagonists become more evident. IDNT [205] showed a reduction in renal dysfunction and failure by the use of irbesartan rather than amlodipine, and LIFE [242] indicated that losartan reduced the incidence of new proteinuria better than atenolol.

In conclusion, in view of the consensus that blood pressure in type 2 diabetic patients must be lowered, whenever possible, to <130/80 mmHg, it appears reasonable to recommend that all effective and well-tolerated antihypertensive agents can be used, generally in combination. Available evidence suggests that renoprotection may benefit from the regular inclusion of an angiotensin receptor antagonist in these combinations and that, in patients with high normal blood pressure, who may sometimes achieve blood pressure goal by monotherapy, the first drug to be used should be an angiotensin II receptor antagonist. Finally, the finding of microalbuminuria in type 1 or 2 diabetics is an indication for antihypertensive treatment, especially by a blocker of the renin-angiotensin system, irrespective of the blood pressure values.

Concomitant cerebrovascular disease

Evidence of the benefits of antihypertensive therapy in patients who had already suffered a stroke or a transient ischaemic attack (secondary prevention) was equivocal, and no definite recommendation could be given until the recent publication of trials which clearly showed the benefits of lowering blood pressure in patients with previous episodes of cardiovascular disease, even when their initial blood pressure was in the normal range. The randomized, double-blind placebo-controlled PATS trial [275] demonstrated that in 5665 patients with a transient ischaemic attack or a history of stroke without severe disability, blood pressure reduction of 5/2 mmHg by diuretic-based treatment (indapamide) reduced the incidence of total stroke by 29% ($P < 0.001$), with 3-year absolute benefit of 29 events per 1000 participants; the results were similar in normotensive and hypertensive patients. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) [154] was also designed to determine the effects of a blood-pressure-lowering regimen in hypertensive and non-hypertensive patients with a history of stroke or transient ischaemic attack (in stable clinical conditions). Active treatment, which comprised a flexible regimen based on an ACE inhibitor, with the addition of indapamide at the discretion of the treating physician, reduced the recurrency of stroke by 28% ($P < 0.0001$) and the incidence of all cardiovascular events by 26% ($P < 0.0001$). There were similar reduc-

tions in the risk of stroke and cardiovascular events in hypertensive and non-hypertensive subgroups (all $P < 0.01$).

Whether elevated blood pressure in acute stroke should be lowered, or to what extent, and how, is still disputed, and there are more questions than answers, but trials are in progress. A statement by a special ISH panel has been published recently [276].

Concomitant coronary heart disease and congestive heart failure

The risk of a recurrent event in patients with coronary heart disease is significantly affected by the blood pressure level [277], and hypertension is frequently a past or present clinical problem in patients with congestive heart failure [278]. However, only a few trials have tested the effects of blood pressure lowering in patients with coronary heart disease or congestive heart failure. The HOT Study showed a significant reduction of strokes the lower was the target blood pressure in hypertensives with previous signs of ischaemic heart disease, and found no evidence of a J-shaped curve [160,164]. The recent INVEST study has shown patients with known coronary heart disease to have similar incidences of new coronary events when treated with a regimen based on verapamil (plus eventually an ACE inhibitor) or a regimen based on a β -blocker (plus eventually a diuretic).

Apart from the INVEST study, many of the more common blood-pressure-lowering agents have been assessed in patients with coronary heart disease or heart failure with objectives other than reduction of blood pressure. β -blockers, ACE inhibitors and anti-aldosterone compounds are well established in the treatment regimens for preventing cardiovascular events and prolonging life in patients after an acute myocardial infarction and with heart failure [279–284], but how much of the benefit is due to concomitant blood pressure lowering and how much to specific drug actions has never been clarified [285]. The large majority (80%) of participants in the HOPE study had coronary heart disease. In these patients, treatment with an ACE inhibitor on top of other medication markedly reduced cardiovascular events and deaths compared to placebo [155], but here blood pressure lowering may have played a major role, an argument supported by the recent evidence in ALLHAT of similar incidence of coronary endpoints in patients treated with a thiazide or a calcium antagonist or an ACE inhibitor (more than 50% of ALLHAT participants had history or signs of atherosclerotic cardiovascular disease) [167]. ALLHAT has also shown thiazide diuretics to be superior to a dihydropyridine calcium antagonist and to an ACE inhibitor in prevention of congestive heart failure [167], but the super-

