

# 1999 World Health Organization–International Society of Hypertension Guidelines for the Management of Hypertension

## Guidelines Subcommittee\*

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### Introduction

The present Guidelines come at a critically important time globally for the management of hypertension and the prevention of associated cardiovascular disorders. The second half of the twentieth century has seen a progressive decrease in cardiovascular mortality in North America, Western Europe, Japan and Australasia [1]. At the same time, the control of hypertension in these regions has improved considerably. For example, the Health Examination Surveys in the United States have demonstrated that whereas 10% of hypertensive subjects had their blood pressure lowered to below 140/90 mmHg in 1976–1980, by 1988–1991 the proportion had risen to 27% [2]. It is important to note that this leaves over 70% of hypertensive subjects with imperfect control (or no treatment at all), as has been reported in many other countries [3], and that there are worrying signs that the rate of improvement has plateaued or even reversed in some cases. In the United Kingdom, a recent survey indicated that only 6% of hypertensive patients had their blood pressure lowered to below 140/90 mmHg [4]. Additionally, in the United States, there is recent evidence that age-adjusted stroke mortality rates have risen slightly and that the rate of decline of coronary heart disease (CHD) mortality has decreased. Moreover, given the ageing population structure of most developed countries, total numbers of strokes and CHD events are typically increasing or remaining static, even in those

countries that continue to experience falling age-adjusted event rates.

Even more worrying is the rapid development of the 'second wave' epidemic of cardiovascular disease that is now flowing through developing countries and the former socialist republics. It is evident that death and disability from CHD and cerebrovascular disease are increasing so rapidly in these parts of the world that they will rank no. 1 and no. 4, respectively, as causes of the global burden of disease by the year 2020 [5]. Given the central role of elevated blood pressure in the pathogenesis of both CHD and stroke, it is clear that one of the biggest challenges facing public health authorities and medical practitioners is the control of hypertension worldwide, both in individual patients and at the population level.

### Scope and purpose of Guidelines

The present Guidelines are written to guide specialist physicians responsible for the care of patients with high blood pressure. They are complemented by a companion set of *Practice Guidelines* for general practitioners and other clinicians caring for patients with hypertension in various regions around the world. The 1999 Guidelines again concentrate on the management of patients with 'mild' hypertension, since there is often uncertainty among clinicians and policy makers about how to manage this condition. Since the determinants

of cardiovascular disease in hypertensive patients are substantially multifactorial, these Guidelines provide recommendations for risk reduction through blood pressure lowering, in a context that recognizes the importance of strategies for the management of other risk factors that commonly affect individuals with hypertension.

The Guidelines do not deal with the management of more severe hypertension except in the most general terms, nor with the management of patients with secondary forms of hypertension. Furthermore, these Guidelines do not deal with the primary prevention and control of hypertension at the population level. These strategies, which are dealt with elsewhere [6], are complementary to the clinical strategy that is the subject of this Report.

### **Box 1 The 1999 Guidelines**

- These Guidelines provide recommendations that are based on the collective expert interpretation by the WHO–ISH Guidelines Subcommittee of the available evidence from epidemiological studies and from clinical trials.
- The primary aim is to offer balanced information to guide clinicians, rather than rigid rules that would constrain their judgement about the management of individual patients, who will differ in their personal, medical, social, ethnic and cultural characteristics.
- The WHO–ISH Guidelines are written for a global audience from communities that vary widely in the nature of their health system and in the availability of resources.
- It is hoped that national and regional experts will use them as a basis for drawing up recommendations that are specifically designed for the management of patients in their own region.

### **Determinants of cardiovascular disease risk in hypertensive patients**

It is well established that in Western populations, stroke, CHD and other common cardiovascular diseases, such as heart failure, have multiple determinants. The main established predictors of these diseases are described briefly in this section. How well these factors predict cardiovascular disease in non-Western populations is less certain, although recent evidence from Eastern Asian populations suggests that for blood pressure and blood cholesterol there may be similar associations in the East and West [7]. There is very little direct evidence about the determinants of common cardiovascular diseases in other large populations

such as those of sub-Saharan Africa, India or South America.

### **Effects of blood pressure on the risk of cardiovascular disease**

#### **Stroke**

Blood pressure levels, both systolic (SBP) and diastolic (DBP), have been shown to be positively and continuously related to the risk of stroke across a wide range of levels in populations from both Western and Eastern hemispheres [7,8]. Among individuals of mostly middle age, a prolonged 5 mmHg lower level of usual DBP was shown to be associated with a 35–40% lower risk of stroke, with no lower level identified below which the risks of stroke did not continue to decline. The slope of the association appears to decline somewhat with increasing age [9]; however, because the incidence of stroke increases so rapidly with age (see below), the elderly still suffer the large majority of blood pressure-related cerebrovascular disease. Blood pressure levels are positively related to both cerebral haemorrhage and cerebral infarction, but the association appears to be somewhat steeper for haemorrhage than infarction [7].

### **Box 2 Hypertension versus normotension**

- Blood pressure levels are continuously related to the risks of cardiovascular disease and the definition of hypertension (or raised blood pressure) is, therefore, arbitrary.
- Much blood pressure-related disease occurs among individuals who would normally be considered normotensive.
- Most of the evidence about the benefits and risks of lowering blood pressure comes from studies in patients selected on the basis of high blood pressure.
- It is not clear whether estimates of treatment effect obtained from trials in hypertensives can be extrapolated to individuals with lower blood pressure levels.
- There is a strong rationale for expecting high-risk patients without hypertension to benefit from blood pressure lowering and trials are required to investigate this possibility.

#### **Coronary heart disease**

Blood pressure levels have also been shown to be positively and continuously related to the risks of major CHD events (CHD death or nonfatal myocardial infarction) [8]. The strength of this association is about two-thirds as steep as that for stroke, and appears to be similar across a broad range of blood pressure levels, that includes both hypertensive and normotensive

individuals. Once again, no lower level has been identified below which the risks do not continue to decline.

#### **Heart failure and renal disease**

The risks of heart failure and of renal disease have been observed to be related to blood pressure levels, but the sizes of the relationships are less well established than those for stroke and CHD. Nevertheless, there is evidence that patients with a history of hypertension have at least six times greater risk of heart failure than do individuals without such a history [10], and that each 5 mmHg lower level of DBP is associated with at least a one-quarter lower risk of end-stage renal disease [11].

#### **Recurrent cardiovascular events**

Among individuals with a history of cerebrovascular disease or previous myocardial infarction, there have been reports of both linear [12–14] and nonlinear (J-shaped) [15,16] associations between blood pressure levels and the risks of recurrent events. However, the associations in patients with prior cardiovascular disease are subject to confounding as a consequence of the effects of disease (or its treatment) on blood pressure and, independently, on the risks of recurrence. Studies that have attempted to control for this (either by excluding patients with more severe disease or by excluding early recurrent events) have consistently demonstrated continuous positive associations between blood pressure levels and the longer-term risks of stroke and CHD recurrence [12–14].

#### **Pulse pressure and arterial distensibility**

There is evidence that pulse pressure (the difference between SBP and DBP) is also positively associated with a variety of cardiovascular diseases [17,18]. However, there remains uncertainty as to whether pulse pressure predicts disease risk independently of either SBP or DBP. Pulse pressure is one index of arterial distensibility. While there are theoretical reasons for expecting arterial distensibility to be independently predictive of cardiovascular disease risk [19–22], there are still few data demonstrating such an association.

#### **Effects of other factors on the risk of cardiovascular disease**

##### **Age**

In most populations, the risks of cardiovascular disease rise steeply with increasing age. For example, among British men, from age 45 to 74, there is a three- to fourfold increase in deaths from stroke and from CHD each decade [23]. This powerful effect of age on disease risk has important consequences for the effects of blood pressure and other risk factors on disease occurrence. Specifically, while the relative effects of

some risk factors decline as age increases, the absolute effects of these risk factors typically *increase* with age because of the markedly higher background risk of cardiovascular disease in older people.

##### **Gender**

At most ages, the risks of cardiovascular diseases are greater in men than women, although this difference declines with increasing age and is greater for CHD than for stroke. For example, in the United States from age 34 to 74, the risks of death from stroke are 30% higher in men than women, whereas the risks of death from CHD are two- to threefold greater in men [23]. After age 75, the risks of death from stroke and from CHD are similar in men and women.

#### **Pre-existing cardiovascular disease**

A history of clinically manifest cardiovascular disease is a particularly important predictor of the future risk of major cardiovascular events. Patients with congestive heart failure, typically experience death rates of 10% or more annually [24]. Patients with a history of stroke or transient ischaemic attack (TIA) experience stroke risks of 3–5% or more annually [25], and the risk of other major cardiovascular events is at least an additional few per cent. Among patients with a history of myocardial infarction or unstable angina, the annual incidence of recurrent infarction or CHD death is 4% or more [26] and the risk of other major cardiovascular events is an additional 1 or 2%.

Subclinical manifestations of cardiovascular disease in asymptomatic patients can also be important predictors of future risk. For example, high rates of major clinical events (a few per cent per year) occur among patients with significant left ventricular dysfunction [27], electrocardiographic (ECG) evidence of Q waves [28] or ECG evidence of left ventricular hypertrophy [29]. Ultrasonographic evidence of left ventricular hypertrophy [30] or carotid atherosclerosis [31,32] is also associated with increased risks of cardiovascular disease events.

#### **Renal disease and microalbuminuria**

Renal disease manifested by raised serum creatinine and proteinuria is an important predictor not only of renal failure but also of major cardiovascular events [33,34]. While most types of renal disease are associated with increased risk, diabetic nephropathy appears to confer the greatest risks [35]. Typically, the risk of CHD events in patients with end-stage renal disease (irrespective of aetiology) is at least as great as that in patients with a clinical history of CHD. Among diabetics without frank renal disease, microalbuminuria has been observed to be associated with a two- to threefold increase in the risk of major cardiovascular events [36].

**Diabetes, hyperinsulinaemia and hyperglycaemia**

Diabetes, whether insulin-dependent or noninsulin-dependent, increases the risks of CHD and ischaemic stroke [37,38], as well as the risk of renal disease. Overall, diabetes typically increases the relative risks of death from CHD and death from stroke about three-fold. Additionally, among individuals without diabetes, the risks of CHD have been observed to be directly and continuously related to blood insulin [39] and blood glucose levels [40].

**Box 3 Contribution of blood pressure and other factors to cardiovascular disease risk**

- Among patients with mild hypertension, differences in the risks of cardiovascular disease are determined not only by the level of blood pressure, but also by the presence or levels of other risk factors.
- For example, a man aged 65 years with diabetes, a history of transient ischaemic attacks and a systolic/diastolic blood pressure of 145/90 mmHg will have an annual risk of a major cardiovascular event that is more than **20 times greater** than that in a man aged 40 years with the same blood pressure but without either diabetes or a history of cardiovascular disease.
- In contrast, a man aged 40 years with a systolic/diastolic blood pressure of 170/105 mmHg will have a risk of a major cardiovascular event that is about two or three times greater than that of a man of the same age with a systolic diastolic blood pressure of 145/90 mmHg and similar other risk factor levels.
- Thus differences in the absolute level of cardiovascular risk between patients with hypertension will often be determined to a greater extent by other risk factors than by the level of blood pressure.

**Smoking**

Cigarette smoking increases the risk of CHD and ischaemic stroke at all ages, but is of particular importance in younger people [41]. In men under 65 years, smoking has been observed to increase the risk of cardiovascular death by twofold, while in men aged 85 years or older, the risk was observed to be increased by 20%. In addition to these effects of smoking on cardiovascular diseases, smoking also increases the risks of a wide variety of noncardiovascular diseases, in particular respiratory and neoplastic diseases [41].

**Lipids and lipoproteins**

Increasing levels of both total and low-density lipoprotein (LDL) cholesterol are associated with increases in the risks of CHD [42]. The relative risks appear to decline with increasing age, although the absolute risks typically increase. A 0.6 mmol/l (23.2 mg/dl) lower total cholesterol in men aged 40 years has been observed to be associated with a 54% lower CHD risk, whereas the same difference in cholesterol in men aged 70 years was associated with a 20% lower risk. The effect of high-density lipoprotein (HDL) cholesterol on CHD risk does not appear to be age-dependent; every 0.03 mmol/l (1.2 mg/dl) increase in HDL cholesterol appears to be associated with at least a 3% reduction in the risk of CHD [43]. It is still unclear whether there is any independent effect of triglyceride levels on the risk of cardiovascular disease.

**Obesity**

Increased body mass index (BMI; kg/m<sup>2</sup>) is associated with increased risks of CHD. Compared with lean men, men with BMI of 25–29 have been observed to have a 70% greater risk of CHD whereas men with BMI of 29–33 had almost a threefold greater risk of CHD [44]. The strength of this association appears to decline with age. The risk associated with obesity is likely to be due in part to blood pressure elevation, but reduced HDL cholesterol and increased insulin and glucose may also be involved [45,46].

**Fibrinogen**

Blood levels of fibrinogen are positively associated with the risk of CHD and ischaemic stroke. In several studies, individuals with fibrinogen in the highest tertile had risks of CHD that were about twice as great as those among individuals with fibrinogen in the lowest tertile [47,48].

**Alcohol**

The risk of CHD appears to be reduced among regular consumers of alcohol (e.g. 1–3 standard drinks per day) [49]. In general, daily consumers of alcohol have a 30–40% lower risk of death from CHD than do nondrinkers [50]. However, high levels of alcohol consumption can cause other cardiac disorders and are associated with increased risks of stroke [51] (particularly after binge drinking), as well as higher blood pressure levels and higher risks of several nonvascular diseases and injury.

**Physical activity**

Regular aerobic exercise reduces the risk of CHD. Individuals performing about 20 min of light to moderate-intensity exercise daily have been observed to have about a 30% lower risk of death from CHD than do sedentary individuals [52]. These benefits may be due in part to the blood-pressure-lowering effects of exer-

cise, but other metabolic factors that may be activated by exercise, such as increased HDL cholesterol, may also be involved [53].

#### **Hormone replacement therapy**

In studies of Western populations, the use of hormone replacement therapy (HRT) has been shown to be associated with 30–50% lower risks of CHD among postmenopausal women [54]. Whether this association reflects a true protective effect of HRT or of the selection of low-risk women for HRT is uncertain. The results of a recent trial of HRT in women with CHD failed to demonstrate any protective effect of HRT for recurrent CHD events [55].

#### **Socio-economic status**

Socio-economic status, as judged from education, employment or income, is a powerful predictor of the risk of most common cardiovascular diseases. In many studies of a variety of mainly Western populations, lower levels of socio-economic status have been observed to be associated with higher risks of cardiovascular disease. The magnitudes of the associations vary between populations but in the United States, individuals with income less than \$18 500 in 1980 have been observed to have cardiovascular death rates that are 40% greater than in individuals with income greater than \$32 000 [56]. These associations appear to be mediated, at least in part, by increased levels of most established risk factors, including smoking [57] among those in lower socio-economic groups. How widely such associations exist outside Western populations is uncertain; however, there is evidence within some Western populations of heterogeneity of associations among different ethnic groups [58].

#### **Ethnicity**

Ethnicity is also powerfully related to the risk of most common cardiovascular diseases. In many countries, ethnic minority groups, such as New Zealand Maori [59] and United States Native Americans [60], have substantially higher risks of CHD than do the Caucasian majority. Moreover, there is evidence that African Americans are generally at greater risk of stroke [61] and of renal disease [62] than are Caucasians from the United States, and that South Asians in the United Kingdom [63] but not Canada [64] are at higher risk of these diseases and CHD than are Caucasians from the same countries. There is uncertainty as to how much of these ethnic differences in risk can be ascribed to differences in levels of the established risk factors for cardiovascular diseases.

#### **Geographic region**

There are major differences between geographic regions in the incidence of cardiovascular diseases. Some particularly important trends include the high rates of both CHD and stroke in Eastern Europe, Russia and

the Baltic states [65,66], and the high rates of stroke and the low rates of CHD in the People's Republic of China [67], compared with Western Europe and North America. In some parts of Africa, there are high rates of stroke and renal disease, but low rates of CHD [5].

#### **Other risk factors**

Many other factors, including passive smoking, blood type, LDL particle size, apolipoproteins, plasma renin activity, blood homocysteine levels, blood uric acid levels, several common genetic polymorphisms, several infective agents, and several psychological factors, have been reported to be independently associated with the risks of cardiovascular diseases. For most of these factors, the evidence of an association with cardiovascular disease is less strong than for most of the factors listed above.

### **Interventions to reduce cardiovascular risk in hypertensive patients**

#### **Effects of blood pressure lowering treatments on mortality and morbidity from cardiovascular disease**

##### ***Trials of diuretic and $\beta$ -blocker based regimens***

Previous randomized controlled trials of diuretic- or  $\beta$ -blocker-based regimens, involving a total of about 47 000 patients with hypertension, have collectively demonstrated that, over an average of about 5 years, such treatment produced much of the epidemiologically expected benefit of the achieved blood pressure reductions [68–70]. A net reduction of 5–6 mmHg in usual DBP was associated with a 38% (SD 4) reduction in stroke risk and a 16% (SD 4) reduction in CHD risk, with similar effects on fatal and nonfatal events. The proportional reductions in the risks of stroke and CHD in these trials appeared to be broadly similar in patients with mild, moderate or more severe hypertension, in older or younger patients, and in patients with or without a history of cerebrovascular disease.

Because of the similarity of the relative risk reductions in different patient groups, the size of the absolute treatment benefits varied in direct proportion to the background level of risk (i.e. patients at highest absolute risk of stroke or CHD experienced the largest absolute reduction in risk). For example [70], there was a 34% reduction in the relative risk of stroke in trials conducted exclusively in older populations and a 43% relative risk reduction in the trials conducted predominantly in individuals of middle age. However, the annual absolute risk reduction was more than doubled in the trials in older patients: specifically, there were five strokes prevented per thousand patients in the trials among older patients, compared with two strokes prevented per thousand patients in the trials among younger patients. The outcome was similar for CHD: there was a 19% reduction in relative risk in the trials

among older patients and a 14% relative risk reduction in the trials among middle-aged patients, but the annual absolute risk reduction was three events per 1000 older patients and one event per 1000 younger patients.