iority of the diuretic over the ACE inhibitor may largely depend on less good blood pressure control (especially in African Americans) in the ACE inhibitor (prescribed without a diuretic according to the study design) group [286,287]. The diagnosis of congestive heart failure in ALLHAT has also been questioned [286]. There are also data in support of the use of angiotensin receptor antagonists in congestive heart failure as alternatives to ACE inhibitors, especially in patients intolerant of ACE inhibitors, or in combination with ACE inhibitors [288,289]. The role of calcium antagonists in prevention of coronary events has been vindicated [290] by ALLHAT, which showed that therapy with a long-acting dihydropyridine had efficacy equal to that with the other antihypertensive agents [167]. Calcium antagonists appear to be less effective in prevention of congestive heart failure, but a long-acting dihydropyridine may be used if hypertension is resistant to other agents [291].

Hypertensive patients with deranged renal function

Renal vasoconstriction is found at the initial stages of essential hypertension and this is reversed by the administration of calcium-channel blockers and ACE inhibitors [292]. In more advanced stages of the disease, renal vascular resistance is permanently elevated as a consequence of structural lesions of the renal vessels (nephrosclerosis). Before antihypertensive treatment became available, renal involvement was frequent in patients with primary hypertension. In 1955 Perera reported that proteinuria was present in 42%, and chronic renal failure in 18%, of a series of 500 patients he had followed until death [293]. In this series, life expectancy after the onset of renal involvement was reported to be no more than 5–7 years. As discussed above, renal protection in diabetes has two main prerequisites: first, to attain very strict blood pressure control (<130/80 mmHg; and even lower, <125/75 mmHg, when proteinuria > 1 g/day is present); and, secondly, to lower proteinuria or albuminuria (micro- or macro-) to values as near to normal as possible. In order to attain the latter goal, blockade of the effects of angiotensin II (either with an ACE inhibitor or with an angiotensin II receptor blocker) is required. In order to achieve the blood pressure goal, combination therapy is often required even in patients with high normal blood pressure [168]. The addition of a diuretic as second-step therapy is usually recommended (a loop diuretic if serum creatinine > 2 mg/l is present), but other combinations, in particular with calcium antagonists, can also be considered. To prevent or retard development of nephrosclerosis, at least in Afro-American hypertensives, blockade of the renin–angiotensin system has been reported to be more important than attaining very low blood pressure [244], but whether this also applies to retardation of non-diabetic renal failure in other ethnic groups is more uncertain. On the whole, it seems

prudent to start antihypertensive therapy in patients (diabetic or non-diabetic) with reduced renal function, especially if accompanied by proteinuria, using an ACE inhibitor or an angiotensin receptor antagonist, and then to add other antihypertensive agents in order to lower blood pressure intensively. A recent study suggests that dual blockade of the renin–angiotensin system (by an ACE inhibitor and an angiotensin receptor antagonist) is quite effective in lowering blood pressure and proteinuria in advanced renal disease [294]. Frequently, an integrated therapeutic intervention (antihypertensives, statins, antiplatelet therapy, etc.) (see below) has to be considered in patients with renal damage, especially diabetics, due to the concomitant elevation in total cardiovascular risk [295].