**Box 4 Underestimation of the effects of blood pressure lowering treatment in randomized controlled trials**

- Estimates of treatment effects in the trials of blood pressure lowering regimens generally provide conservative estimates of the full potential effects of treatment.
- In the trials, there was considerable crossover between treatment groups:
  - proportion of patients assigned to active therapy groups stopped treatment; and
  - proportion of those assigned to control groups began active treatment.
- Such crossover is likely to have reduced the average difference in diastolic blood pressure between groups by 1–2 mmHg, in which case, the full relative effects of treatment on stroke and coronary heart disease would be somewhat greater than the effects observed.
- The average duration of treatment in the trials was only about 5 years, and it is possible that longer-term treatment over many years, as is usual for hypertensive patients, might have led to larger relative risk reductions
- Low-risk patients were recruited to many trials, and the absolute effects of treatment among higher-risk patients seen in broader clinical practice are, therefore, likely to be greater than those typically observed (see Box 5).

There was evidence of reduced stroke risks both in trials of diuretic-based regimens and in trials of  $\beta$ -blocker-based regimens. It has been observed that the evidence for reduced CHD risk was somewhat stronger for diuretic-based therapy than for  $\beta$ -blocker-based therapy, particularly in trials conducted in the elderly [71]. However, data from the four trials that directly compared the effects of diuretic- and  $\beta$ -blocker-based regimens on the risks of stroke and CHD in younger and older patients provided no clear evidence of a difference between the regimens in their effects on stroke or CHD [72–75]. Nevertheless, even in combination, these studies lacked adequate statistical power to determine reliably any modest but potentially important treatment differences (e.g. a 10–15% difference in the relative risk of CHD).

While there are comparatively few data available from these trials about the effects of treatment on heart failure or renal disease, there was evidence of an approximate halving of the risk of heart failure in the trials of diuretic- and  $\beta$ -blocker-based regimens [76,77]. Additional evidence about the effects of  $\beta$ -blockers on such outcomes is provided by the trials of these agents in patients with heart failure (see section on Co-existing cerebrovascular or cardiac disease, p.174). Similarly, more evidence about the effects of  $\beta$ -blockers on CHD risk is provided by the trials of these agents in patients with prior myocardial infarction (see section on Co-existing cerebrovascular or cardiac disease, p.175).

**Trials of other treatment regimens**

There are fewer data available from which to determine the effects on cardiovascular disease risks of blood-pressure-lowering regimens based on the newer classes of agents in hypertensive patients, although the available evidence is increasing rapidly. Data on the effects of calcium antagonists on cardiovascular disease risks in patients with hypertension are available from one moderate-to-large scale randomized, placebo-controlled trial: in the Systolic Hypertension in Europe (Syst-Eur) trial, nitrendipine-based therapy produced an approximate 10/5 mmHg reduction in SBP/DBP in patients with systolic hypertension and a 42% reduction in the risk of stroke [78]. Similar results were observed in two large, nonrandomized, placebo-controlled trials (with alternate treatment assignment): the Shanghai Trial Of Nifedipine in the Elderly (STONE) [79] and the Systolic Hypertension in China (Syst-China) trial [80]. Collectively, these studies provide evidence that calcium antagonists reduce the risk of stroke, and that the magnitude of this effect appears to be similar to that seen in trials of diuretic- or beta-blocker-based therapy. However, there were few CHD events recorded in these trials and, in consequence, it is not possible to assess reliably the effects of calcium antagonists on the risk of CHD in these trials. More evidence about the effects of calcium antagonists on CHD events is provided by trials of these agents in patients with a history of myocardial infarction (see section on Co-existing cerebrovascular or cardiac disease, p.174).

To date, only one large-scale trial has provided evidence about the effects of angiotensin converting enzyme (ACE) inhibitor-based therapy in patients with uncomplicated hypertension. The Captopril Primary Prevention Project (CAPPP) compared the effects of a captopril-based regimen with other therapy (principally diuretic- or  $\beta$ -blocker-based regimens) among 10 985 patients with hypertension [81]. However, imbalances in the assignment of treatment resulted in a 2 mmHg higher average DBP level at entry in the group assigned captopril-based therapy. This difference in blood pressure alone would be sufficient to confer an

### Box 5 Relative and absolute effects of treatment

- The relative effect of treatment reflects the proportional difference between treatment groups in the incidence of disease events:
  - In the Systolic Hypertension in the Elderly (SHEP) trial [82], the incidence of major coronary heart disease (CHD) events over 4.5 years in patients assigned active treatment was 4.4% while in those assigned placebo it was 5.9%. This represents a relative risk of 0.73 or a relative risk reduction of 27%.
- The absolute effect of treatment is generally of greatest interest to doctors and patients:
  - In the SHEP trial, the absolute reduction in CHD risk over 4.5 years was 1.4%. This indicates that 14 events were prevented among every 1000 patients assigned active treatment, and that one major CHD event was avoided among every 71 patients assigned active treatment.
- Estimates of *relative* treatment effects from randomized trials provide a guide to the likely relative effects of treatment in other nonstudy patient populations. However, estimates of *absolute* treatment effects from trials of blood pressure lowering are of limited generalizability because complex inclusion and exclusion criteria frequently resulted in the recruitment of patients at lower average risk than those seen in broader clinical practice.
- The best predictor of absolute treatment effects for any individual patient will be provided by application of the estimate of the relative risk reduction from trials to an estimate of the absolute disease risk for the individual in question.
- A simple table for estimating the absolute cardiovascular disease risk of individual hypertensive patients is provided for use with these guidelines (Table 3).

increase of 20% in the risk of stroke and an increase in the risk of CHD of 10% among individuals of middle age, such as those included in this study. Hence the imbalance in blood pressure levels could mask real differences that may exist between the regimens in their effects on CHD, and could explain the greater risk of stroke observed among patients assigned the captopril-based therapy. The CAPPP study also reported a reduced risk of diabetes among patients assigned captopril-based therapy, a result that appears less likely to be explained by the observed imbalances at baseline. Additional evidence about the effects of ACE inhibitors on CHD risk is provided by trials in patients with left ventricular dysfunction or heart fail-

ure (see section on Co-existing cerebrovascular or cardiac disease, p.174).

Two small studies have reported fewer CHD events among diabetic hypertensive patients randomized to ACE inhibitor-based versus calcium antagonist-based regimens [68,69]. However, each of these studies recorded only a small number of CHD events, and, as a consequence, the apparent difference in the effects of these agents requires verification in larger studies. The UK Prospective Diabetes Study (UKPDS 39) involved 1148 hypertensive patients with type 2 diabetes, and over a median follow-up period of 8 years, there were similar benefits of ACE inhibitor- and  $\beta$ -blocker-based therapy for a variety of both macrovascular and microvascular disease outcomes [83] (see section on Trials of different blood pressure targets, below). Additional evidence about the effects of ACE inhibitors in patients with diabetes is provided by trials of these agents in patients with renal disease (see section on Renal disease, p.175).

At present, no reliable evidence is available from randomized controlled trials about the effects on cardiovascular disease risk of  $\alpha$ -adrenergic blockers or angiotensin II antagonists. However, large-scale trials involving both these drug types are ongoing.

#### **Trials of different blood pressure targets**

The Hypertension Optimal Treatment (HOT) trial used a calcium antagonist (felodipine)-based regimen (with the stepped addition of ACE inhibitors,  $\beta$ -blockers and diuretics) to investigate the effects of lowering blood pressure to three different targets ( $\leq 80$  mmHg,  $\leq 85$  mmHg and  $\leq 90$  mmHg) in 18 790 hypertensive patients [84]. By the end of follow-up, blood pressure had been substantially reduced in all three groups but there were only modest differences in SBP and DBP (about 2 mmHg) between adjacent target groups. These blood pressure differences were less than expected, and the study was not able to determine reliably the most plausible effect of such modest blood pressure differences. There was a nonsignificant trend towards lower cardiovascular event risk and a marginally significant trend towards fewer CHD events in the group with the lowest target. In the subgroup with diabetes, the trend for total cardiovascular events reached statistical significance. This is consistent with evidence from UKPDS 38, demonstrating that a lower blood pressure target (using either ACE inhibitor- or  $\beta$ -blocker-based therapy) was associated with reduced risks of major macrovascular events as well as microvascular disease outcomes [85]. In that study, the 'tight' blood pressure control group achieved average SBP/DBP of 144/82 mmHg whereas the less tight control group achieved blood pressures of 154/87 mmHg. This 10/5 mmHg reduction in blood pressure was associated

with a one-third reduction in diabetic deaths, almost a halving of stroke risk and a one-third reduction in microvascular complications.

#### **Effects of blood pressure lowering treatments on other major disease outcomes**

The trials of diuretic- and  $\beta$ -blocker-based therapy in patients with hypertension provide evidence of almost identical rates of death from noncardiovascular causes in patients assigned active treatment or control [68–70]. The results of these trials therefore suggest that treatment with these agents is not only effective for cardiovascular disease prevention, but is also safe in terms of the overall risk of death from noncardiovascular causes during the 5 years of treatment and follow-up in these trials. For the newer agents, there is less evidence from trials in hypertensive patients about the effects of treatment on noncardiovascular outcomes. However, data from all trials in patients with either hypertension or CHD provide no clear evidence of any excess mortality from noncardiovascular causes among patients assigned treatment with either ACE inhibitors or calcium antagonists. While there has been debate about possible adverse effects of calcium antagonists on cancer and bleeding risks [86] and beneficial effects of ACE inhibitors on cancer risk [87], these observations have been generated primarily by results from a few, potentially biased nonrandomized studies. Detailed review of the available evidence from observational studies and randomized trials did not provide clear evidence of an adverse effect of calcium antagonists on the risk of cancer or of bleeding [86]. Recent data from the Syst-Eur trial suggest that a calcium antagonist-based blood-pressure-lowering regimen may reduce the risks of dementia in elderly patients with systolic hypertension [88].

#### **Effectiveness of hypertension management as provided in community practice**

##### ***Control of blood pressure***

A number of studies have investigated the effectiveness of antihypertensive therapy for the control of hypertension in representative population samples [3,4,89]. The results of these studies indicate that in most populations studied, a moderate proportion of all hypertensive patients are untreated and a large proportion of treated hypertensive patients still have frankly elevated blood pressure, defined most frequently as SBP > 160 mmHg or DBP > 95 mmHg. On average, about half of all treated patients in these studies had continuing blood pressure elevation above 160/95 mmHg and three-quarters had blood pressure levels above 140/90 mmHg, although there was wide regional variation. Several studies have reported changes in blood pressure control over time, and these have generally shown trends towards improved control. Male gender and residence in a developing country have been

identified as factors associated with poorer blood pressure control [90]. The observations in China [90] and several other developing countries that only about 10% of treated hypertensive patients reached blood pressures below about 160/95 mmHg are particularly important in this regard. However, very low rates of blood pressure control have also been observed in some studies of Western populations [4].

##### ***Control of cardiovascular risk***

Despite the benefits of blood-pressure-lowering treatment established in randomized controlled trials, several population studies have demonstrated that treated hypertensive patients continue to experience substantially higher risks of CHD, stroke and overall mortality than do nonhypertensive individuals some years after beginning antihypertensive drug therapy [34,91]. These observations are consistent with other findings indicating more advanced atherosclerosis and more marked left ventricular hypertrophy among treated hypertensive patients compared with nonhypertensive controls [30]. The reasons for this persisting risk of cardiovascular complications are uncertain but are likely to involve both modifiable and nonmodifiable factors. Nonmodifiable factors may include a more frequent history of prior cardiovascular disease, diabetes or a genetic predisposition to cardiovascular complications. Potentially modifiable factors could include blood pressure levels that remain in the upper part of the population distribution and metabolic abnormalities, such as reduced levels of HDL cholesterol and increased levels of LDL cholesterol, insulin and glucose [92]. Each of these modifiable factors is associated with obesity, which is also more frequent in treated hypertensive patients than nonhypertensive individuals

#### **Effects of modification of other risk factors on mortality and morbidity from cardiovascular disease**

##### ***Smoking cessation***

Smoking cessation confers reduced risks of a large number of diseases including stroke and CHD [41]. In particular, there are large reductions in risk among those who quit in middle age or younger. Those who quit before 35 years or middle age typically have a life expectancy that is not different to that of lifelong nonsmokers.

##### ***Cholesterol lowering***

A large body of evidence has demonstrated that cholesterol lowering reduces the risks of CHD events in patients with high cholesterol levels or a history of CHD [42]. Dietary restriction of saturated fats can produce modest reductions in cholesterol [93] and the newer drug therapies reliably produce large reductions [94]. The size of the reduction in CHD risk appears to be proportional to the size of the cholesterol reduction achieved, such that reductions of about 1–1.5 mmol/l

(40–60 mg/dl) produced by 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors reduce the risk of major CHD events by between a fifth and a third [26,94–97]. The effects of these agents on fatal and nonfatal CHD events appear to be of similar magnitude. Reductions in stroke risk have also been observed in the trials of HMG CoA reductase inhibitors, but not in the trials of other cholesterol-lowering agents. In the few trials that provided data on cerebral infarction, there was some evidence of reduction in the risk of this stroke subtype.

#### **Treatment of diabetes**

There has been uncertainty as to whether blood glucose control in diabetic patients alters the risks of macrovascular disease. The results of UKPDS 33 among 3867 patients with newly diagnosed type 2 diabetes indicated that therapy with insulin or sulphonylureas over 10 years produced a one-quarter reduction in microvascular disease events, but no clear reduction in macrovascular disease events, although there was a trend towards fewer CHD events in the intensive blood glucose control group [98]. Similar results were achieved with metformin therapy in a separate trial by the same group in overweight patients with type 2 diabetes (UKPDS 34) [99]. The UKPDS results indicate that blood pressure lowering therapy offers more definite reductions in macrovascular disease for diabetic patients than do interventions for blood glucose control [85].

#### **Antiplatelet therapy**

For patients with a history of CHD or cerebrovascular disease, there is strong evidence that long-term therapy with aspirin and some other antiplatelet agents reduces the risks of fatal and nonfatal coronary events, stroke and cardiovascular death [100]. For patients without a history of cardiovascular disease, there is evidence of reduced risks of CHD but no clear evidence of reduced risks of stroke or of total cardiovascular death [100]. The Hypertension Optimal Treatment (HOT) study investigated the effects of 75 mg aspirin daily on cardiovascular events in patients with hypertension, and demonstrated a one-third reduction in the risk of CHD events, but no clear reduction in either ischaemic stroke or cardiovascular death [84]. In this study and others, aspirin was shown to increase noncerebral bleeding risks about twofold. There was no detectable increase in the risk of cerebral haemorrhage in the HOT study.

#### **Other factors**

The effects of modifying other factors that are known to determine cardiovascular disease risk are less certain. The evidence cited above (see section on Determinants of Cardiovascular Disease risk in hypertensive patients, p.152) suggests the potential for modification

of weight, exercise, alcohol intake and plasma fibrinogen to alter cardiovascular disease risks, but this has not yet been demonstrated in intervention studies. There has also been much recent interest in the possible effects of antioxidant vitamins such as vitamins E and C on the risks of CHD and stroke. While there is a rationale for believing that increased dietary intakes of these vitamins may confer worthwhile benefits and little risk, there is presently little direct evidence to support this [101]. Several ongoing trials of vitamin supplements should provide reliable evidence about the effects of such interventions on a range of outcomes within the next few years.

#### **Clinical evaluation**

The clinical and laboratory evaluation of the hypertensive patient should be conducted with four aims in mind:

- To confirm a chronic elevation of blood pressure and determine its level.
- To exclude or identify secondary causes of hypertension.
- To determine the presence of target-organ damage and to quantify its extent.
- To search for other cardiovascular risk factors and clinical conditions that may influence prognosis and treatment.

#### **Clinical history**

A comprehensive clinical history is essential and should include:

- family history of hypertension, diabetes, dyslipidaemia, CHD, stroke or renal disease;
- duration and previous levels of high blood pressure, and results and side effects of previous antihypertensive therapy;
- past history or current symptoms of CHD and heart failure, cerebrovascular disease, peripheral vascular disease, diabetes, gout, dyslipidaemia, bronchospasm, sexual dysfunction, renal disease, other significant illnesses and information on the drugs used to treat those conditions;
- symptoms suggestive of secondary causes of hypertension;
- careful assessment of lifestyle factors including dietary intake of fat, sodium and alcohol, quantitation of smoking and physical activity, and enquiry of weight gain since early adult life as a useful index of excess body fat;
- detailed enquiry of intake of drugs or substances that can raise blood pressure, including oral contraceptives, nonsteroidal anti-inflammatory drugs, liquorice, cocaine and amphetamines, and attention should be paid to the use of erythropoietin, cyclosporins or steroids for concomitant disorders; and

- personal, psychosocial and environmental factors that could influence the course and outcome of antihypertensive care, including family situation, work environment and educational background.

#### **Physical examination**

A full physical examination is essential and will include careful measurement of blood pressure as described below. Other important elements of the physical examination include:

- measurement of height and weight, and calculation of BMI (weight in kilograms divided by height in metres, squared);
- examination of the cardiovascular system, particularly for heart size, for evidence of heart failure, for evidence of arterial disease in the carotid, renal and peripheral arteries and for coarctation of the aorta;
- examination of the lungs for rales and bronchospasm and of the abdomen for bruits, enlarged kidneys and other masses; and
- examination of the optic fundi and of the nervous system for evidence of cerebrovascular damage.

#### **Blood pressure measurement**

Because blood pressure is characterized by large spontaneous variations [102], the diagnosis of hypertension should be based on multiple blood pressure measurements, taken on several separate occasions.

#### **Office or clinic blood pressure measurement**

Blood pressure should be measured as described in standard textbooks [103,104], with the patient in a sitting position, using a mercury sphygmomanometer or other noninvasive device. The accuracy of nonmercury devices should be ensured by comparison with values simultaneously obtained from a mercury sphygmomanometer. Since the medical use of mercury is likely to be progressively restricted around the world, the calibration and accuracy of nonmercury devices will become increasingly important.

When measuring blood pressure, particular care should be taken to:

- allow the patient to sit for several minutes in a quiet room before beginning blood pressure measurement;
- use a standard cuff with a bladder that is 12–13 cm by 35 cm, with a larger bladder for fat arms and a smaller bladder for children;
- use phase V Korotkoff sounds (disappearance) to measure DBP;
- measure the blood pressure in both arms first visit if there is evidence of peripheral vascular disease;
- measure the blood pressure in standing position in elderly subjects, diabetic patients and in other conditions in which orthostatic hypotension is common; and

- place the sphygmomanometer cuff at heart level, whatever the position of the patient.