Hypertension in pregnancy

Hypertensive disorders in pregnancy remain a major cause of maternal, fetal and neonatal morbidity and mortality, not only in less-developed but also in industrialized countries. Physiologically, blood pressure normally falls in the second trimester, reaching a mean of 15 mmHg lower than levels before pregnancy. In the

Box 14 Position statement: Antihypertensive therapy in patients with deranged renal function

- Before antihypertensive treatment became available, renal involvement was frequent in patients with essential hypertension.
- Renal protection in diabetes has two main requirements:
 - strict blood pressure control (<130/80 mmHg and even lower if proteinuria is >1 g/day);
 - lowering proteinuria to values as near to normal as possible.
- To reduce proteinuria either an angiotensin receptor blocker or an ACE inhibitor is required.
- To achieve the blood pressure goal, combination therapy is usually required, with addition of a diuretic and a calcium antagonist.
- To prevent or retard nephrosclerosis in hypertensive non-diabetic patients, blockade of the renin–angiotensin system appears more important than attaining very low blood pressure, but evidence is so far restricted to Afro-American hypertensives, and suitable studies in other ethnic groups are required. It appears prudent, however, to lower blood pressure intensively in all hypertensive patients with deranged renal function.
- An integrated therapeutic intervention (antihypertensives, statins, antiplatelet therapy, etc.) frequently has to be considered in patients with renal damage.0000

third trimester, it returns to, or may exceed, the pre-pregnancy levels. This fluctuation occurs in both normotensive and previously hypertensive women, and in those who will develop pregnancy-specific hypertension.

The definition of hypertension in pregnancy is not uniform [2,296,297]. It used to include an elevation in blood pressure during the second trimester from a baseline reading in the first trimester, or to pre-pregnancy levels, but a definition based on absolute blood pressure values (systolic blood pressure \geq 140 mmHg or diastolic blood pressure \geq 90 mmHg) is now preferred [297].

It is essential to confirm high blood pressure readings on two occasions. It is recommended that both Phase IV and V Korotkoff sounds be recorded. Phase IV should be used for initiating clinical investigation and management.

Hypertension in pregnancy is not a single entity [298] but comprises:

- *Pre-existing hypertension*, which complicates 1–5% of pregnancies and is defined as blood pressure \geq 140/90 mmHg that either predates pregnancy or develops before 20 weeks of gestation, and normally persists more than 42 days postpartum. It may be associated with proteinuria.
- *Gestational hypertension*, which is pregnancy-induced hypertension without proteinuria. Gestational hypertension associated with significant proteinuria ($>$ 300 mg/l or $>$ 500 mg/24 h or dipstick 2+ or more) is known as *pre-eclampsia*. Hypertension develops after 20 weeks' gestation. In most cases, it resolves within 42 days postpartum. Gestational hypertension is characterized by poor organ perfusion.
- *Pre-existing hypertension plus superimposed gestational hypertension with proteinuria*. Pre-existing hypertension is associated with further worsening of blood pressure and protein excretion \geq 3 g/day in 24-h urine

collection after 20 weeks' gestation; it corresponds to previous terminology 'chronic hypertension with superimposed pre-eclampsia'.

- *Antenatally unclassifiable hypertension*. Hypertension with or without systemic manifestations, if blood pressure was first recorded after 20 weeks' gestation. Re-assessment is necessary at or after 42 days postpartum. If hypertension is resolved by then, the condition should be re-classified as gestational hypertension with or without proteinuria. If the hypertension is not resolved by then, the condition should be reclassified as pre-existing hypertension.

Oedema occurs in up to 60% of normal pregnancies, and is no longer used in the diagnosis of pre-eclampsia.

Hypertensive disorders in pregnancy, particularly gestational hypertension with or without proteinuria, may produce changes in the haematologic, renal and hepatic profiles that may adversely affect prognosis and both neonatal and maternal outcomes. Basic laboratory investigations recommended for monitoring patients with hypertension in pregnancy are presented in Table 8.

The majority of women with pre-existing hypertension in pregnancy have mild to moderate hypertension (140–179/90–109 mmHg), and are at low risk for cardiovascular complications within the short timeframe of pregnancy. Women with essential hypertension and normal renal function have good maternal and neonatal outcomes, they are candidates for non-drug therapy because there is no evidence that pharmacological treatment results in improved neonatal outcome [299,300].