#### **Home and ambulatory blood pressure measurement**

Noninvasive semi-automatic and automatic devices are now available for blood pressure measurement at home and for ambulatory blood pressure monitoring over periods of 24 h or more. Both of these approaches provide useful additional clinical information and have a place in the management of the hypertensive patient, but in both cases there are three important limitations:

- First, there are limited data available about the prognostic value of both home [105] and ambulatory blood pressure measurements [106]. Further prospective studies are required to determine whether such measurements offer material advantages over conventional blood pressure measurements for the prediction of morbidity and mortality. Therefore information obtained from these methods must be regarded as supplementary to conventional measurements, not as a substitute.
- Second, studies conducted in general populations and in hypertensive individuals have demonstrated that blood pressure values obtained by home measurements or by ambulatory monitoring are several mmHg lower than those obtained by office measurements with 24 h average or home blood pressure values of around 125/80 mmHg corresponding to clinic pressures of 140/90 mmHg [107].
- Third, the devices used should be checked for accuracy and performance over time against other well-validated blood pressure measurement devices using standardized protocols. Currently available home devices that measure the pressure in the fingers or the arm below the elbow should be avoided.

The advantages of home blood pressure measurement are that it may provide numerous values on different days in a setting closer to daily life conditions than the doctor's office. It may also favourably affect patients' perceptions of their 'hypertension' problems and improve adherence to treatment. It may therefore be a valuable adjunct for checking the effectiveness of treatment [108].

Ambulatory blood pressure monitoring also offers the advantages of providing a more realistic setting for blood pressure measurements and of improving patient perceptions and adherence to treatment. More important however, is the large body of evidence indicating that the target-organ damage associated with hypertension is more closely related to 24 h or daytime average blood pressure than to clinic blood pressure [106,109], particularly if only few office values are obtained [110]. There is also evidence that pretreat-

**Box 6 Situations in which ambulatory blood pressure monitoring should be considered**

- Unusual variability of blood pressure over the same or different visits.
- Office hypertension in subjects with low cardiovascular risk.
- Symptoms suggesting hypotensive episodes.
- Hypertension resistant to drug treatment.

ment ambulatory blood pressure has a prognostic value [111–114] and a recent prospective study suggests that regression of target-organ damage such as left ventricular hypertrophy is more closely related to changes in 24 h average than to changes in office blood pressure values [115]. While ambulatory blood pressure monitoring is not a substitute for office measurement, it provides an important research tool for investigations of normal and deranged mechanisms of cardiovascular regulation, of the clinical relevance of phenomena such as blood pressure variability and nocturnal hypotension, and of the time-course and homogeneity of the anti-hypertensive effect of newer drugs or drug combinations [106,116].

**Laboratory investigations**

In all regions of the world, routine investigations should include urinalysis for blood, protein and glucose, and microscopic examination of urine. Blood chemistry should include measurements of potassium, creatinine, fasting glucose and total cholesterol. An ECG should also be performed. In some regions of the world this list of routine investigations is frequently expanded to include some of the optional investigations listed below.

Optional investigations will be guided by the findings from the history, examination and routine investigations. Such investigations should be conducted if the results are likely to have important implications for the management of the individual patient in question. These tests may include measurement of HDL cholesterol, LDL cholesterol and triglycerides, of uric acid, and of hormone assays such as plasma renin activity, plasma aldosterone and urinary catecholamines. Echocardiography should be performed whenever the clinical assessment reveals the presence of target-organ damage or suggests the possibility of left ventricular hypertrophy or of other cardiac disease, since increased left ventricular mass is associated with increased cardiovascular risk and this information should be helpful in deciding whether to institute drug treatment. Similarly, vascular ultrasonography should be performed when-

**Box 7 Isolated office ('white-coat') hypertension**

- In some patients, office blood pressure is persistently elevated whereas daytime blood pressure outside the clinic environment is not.
- This condition is widely known as 'white-coat' hypertension [117], although the term 'isolated office' hypertension is preferable because the office–daytime blood pressure difference presumably depends on multiple factors [118] and does not correlate with the pressor response to blood pressure measurements by the doctor [119], the so-called 'white-coat' effect.
- It is likely that only a small fraction of the hypertensive population exhibits isolated office hypertension, if the diagnosis is restricted to subjects whose ambulatory systolic/diastolic blood pressure measurements are truly normal (below 125/80 mmHg) [118].
- Furthermore, there is continuing debate as to whether isolated office hypertension is an innocent phenomenon or whether it carries an increased burden of cardiovascular risk [120].
- Physicians should aim at its identification (by use of home or ambulatory blood pressure measurements) whenever clinical suspicion is raised.
- The decision to treat or not should be based on the overall risk profile and the presence or absence of target-organ damage. Close follow-up is essential for subjects with isolated office hypertension whom the physician chooses not to treat.

ever the presence of arterial disease is suspected in the aorta, carotid or peripheral arteries. Assessment of arterial distensibility might also be considered in some patients, although the complexity of the techniques involved, the lack of standardization of procedures and uncertainty about its place in management make it largely a research tool. Renal ultrasonography should be performed if renal disease is suspected. The cost of investigations should be considered in the context of the needs of the individual patient and the availability of resources in the particular health system or region.

**Definition and classification of hypertension**

The continuous relationship between the level of blood pressure and the risk of cardiovascular events, and the arbitrary nature of the definition of hypertension have contributed to the variation in the definitions issued by various national and international authorities and particularly by the Joint National Committee (JNC) in the United States [121,122] and the WHO–ISH Guidelines

Committee [123]. Accordingly, in order to reduce confusion and provide more consistent advice to clinicians around the world, the WHO-ISH Guidelines Committee has agreed to adopt in principle the definition and classification provided in JNC VI. This new definition defines the lower limits of hypertension as 140 mmHg SBP and 90 mmHg DBP, the same as the lower limits for the borderline subgroup of mild hypertension in the 1993 WHO-ISH Guidelines [123]. The new Guidelines emphasize that the decision to lower the elevated pressure in a particular patient is not based on the level of blood pressure alone but on assessment of the total cardiovascular risk in that individual.

Hypertension is therefore defined as a SBP of 140 mmHg or greater and/or a DBP of 90 mmHg or greater in subjects who are not taking antihypertensive medication. A classification of blood pressure levels in adults over the age of 18 is provided in Table 1. The terms 'grades 1, 2 and 3' have been chosen rather than the terms 'stages 1, 2 and 3' used by JNC VI, since the word 'stage' implies progression over time in a way that does not necessarily apply here [124]. Otherwise, the values chosen and the terms used are those used in JNC VI. The terms 'mild', 'moderate' and 'severe' used in previous versions of the WHO-ISH Guidelines, would correspond to grades 1, 2 and 3, respectively. The widely used term 'borderline hypertension' becomes a subgroup within grade 1 hypertension. It must be emphasized that the term 'mild hypertension' does not imply a uniformly benign prognosis, but is used simply to contrast with more severe elevations of blood pressure.

In contrast to the 1993 Guidelines, the present report does not deal separately with hypertension in the elderly nor with isolated systolic hypertension. Rather, discussion of these two conditions is now part of the main text, since it is widely agreed that the treatment of these conditions is at least as effective in reducing cardiovascular risk as the treatment of classical essential hypertension in middle-aged subjects.

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

Category	Systolic	Diastolic
Optimal	< 120	< 80
Normal	< 130	< 85
High-normal	130-139	85-89
Grade 1 hypertension (mild)	140-159	90-99
Subgroup: borderline	140-149	90-94
Grade 2 hypertension (moderate)	160-179	100-109
Grade 3 hypertension (severe)	≥ 180	≥ 110
Isolated systolic hypertension	≥ 140	< 90
Subgroup: borderline	140-149	< 90

When a patient's systolic and diastolic blood pressures fall into different categories, the higher category should apply.

### Stratification of patients by absolute level of cardiovascular risk

Decisions about the management of patients with hypertension should not be based on the level of blood pressure alone, but also on the presence of other risk factors, concomitant diseases such as diabetes, target-organ damage and cardiovascular or renal disease, as well as other aspects of the patient's personal, medical and social situation. To assist with this, these Guidelines provide a simple method by which to estimate the combined effect of several risk factors and conditions on the future absolute risk of major cardiovascular events. The estimates are based on age, gender, smoking, diabetes, cholesterol, history of premature cardiovascular disease, the presence of target-organ damage and history of cardiovascular or renal disease. They were calculated from data on the average 10 year risk of cardiovascular death, nonfatal stroke or nonfatal myocardial infarction among participants (average initial age of 60 years; range 45-80 years) in the Framingham Study.

Four categories of absolute cardiovascular disease risk are defined (low, medium, high and very high risk). Each category represents a range of absolute disease risks. Within each range, the risk of any one individual will be determined by the severity and number of risk factors present. So, for example, individuals with very high levels of cholesterol or a family history of premature cardiovascular disease in several first-degree relatives will typically have absolute risk levels that are at the higher end of the range provided. Similarly, individuals with other risk factors listed in Table 2 may also have absolute risk levels that are towards the higher end of the range for the category.

How well these estimates predict the absolute risk of cardiovascular disease in Asian, African or other non-Western populations is uncertain. In those countries in which CHD incidence is relatively low and heart failure or renal disease is more common, the risk factors used to stratify risk in Table 3 should also be useful in stratifying the risk of these diseases.

#### Low-risk group

The low-risk group includes men below 55 and women below 65 years of age with grade 1 hypertension and no other risk factors. Among individuals in this category, the risk of a major cardiovascular event in the next 10 years is typically less than 15%. The risk will be particularly low in patients with borderline hypertension.

#### Medium-risk group

This group includes patients with a wide range of blood pressures and risk factors for cardiovascular disease. Some have lower blood pressures and multiple risk

Table 2 Factors influencing prognosis

Risk factors for cardiovascular diseases	Target-organ damage	Associated clinical conditions
<p>I Used for risk stratification</p> <ul style="list-style-type: none"> <li>Levels of systolic and diastolic blood pressure (grades 1–3)</li> <li>Men &gt; 55 years</li> <li>Women &gt; 65 years</li> <li>Smoking</li> <li>Total cholesterol &gt; 6.5 mmol/l (250 mg/dl)</li> <li>Diabetes</li> <li>Family history of premature cardiovascular disease</li> </ul> <p>II Other factors adversely influencing prognosis</p> <ul style="list-style-type: none"> <li>Reduced HDL cholesterol</li> <li>Raised LDL cholesterol</li> <li>Microalbuminuria in diabetes</li> <li>Impaired glucose tolerance</li> <li>Obesity</li> <li>Sedentary lifestyle</li> <li>Raised fibrinogen</li> <li>High-risk socioeconomic group</li> <li>High-risk ethnic group</li> <li>High-risk geographic region</li> </ul>	<ul style="list-style-type: none"> <li>Left ventricular hypertrophy (electrocardiogram, echocardiogram or radiogram)</li> <li>Proteinuria and/or slight elevation of plasma creatinine concentration (1.2–2.0 mg/dl)</li> <li>Ultrasound or radiological evidence of atherosclerotic plaque (carotid, iliac and femoral arteries, aorta)</li> <li>Generalized or focal narrowing of the retinal arteries</li> </ul>	<p>Cerebrovascular disease</p> <ul style="list-style-type: none"> <li>Ischaemic stroke</li> <li>Cerebral haemorrhage</li> <li>Transient ischaemic attack</li> </ul> <p>Heart disease</p> <ul style="list-style-type: none"> <li>Myocardial infarction</li> <li>Angina</li> <li>Coronary revascularization</li> <li>Congestive heart failure</li> </ul> <p>Renal disease</p> <ul style="list-style-type: none"> <li>Diabetic nephropathy</li> <li>Renal failure (plasma creatinine concentration &gt; 2.0 mg/dl)</li> </ul> <p>Vascular disease</p> <ul style="list-style-type: none"> <li>Dissecting aneurysm</li> <li>Symptomatic arterial disease</li> </ul> <p>Advanced hypertensive retinopathy</p> <ul style="list-style-type: none"> <li>Haemorrhages or exudates</li> <li>Papilloedema</li> </ul>

Target-organ damage corresponds to previous World Health Organization (WHO) stage 2 hypertension [6], and Associated clinical conditions corresponds to previous WHO stage 3 hypertension [6].

## Stratification of Risk to Quantify Prognosis

Table 3

Other Risk Factors & Disease History	Blood Pressure (mmHg)		
	Grade 1 (mild hypertension) SBP 140-159 or DBP 90-99	Grade 2 (moderate hypertension) SBP 160-179 or DBP 100-109	Grade 3 (severe hypertension) SBP ≥ 180 or DBP ≥ 110
I no other risk factors	LOW RISK	MED RISK	HIGH RISK
II 1-2 risk factors	MED RISK	MED RISK	V HIGH RISK
III 3 or more risk factors or TOD or diabetes	HIGH RISK	HIGH RISK	V HIGH RISK
IV ACC	V HIGH RISK	V HIGH RISK	V HIGH RISK

factors, whereas others have higher blood pressures and no or few other risk factors. This is the patient group for which the clinical judgement of the responsible doctor will be paramount in determining the need for drug treatment and the time interval before it should be instituted. Among subjects in this group, the risk of a major cardiovascular event over the next 10 years is

typically about 15–20%. The risk will be closer to 15% in those patients with grade 1 (mild) hypertension and only one additional risk factor.

### High-risk group

This group includes patients with grade 1 or grade 2 hypertension who have three or more risk factors listed

in Table 2, diabetes or target-organ damage and patients with Grade 3 (severe) hypertension without other risk factors. Among these patients the risk of a major cardiovascular event in the following 10 years is typically about 20–30%.

### **Very-high-risk group**

Patients with grade 3 hypertension and one or more risk factors and all patients with clinical cardiovascular disease or renal disease (as defined in Table 2) carry the highest risk of cardiovascular events, of the order of 30% or more over 10 years, and thus qualify for the most intensive and rapidly instituted therapeutic regimens.

## **Treatment**

### **Goals of treatment**

The primary goal of treatment of the patient with high blood pressure is to achieve the maximum reduction in the total risk of cardiovascular morbidity and mortality. This requires treatment of all the reversible risk factors identified, such as smoking, raised cholesterol or diabetes and the appropriate management of associated clinical conditions, as well as treatment of the raised blood pressure *per se*. The intensity with which the clinician treats these risk factors will plainly increase with the number and severity of risk factors, with the existence of associated clinical conditions, and with increasing absolute risks of major cardiovascular events, as indicated in Table 3.

As the relationship between cardiovascular risk and blood pressure is continuous, without a lower threshold, the goal of antihypertensive therapy should be to restore blood pressure to levels defined as 'normal' or 'optimal' (Table 1). Indeed, there is evidence that a major determinant of the risk reduction conferred by antihypertensive therapy is the level of blood pressure achieved [91,125]. Comparison of outcomes between the three randomized blood pressure target groups in the HOT study (DBP  $\leq$  90, 85 or 80 mmHg) was unable to detect significant differences in the risk of cardiovascular disease between adjacent target groups [84]. However, the results of that study confirm that there is no increase in cardiovascular risk in the patients randomized to the lowest target group (DBP  $\leq$  80 mmHg). Among diabetic patients in the HOT study, there were significantly lower risks of cardiovascular disease in those patients assigned to the lowest blood pressure target. Similarly, the results of the UKPDS [85] demonstrated that tight blood pressure control (with an average achieved SBP/DBP of 144/82 mmHg) conferred a substantial reduction in the risk of major cardiovascular events compared to less tight blood pressure control (with an average achieved blood pressure of 154/87 mmHg). It would seem desir-

able to achieve optimal or normal blood pressures in young, middle-aged or diabetic subjects (below 130/85 mmHg; Table 1) and at least high normal blood pressures in elderly patients (below 140/90 mmHg; Table 1).

Stratification of patients in terms of their total cardiovascular risk (Table 3) is not only useful for determining the threshold for initiating antihypertensive drug treatment; it is also useful for setting the goal blood pressure that should be achieved and the intensity with which this goal should be pursued. Plainly, the higher the risk, the more important it becomes to reach the goal blood pressure that is set, and to treat the other risk factors that have been identified.

When home or ambulatory blood pressure measurements are used to evaluate the efficacy of treatment, it must be remembered that daytime values provided by these methods (compared with office measurements) are on average around 10–15 mmHg lower for SBP and 5–10 mmHg lower for DBP. Treatment goals should therefore be modified appropriately when these methods are used.

### **Management strategy**

Having assessed the patient and determined the overall risk profile, including the level of blood pressure elevation, the responsible physician should determine whether the patient is at low, medium, high or very high risk of cardiovascular disease events, as shown in Table 3. This will help the physician, in consultation with the patient, to determine whether to:

- Institute immediate drug treatment for the hypertension and the other risk factors or conditions present (high and very high risk groups).
- Monitor blood pressure and other risk factors for several weeks and obtain further information before deciding whether to institute drug treatment (medium risk group).
- Observe the patient over a significant period of time before deciding whether to institute drug treatment (low risk).

In situations where resources are limited it becomes imperative to direct drug treatment to individuals in the high- and very-high-risk groups before considering their use in lower-risk patients.

Having decided on the broad strategy for management, the physician should then determine the specific therapeutic goals for the individual patient, and draw up a comprehensive therapeutic plan to lower the blood pressure and reduce the overall cardiovascular risk in order to attain these goals. This plan will include consideration of:

- monitoring: of blood pressure and other risk factors;
- lifestyle measures: to lower the blood pressure and control the other risk factors; and
- drug treatment: to lower blood pressure and to control the other risk factors and clinical conditions present.

Lifestyle measures should be instituted wherever appropriate in all patients including those who require drug treatment.

#### **Lifestyle measures**

While there is no direct randomized evidence demonstrating that reducing blood pressure through lifestyle measures reduces the risk of cardiovascular disease, this seems likely given all the other evidence suggesting that the benefits of antihypertensive treatment are determined primarily by the blood pressure reduction *per se* rather than by any other independent effect of particular treatment modalities.

Lifestyle measures (or nonpharmacological treatments) are used for a number of complementary reasons as outlined in the WHO Technical Report *Hypertension control* [6]:

- To lower the blood pressure in the individual patient.
- To reduce the need for antihypertensive drugs and maximize their efficacy.
- To address the other risk factors present.
- For primary prevention of hypertension and associated cardiovascular disorders in populations.