Non-pharmacological management [301] should be considered for pregnant women with SBP of 140–149 mmHg or DBP of 90–99 mmHg or both, measured in a clinical setting. Management, depending on BP, gestational age and presence of associated maternal and fetal risk factors, includes close supervision, limitation of activities, and some bed rest in the left lateral

Table 8 Basic laboratory investigations recommended for monitoring patients with hypertension in pregnancy

Haemoglobin and haematocrit	Haemoconcentration supports diagnosis of gestational hypertension with or without proteinuria. It indicates severity. Levels may be low in very severe cases because of haemolysis
Platelet count	Low levels $<$ 100 000 \times 10 ⁹ /l may suggest consumption in the microvasculature. Levels correspond to severity and are predictive of recovery rate in postpartum period, especially for women with HELLP syndrome
Serum AST, ALT	Elevated levels suggest hepatic involvement. Increasing levels suggest worsening severity
Serum LDH	Elevated levels are associated with haemolysis and hepatic involvement. May reflect severity and may predict potential for recovery postpartum, especially for women with HELLP syndrome
Proteinuria (24-h urine collection)	Standard to quantify proteinuria. If in excess of 2 g/day, very close monitoring is warranted. If in excess of 3 g/day, delivery should be considered
Urinalysis	Dipstick test for proteinuria has significant false-positive and false-negative rates. If dipstick results are positive (\geq 1), 24-h urine collection is needed to confirm proteinuria. Negative dipstick results do not rule out proteinuria, especially if DBP \geq 90 mmHg
Serum uric acid	Elevated levels aid in differential diagnosis of gestational hypertension and may reflect severity
Serum creatinine	Levels drop in pregnancy. Elevated levels suggest increasing severity of hypertension; assessment of 24-h creatinine clearance may be necessary

HELLP, haemolysis, elevated liver enzyme levels and low platelet count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase.

position. A normal diet without salt restriction is advised. Preventive interventions, aimed at reducing the incidence of gestational hypertension, especially pre-eclampsia, including calcium supplementation (2 g/d) [302], fish oil supplementation [303] and low-dose acetylsalicylic acid therapy [304] have failed to produce consistently the benefits initially expected, especially on the fetus. Low-dose aspirin is, however, used prophylactically in women who have a history of early onset (<28 weeks) pre-eclampsia. Although weight reduction may be helpful in reducing BP in non-pregnant women, it is not recommended during pregnancy in obese women. Weight reduction can be associated with reduced neonatal weight and lower subsequent growth in infants of dieting obese mothers.

The value of continued administration of antihypertensive drugs to pregnant women with chronic hypertension continues to be an area of debate. While there is a consensus that drug treatment of severe hypertension in pregnancy is required and beneficial [305], treatment of less severe hypertension is controversial. Although it might be beneficial for the mother with hypertension to reduce her blood pressure, lower pressure may impair uteroplacental perfusion and thereby jeopardize fetal development [306,307]. Much uncertainty about the benefits of lowering blood pressure in pregnant women with mild pre-existing hypertension stems from published trials that are too small to detect a modest reduction in obstetrical complications.

While the goal of treating hypertension is to reduce maternal risk, the agents selected must be efficacious and safe for the fetus [308,309]. SBP \geq 170 or DBP \geq 110 mmHg in a pregnant woman should be considered an emergency, and hospitalization is absolutely essential. Pharmacological treatment with intravenous labetalol, or oral methyldopa, or nifedipine should be considered. Intravenous hydralazine should no longer be thought of as the drug of choice as its use is associated with more perinatal adverse effects than other drugs [310]. Otherwise, the thresholds at which to start antihypertensive treatment are SBP of 140 mmHg or DBP of 90 mmHg in women with gestational hypertension without proteinuria or pre-existing hypertension before 28 weeks' gestation, those with gestational hypertension and proteinuria or symptoms at any time during the pregnancy, those with pre-existing hypertension and underlying conditions of target organ damage, and those with pre-existing hypertension and superimposed gestational hypertension. The thresholds in other circumstances are SBP of 150 mmHg and DBP of 95 mmHg. For non-severe hypertension, methyldopa, labetalol, calcium antagonists and β -blockers are the drugs of choice. β -Blockers appear to be less effective than calcium antagonists [310]. However, calcium antagonists should not be given concomitantly with