#### **Smoking cessation**

Smoking cessation is perhaps the single most powerful lifestyle measure for the prevention of both cardiovascular and noncardiovascular diseases in hypertensive patients. All hypertensive patients who smoke should receive appropriate counselling for smoking cessation. Nicotine replacement therapy should also be considered, since it appears to augment other interventions for smoking cessation [126].

#### **Weight reduction**

Excess body fat contributes to blood pressure levels from infancy and is the most important factor causing a predisposition to hypertension [127]. Weight reduction of as little as 5 kg reduces blood pressure in a large proportion of hypertensive individuals who are more than 10% overweight and also has a beneficial effect on associated risk factors such as insulin resistance, diabetes, hyperlipidaemia and left ventricular hypertrophy. The blood pressure lowering effects of weight reduction may be enhanced by simultaneous increase in physical exercise [128], by alcohol moderation in overweight drinkers [129] and by reduction of sodium

#### **Box 8 Lifestyle and blood pressure**

- It is important that lifestyle measures be instituted within the framework of a structured plan that includes the use of counselling and monitoring by appropriate health professionals such as nurses, dietitians, clinical psychologists and other therapists, as well as the responsible physician.
- Recommendations should be tailored for each individual and greater use should be made of modern and well-validated counselling techniques.
- Lifestyle measures that are widely agreed to lower the blood pressure and that should be considered in all patients in whom they may apply are weight reduction, reduction of excessive alcohol consumption, reduction of high salt intake and increase in physical activity.
- Particular emphasis should be placed on cessation of smoking and on healthy eating patterns that contribute to the treatment of associated risk factors and cardiovascular diseases.

intake in older hypertensive subjects (Trial Of Non-pharmacologic interventions in the Elderly, TONE) [130]. Weight loss of at least 5 kg should be recommended in the first instance, with further increments of 5 kg depending upon the response and the patient's weight.

#### **Moderation of alcohol consumption**

Notwithstanding the evidence that an alcohol intake of up to three 'standard' drinks a day may lower the risk of CHD [131], there is a linear relationship between alcohol consumption, blood pressure levels and the prevalence of hypertension in populations. Alcohol attenuates the effects of antihypertensive drug therapy but its pressor effect is, at least partially, reversible within 1–2 weeks by moderation of drinking by around 80% [132]. Heavier drinkers (five or more standard drinks a day) may experience a rise in blood pressure after acute alcohol withdrawal and be 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 per day for men, and no more than 10–20 g ethanol per day for women. They should be warned against the heightened risks of stroke associated with binge drinking.

#### **Reduction in salt intake**

Epidemiologic studies suggest that dietary salt intake is a contributor to blood pressure elevation and to the

prevalence of hypertension [133]. 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 around 4–6 mmHg SBP [134]. However, individuals vary considerably in their responses to changes in dietary salt, with black, obese and elderly subjects the most sensitive. A recent study in older hypertensive patients showed no adverse effects of a reduction in sodium of 40 mmol (2.3 g) per day and after 18 months there was a significant reduction in the need for antihypertensive drug therapy [130]. The aim of dietary sodium reduction should be to achieve an intake of less than 100 mmol (5.8 g) per day of sodium or less than 6 g per day of sodium chloride. Patients should be advised to avoid added salt, to avoid obviously salted foods, particularly processed foods, and to eat more meals cooked directly from natural ingredients. Counselling by trained dietitians and monitoring of urinary sodium are necessary in most cases. The high sodium–low potassium content of many preserved foods is drawn to the attention of the food industry.

#### **Complex dietary changes**

Vegetarians have lower blood pressure than meat-eaters [135] and vegetarian dietary patterns can lower blood pressure in hypertensive patients [136]. A series of controlled dietary trials indicate that these effects depend on a combination of effects of fruit, vegetables, fibre and low saturated fat intake rather than the presence or absence of meat protein. This conclusion has been confirmed in a recent study in which older subjects with mild or borderline hypertension were randomized for 8-week periods to continue their normal diet, to increase fruit and vegetable consumption alone or to also reduce their consumption of total and saturated fat [137]. Increasing fruit and vegetable consumption alone caused SBP/DBP to fall by 3/1 mmHg while the added measure of reducing fat intake led to a fall of 6/3 mmHg. In the patients with higher initial blood pressures, there was a fall of 11/6 mmHg with the combined dietary regime. The presence of higher intakes of calcium, magnesium or potassium may have contributed to the beneficial effects of some of these diets. Regular fish consumption as part of a weight reducing diet may enhance blood pressure reduction in obese hypertensive patients and yield additional benefits on lipid profiles [138]. Hypertensive patients should be advised to eat more fruit and vegetables, to eat more fish and to reduce their fat intake.

#### **Increased physical activity**

Sedentary patients should be advised to take up modest levels of aerobic exercise on a regular basis, such as a

brisk walk or a swim for 30–45 min, three to four times a week [139]. Such mild exercise may be more effective in lowering the blood pressure than more strenuous forms of exercise such as running or jogging, and may lower SBP by about 4–8 mmHg [140–142]. Isometric exercise such as heavy weight lifting can have a pressor effect and should be avoided.

#### **Psychological factors and stress**

Psychological factors, personality factors and stress are associated with the adoption of many less healthy lifestyle patterns associated with hypertension and increased risk of cardiovascular disease [143,144]. In this sense, helping individuals to cope with stress may have an important impact on their blood pressure and on compliance with antihypertensive medications [145,146]. Whether there are more direct effects of sustained stress on long-term blood pressure levels is a subject requiring ongoing research. To date, trials of various stress management procedures for blood pressure control have been unconvincing.

#### **Other measures**

Lifestyle measures are fundamental for the management of diabetes and the treatment of hyperlipidaemia, and appropriate measures should be instituted when these disorders are present in the hypertensive patient. These will generally include a diet low in saturated fat and rich in vegetables and fruit.

Interventions with limited or unproven efficacy in lowering blood pressure include bio-feedback, micronutrient alterations and dietary supplementation with calcium, magnesium and fibre.

#### **Drug treatment for lowering blood pressure**

The six main drug classes used, worldwide, for blood pressure lowering treatment are diuretics,  $\beta$ -blockers, calcium antagonists, ACE inhibitors, angiotensin II antagonists and  $\alpha$ -adrenergic blockers. In some parts of the world, reserpine and methyldopa are also used frequently. There is no reliable or consistent evidence that indicates substantive differences between drug classes in their effects on blood pressure, although there are important differences in the side-effect profiles of each class. There are also important differences between classes in the amount of evidence available from randomized controlled trials on the effects of treatment on morbidity and mortality. While there is a large body of data demonstrating the benefits of the older agents such as diuretics and  $\beta$ -blockers, there are fewer data available about calcium antagonists and ACE inhibitors, and no reliable data available about  $\alpha$ -blockers or the most recent classes of agents such as angiotensin II antagonists.

### Box 9 Benefits of drug treatment

- All classes of antihypertensive drugs have specific advantages and disadvantages for particular patient groups (Table 4).
- There is as yet no evidence that the main benefits of treating hypertension are due to any particular drug property rather than to lowering of blood pressure *per se*.
- The randomized trials conducted to date have not provided any clear evidence of differential effects on outcome of different agents producing the same blood pressure reduction.
- However, most individual studies have been too small to detect plausibly modest differences in important outcomes such as stroke or myocardial infarction.

### Principles of drug treatment

There is general agreement on the principles governing the use of antihypertensive drugs to lower blood pressure, independent of the choice of particular drugs. These principles include:

- The use of low doses of drugs to initiate therapy, beginning with the lowest available dose of the particular agent, in an effort to reduce adverse effects. If there is a good response to a low dose of a single drug but the pressure is still short of adequate control, it is reasonable to increase the dose of the same drug, provided that it has been well tolerated.
- The use of appropriate drug combinations (see Box 11) to maximize hypotensive efficacy while minimizing side effects. It is often preferable to add a small dose of a second drug rather than increasing the dose of the original drug. This allows both the first and second drugs to be used in the low dose range that is more likely to be free of side effects. In this context, the use of the fixed low-dose combinations that are increasingly available in the United States and Europe may be advantageous [122].
- Changing to a different drug class altogether if there is very little response or poor tolerability to the first drug used, before increasing the dose of the first drug or adding a second drug.
- The use of long-acting drugs providing 24 h efficacy on a once-daily basis. The advantages of such drugs include improvement in adherence to therapy and minimization of blood pressure variability, as a consequence of smoother, more consistent blood pressure control. This may provide greater protection against the risk of major cardiovascular events and the development of target-organ damage [147,148].

### Initiation of drug treatment

For patients in the high- and very-high-risk groups drug treatment should be instituted within a few days, as soon as repeated measurements have confirmed the patient's blood pressure.

For patients in the medium- and low-risk groups the initiation of drug therapy will be influenced by:

- consultation with the patient on preferred strategies;
- the degree of blood lowering achieved with lifestyle measures;
- the degree of control achieved for other risk factors; and
- the availability of resources in the prevailing health system.

For patients in the medium-risk group it is desirable to continue with lifestyle measures and to reinforce these if necessary for at least 3 months before considering drug treatment. If, however, goal blood pressures are not attained within a maximum of 6 months, drug treatment should be initiated.