magnesium sulphate (because there is a risk of hypotension due to potential synergism). ACE inhibitors and angiotensin II antagonists should not be used in pregnancy. The plasma volume is reduced in pre-eclampsia; diuretic therapy is therefore inappropriate unless there is oliguria. Magnesium sulphate i.v. has been proved effective in the prevention of eclampsia and the treatment of seizures [311]. Induction of delivery is appropriate in gestational hypertension with proteinuria and adverse conditions such as visual disturbances, coagulation abnormalities or fetal distress.

Breast-feeding does not increase BP in the nursing mother. All antihypertensive agents taken by the nursing mother are excreted into breast milk. Most of the antihypertensive drugs are present at very low concentrations, except for propranolol and nifedipine, concentrations of which are similar in breast milk to those in maternal plasma.

Resistant hypertension

Hypertension may be termed resistant to treatment, or refractory, when a therapeutic plan that has included attention to lifestyle measures and the prescription of at least three drugs in adequate doses has failed to lower systolic and diastolic blood pressure sufficiently. In these situations, referral to a specialist should be considered, as resistant hypertension is known to be often associated with target organ damage [312].

There are many causes for resistance to treatment, including cases of spurious hypertension, such as isolated office (white-coat) hypertension, and failure to use large cuffs on large arms. One of the most important causes of refractory hypertension is poor compliance or adherence to therapy, and in this situation, after all else fails, it can be helpful to suspend all drug therapy under close medical supervision. A fresh

Box 15 Causes of resistant hypertension

- Unsuspected secondary cause.
- Poor adherence to therapeutic plan.
- Continued intake of drugs that raise blood pressure.
- Failure to modify lifestyle including:
 - weight gain;
 - heavy alcohol intake (NB binge drinking).
- Volume overload due to:
 - inadequate diuretic therapy;
 - progressive renal insufficiency;
 - high sodium intake.

Causes of spurious resistant hypertension

- Isolated office (white-coat) hypertension.
- Failure to use large cuff on large arm.

start with a new and simpler regimen may help break a vicious cycle.

Treatment of associated risk factors

Lipid-lowering agents

Two trials – ALLHAT [313] and ASCOT [314] – have recently evaluated the benefits associated with the use of statins, specifically among patients with hypertension. Prior to these recent trial results, other randomized controlled trial data were available from analyses of the hypertensive subgroups from lipid-lowering trials in secondary [315–318] and primary prevention [319,320] and from the largest statin trial, the Heart Protection Study (HPS) [321], which included over 20 000 patients, most of whom had established vascular disease. In the HPS 41% of the patients were hypertensive, but 62% of the elderly patients in the PROSPER trial [322] were hypertensive. This trial, like HPS, mainly included patients with established vascular disease. Analyses of the hypertensive subgroups from these trials demonstrate that the benefits of lipid lowering – primarily with statins – in terms of preventing major coronary events are similar for hypertensive and

normotensive patients. Somewhat more surprising, in view of the limited epidemiological association between serum cholesterol levels and stroke risk [323], is the finding that in the statin trials stroke risk was reduced by an average of 15 and 30% in primary and secondary prevention settings, respectively [324].

ALLHAT compared the impact of 40 mg/day pravastatin with usual care in over 10 000 hypertensive patients, 14% of whom had established vascular disease [313]. The differential effect of pravastatin on total and LDL cholesterol (11 and 17% respectively) was smaller than expected due to extensive statin use in the usual care group and was associated with a modest, non-significant 9% reduction in fatal coronary heart disease and non-fatal myocardial infarction, and 9% reduction in fatal and non-fatal stroke. No impact on all-cause mortality – the primary endpoint of the trial – was apparent [313]. By contrast, the results of ASCOT [314], which also included over 10 000 hypertensive patients, showed highly significant cardiovascular benefits (36% reduction in the primary endpoint of total coronary heart disease and non-fatal myocardial infarction and 27% reduction in fatal and non-fatal stroke) associated with the use of atorvastatin 10 mg/day compared with placebo in patients with total cholesterol \leq 6.5 mmol/l [314]. The apparent difference in effect seen in ALLHAT and ASCOT probably reflects the greater relative difference in total and LDL-cholesterol achieved among the actively treated groups in ASCOT. Whilst acknowledging the continuum of disease from primary to secondary prevention, for simplicity, recommendations regarding the use of lipid-lowering therapy for patients with hypertension may be subdivided into those relating to secondary and to primary prevention.

Secondary prevention. Based on the HPS results [321], all patients up to the age of at least 80 with total cholesterol $>$ 3.5 mmol/l (135 mg/dl) with active coronary heart disease, peripheral arterial disease or a history of ischaemic stroke, should receive lipid lowering with a statin. In light of the high coronary event rates observed among many patients with type 2 diabetes [321], and the high long- and short-term fatality rates for such patients [325], it is recommended that patients with type 2 diabetes – diagnosed at least 10 years ago and/or aged 50 years or more – should be considered as ‘coronary heart disease risk equivalents’ [326] as far as lipid lowering is concerned, and hence should be treated as for secondary prevention. Other patients with type 2 diabetes should be considered as for primary prevention. Therapy should be titrated so as to lower total or LDL-cholesterol by 30 and 40%, respectively, and to $<$ 4.0 mmol/l (155 mg/dl) and $<$ 2.0 mmol/l (77 mg/dl) respectively, whichever is the greater reduction.

Primary prevention. The use of statins should be based

Box 16 Position statement: Treatment of associated risk factors

Lipid-lowering agents

- All patients up to the age of 80 with active coronary heart disease, peripheral arterial disease, history of ischaemia, stroke and long-standing type 2 diabetes should receive a statin if their total cholesterol is $>$ 3.5 mmol/l (135 mg/dl), with the goal of reducing it by about 30%.
- Patients without overt cardiovascular disease or with recent-onset diabetes, whose estimated 10-year cardiovascular risk is \geq 20% (‘high’ risk in Table 2), should also receive a statin if their total cholesterol is $>$ 3.5 mmol/l (135 mg/dl).

Antiplatelet therapy

- Antiplatelet therapy, in particular low-dose aspirin, should be prescribed to patients with previous cardiovascular events, as it has been shown to reduce the risk of stroke and myocardial infarction (provided patients are not at an excessive risk of bleeding).
- In hypertensive patients, low-dose aspirin has been shown to be beneficial (reduction of myocardial infarction greater than the risk of excess bleeding) in patients older than 50 with an even moderate increase in serum creatinine, or with a 10-year total cardiovascular risk \geq 20% (‘high’ risk in Table 2).
- In hypertensives, low-dose aspirin administration should be preceded by good blood pressure control.

on results of total risk assessment (see above). Randomized placebo-controlled trial evidence has demonstrated significant benefits of statin therapy among normotensive and hypertensive adults with an estimated mean 10-year coronary heart disease risk of as low as 6% [320]. However, in several European countries the majority of adults over the age of 40 are at or above a 6% 10-year coronary heart disease risk, and consequently it is not financially feasible nor conceptually ideal to treat all people at and above this level of risk. The HPS [321] included only 1% of patients who were hypertensive but did not have either a history of a cardiovascular event, active vascular disease, and/or diabetes, and hence does not provide a robust database on which to base recommendations for primary prevention of cardiovascular disease in hypertensive patients. However, in view of the results of ASCOT [314] and other currently available trial data [320] it seems reasonable to treat all those patients at least up to the age of 80 years with a total cholesterol > 3.5 mmol/l (135 mg/dl) who have an estimated 10-year cardiovascular risk of 20% or more (see above) with a statin. It should be recognised that earlier European guidelines [4], recommending a total cholesterol threshold > 5 mmol/l (193 mg/dl), have yet to be incorporated in practice, and hence it could be argued that there is little point making more aggressive treatment recommendations. However, in acknowledgement of the advances in evidence-base, these guidelines have lowered thresholds and targets for lipid-lowering treatment.

Target levels should be as for secondary prevention. The vast majority of patients will reach recommended total cholesterol or LDL cholesterol targets using statin drugs at appropriate doses in combination with non-pharmacological measures [327]. For patients who do not reach targets, or whose HDL-cholesterol or triglyceride levels remain abnormal (e.g. < 1.0 mmol/l, > 2.3 mmol/l, respectively) despite reaching LDL targets, referral to lipid specialists may be indicated for consideration of the addition of fibrate or other therapy. It remains to be seen whether in those patients, such as many type 2 diabetics, whose primary lipid abnormality is a low HDL-cholesterol and raised triglycerides, the use of a fibrate might be preferable to a statin. However, pending future evidence, statins at suitable doses should still be the drugs of choice in these patients also.

Antiplatelet therapy

Antiplatelet therapy, in particular low-dose aspirin, has been shown to reduce the risk of stroke and myocardial infarction when given to patients with previous cardiovascular events or at high cardiovascular risk [328]. Evidence about benefits and possible harms of administering low-dose aspirin to hypertensive patients was obtained from the HOT study [160], which showed a significant 15% reduction in major cardiovascular

events, and a 36% reduction in acute myocardial infarction, with no effect on stroke (but no increased risk of intracerebral haemorrhage). However, these benefits were accompanied by a 65% increased risk of major haemorrhagic events. Subgroup analyses of the HOT data [329] indicates which groups of hypertensive patients are likely to have greater absolute benefits than harms. Patients with serum creatinine > 115 μ mol/l (> 1.3 mg/dl) had a significantly greater reduction of cardiovascular events and myocardial infarction (-13 and -7 events/1000 patient-years), while risk of bleeding was not significantly different between subgroups (1–2 bleeds/1000 patient-years). In addition to patients with higher creatinine, a favourable balance between benefits and harm of aspirin was found in subgroups of patients at higher total baseline risk, and higher baseline systolic or diastolic blood pressure (benefit, -3.1 to -3.3 cardiovascular events; harm, 1.0–1.4 bleeds/1000 patient-years). These observations are in line with those of two recent meta-analyses of primary prevention studies, also including non-hypertensive patients [330,331].

In summary, definite recommendations may be given to use low-dose aspirin in hypertensive patients with a moderate increase in serum creatinine, and low-dose aspirin can also be considered in hypertensive patients above age 50 years at high or very high total cardiovascular risk or with higher initial blood pressure values. It should be underlined that aspirin benefits were seen in patients with very good blood pressure control (practically all patients in the HOT study had diastolic blood pressure ≤ 90 mmHg), and it is possible that the good blood pressure control was instrumental in avoiding an increment in intracerebral haemorrhage. Therefore, aspirin should be prescribed only when reasonable blood pressure control has been achieved.

Glycaemic control

Concentrations of fasting glucose or haemoglobin A_{1c} (HbA_{1c}) just above the normal range are associated with an increased cardiovascular risk [332–334]. A reduction in cardiovascular events can therefore be anticipated in response to an improvement in glucose control. In patients with type 1 diabetes, although intensive care (providing a mean HbA_{1c} of 7%) does not seem to be better than standard care (providing a mean HbA_{1c} of 9%) in the prevention of macrovascular complications, it decreases significantly the rate and the progression of microvascular complications (retinopathy, nephropathy, neuropathy) [335]. Hypertensive patients with type 2 diabetes also benefit from intensive blood glucose control mostly in terms of microvascular complications [334]. A direct association exists between these complications and the mean HbA_{1c}, with no indication of a threshold of HbA_{1c} values below which the risk no longer decreases. The treatment goals are set to ≤ 6.0 mmol/l (110 mg/dl) for plasma preprandial glu-

cose concentrations (average of several measurements), and at less than $\leq 6.5\%$ for HbA_{1c} [336].

Follow-up

The frequency of follow-up visits will depend on the overall risk category of the patient, as well as on the level of blood pressure. Once the goals of therapy have been reached, including the control of other risk factors and the achievement of goal blood pressure, the frequency of visits can be reduced considerably, particularly if self-measurement of blood pressure at home is encouraged. New technologies for tele-transmission of home blood pressure values to the physician's office may further assist more effective follow-up. Patients with a low risk profile and milder degrees of blood pressure elevation (high normal or grade 1), managed on a single drug, could well be seen every 6 months. It is important that patients not on drug treatment understand the need for monitoring and follow-up and for periodic reconsideration of the need for drug treatment. In more complex cases, patients should be seen at more frequent intervals. If the therapeutic goals, including the control of blood pressure, have not been reached within 6 months, the physician should consider referral to a hypertension specialist. Antihypertensive therapy is generally for life. Cessation of therapy by patients who have been correctly diagnosed as hypertensive is usually followed, sooner or later, by the return of blood pressure to pretreatment levels. Nevertheless, after prolonged blood pressure control, it may be possible to attempt a careful progressive reduction in the dose or number of drugs used, particularly among patients strictly observing lifestyle (non-drug) measures. Such attempts to 'step down' treatment should be accompanied by careful continued supervision of the blood pressure.

Implementation of guidelines: Closing the gap between experts' recommendations and poor blood pressure control in medical practice

Despite major efforts to diagnose and to treat hypertension, this condition remains worldwide a leading cause of cardiovascular morbidity and mortality [337], and goal blood pressure levels are seldom achieved [9,255,338–340]. It is therefore highly desirable to improve this unsatisfactory delivery of care. In the field of hypertension an increasing number of clinical trials allow the formulation of guidelines to support a more effective strategy. The availability of guidelines should not only help clinicians to take decisions in everyday practice, but also make the health authorities in all countries aware of the critical points to consider in order to improve hypertension management. The experience accumulated so far suggests that the impact of guidelines in changing clinical practice is rather small [341]. Multifaceted interventions are required to imple-

ment guidelines successfully, going from the dissemination of recommendations to educational programmes at the practice site [341,342]. This requires the participation of all professionals involved in health care, from governmental level to the individual physician. Consequently, broad acceptance of the present guidelines by national hypertension societies and leagues is a prerequisite to promoting behavioural changes in practice and, thereby, improving patient outcomes. In this context, the present guidelines have been prepared in concert with the Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention, in view of their incorporation in the comprehensive guidelines on prevention of cardiovascular diseases in clinical practice these societies are preparing.

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Key to references

CT, controlled trial; GL, guidelines/experts' opinion; MA, meta-analysis; OS, observational study; RT, randomised trial; RV, review.

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Appendix

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Acknowledgement

The expert contribution of Prof. Fiona Broughton-Pipkin, Nottingham, UK, in advising on the section about hypertension in pregnancy is gratefully acknowledged.

Conflict of interest disclosures

No member of the Guidelines Committee owns stock of pharmaceutical or biomedical industries except W. Kiowski (Novartis, Pfizer, Roche) and E. O'Brien (minority interest in Medical Management Systems Ltd).

The following members have served as consultants for, received personal compensation from, or were grant recipients of the following industries or government or private health providers during the past 5 years:

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