For patients in the low-risk group having grade 1 (mild) hypertension, lifestyle measures should be used assiduously for 6 months before considering drug treatment. If however, goal blood pressures are not achieved, drug treatment should be instituted within 1 year.

The exception to this recommendation is for patients in the borderline subgroup with DBP between 90 and 94 mmHg or SBP between 140 and 149 mmHg. In this group, the doctor, in consultation with the patient, may choose to persevere with lifestyle measures alone to lower the pressure and reduce cardiovascular risk.

There is one other group of patients that deserves special mention: this is patients with high-normal SBP/DBP (130–139/85–89 mmHg) who also have diabetes mellitus and/or renal insufficiency. For these patients early and active drug treatment should also be considered, since this has been shown to reduce the rate of loss of renal function (see sections on Renal disease and Diabetes mellitus, p.175)

### Choice of antihypertensive drugs

All available drug classes are suitable for the initiation and maintenance of antihypertensive therapy, but the choice of drugs will be influenced by many factors illustrated in Table 4, including:

- socio-economic factors that determine drug availability in different countries or regions;
- the cardiovascular risk factor profile of the individual patient;

**Box 10 Absolute effects of treatment on cardiovascular risk**

- From the results of randomized controlled trials, it appears that each reduction of 10–14 mmHg in systolic blood pressure and 5–6 mmHg in diastolic blood pressure confers about two-fifths less stroke, one-sixth less coronary heart disease and, in Western populations, one-third less major cardiovascular events overall.
- In patients with grade 1 hypertension, monotherapy with most agents will produce reductions in systolic/diastolic blood pressure of about 10/5 mmHg. In patients with higher grades of hypertension, it is possible to achieve sustained blood pressure reductions of 20/10 mmHg or more, particularly if combination drug therapy is used.
- The estimated absolute effects of such blood pressure reductions on cardiovascular disease (CVD) risks (fatal plus nonfatal stroke or myocardial infarction) are as follows:

Patient group	Absolute risk (CVD events over 10 years)	Absolute treatment effects (CVD events prevented per 1000 patient-years)	
		10/5 mmHg	20/10 mmHg
Low-risk patients	< 15%	< 5	< 9
Medium-risk patients	15–20%	5–7	8–11
High-risk patients	20–30%	7–10	11–17
Very-high-risk patients	> 30%	> 10	>17

- Between these strata, the estimated absolute treatment benefits will range from less than five events prevented per thousand patient years of treatment (low risk) to more than 17 events prevented per thousand patient years of treatment (very high risk).
- The absolute benefits for stroke and coronary heart disease will be augmented by smaller absolute benefits for congestive heart failure and renal disease.
- These estimates of benefit are based on relative risk reductions observed in trials of about 5 years' duration. Longer-term treatment over decades could produce larger risk reductions (see Box 4).

- the presence of target-organ damage, of clinical cardiovascular disease, renal disease and diabetes;
- the presence of other co-existing disorders that may

- either favour or limit the use of particular classes of antihypertensive drugs;
- variation in individual patient responses to drugs from different classes;
- the possibility of interactions with drugs used for other conditions present in the patient; and
- the strength of the evidence for reduction of cardiovascular risk with the drug class in question.

The physician should tailor the choice of drug to the individual patient, after taking all these factors, together with patient preference, into account in each case. A practical framework for the management of patients with grade 1 or grade 2 hypertension is shown in Figure 1.

*Diuretics.* Diuretics constitute one of the most valuable classes of antihypertensive drugs. They are inexpensive, effective, generally well tolerated in low doses, and diuretic-based treatment regimens have been clearly shown to prevent major cardiovascular events, including stroke and CHD, in a variety of hypertensive patient groups. Many of the unwanted side effects of diuretics such as potassium depletion, reduced glucose tolerance, ventricular ectopic beats and impotence were associated with the use of high doses of diuretics of the order of 50–100 mg daily of hydrochlorothiazide and chorthalidone in the 1970s and 1980s. While there is some evidence from observational studies that the risk of sudden cardiac death in patients treated with nonpotassium-sparing diuretics can be reduced by their combination with potassium-sparing diuretics [149,150], this issue can only be resolved by prospective randomized controlled trials.

Diuretics should be used in low doses equivalent to a maximum of 25 mg daily of hydrochlorothiazide, and often half or less this dose, in order to reduce the adverse effects while still reaping the benefits. Diuretics are particularly recommended for the treatment of elderly patients with systolic hypertension [82] and of black patients.

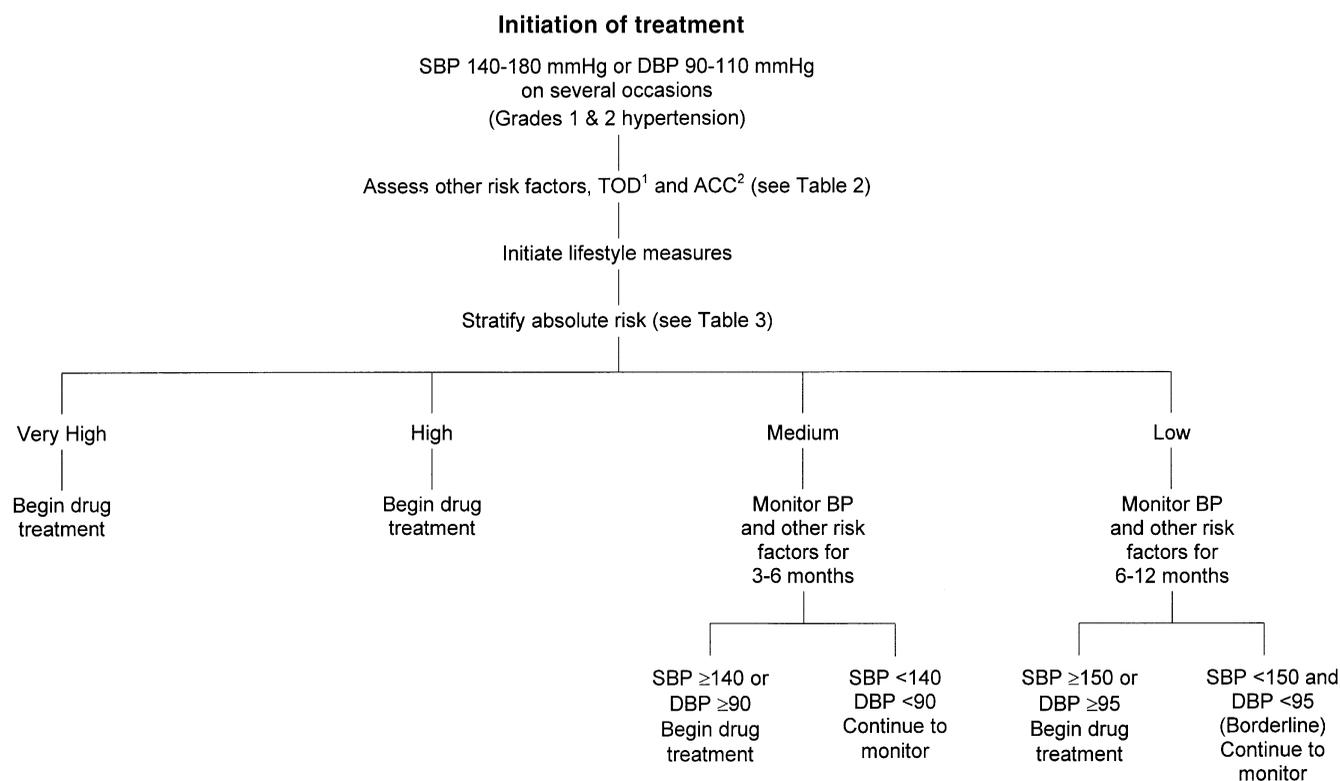
*β-Blockers.* β-Adrenoceptor-blocking drugs (β-blockers) are safe, cheap and effective for use as monotherapy or in combination with diuretics, dihydropyridine calcium antagonists and α-blockers. Whereas heart failure used to be a clear contraindication to the use of β-blockers in standard doses [121,123], there is emerging evidence that they may have a beneficial effect when used in very low starting doses in some patients with heart failure [151]. β-Blockers should be avoided in patients with obstructive airways disease and peripheral vascular disease. There have been reports that β-blockers can aggravate spastic or variant angina in Japanese patients [152]. They are often less effective in black patients.

Table 4 Guidelines for selecting drug treatment of hypertension

Class of drug	Compelling indications	Possible indications	Compelling contraindications	Possible contraindications
Diuretics	Heart failure Elderly patients Systolic hypertension	Diabetes	Gout	Dyslipidaemia Sexually active males
$\beta$ -Blockers	Angina After myocardial infarct Tachyarrhythmias	Heart failure Pregnancy Diabetes	Asthma and COPD Heart block <sup>a</sup>	Dyslipidaemia Athletes and physically active patients Peripheral vascular disease
ACE inhibitors	Heart failure Left ventricular dysfunction After myocardial infarct Diabetic nephropathy		Pregnancy Hyperkalaemia Bilateral renal artery stenosis	
Calcium antagonists	Angina Elderly patients Systolic hypertension	Peripheral vascular disease	Heart block <sup>b</sup>	Congestive heart failure <sup>c</sup>
$\alpha$ -Blockers	Prostatic hypertrophy	Glucose intolerance Dyslipidaemia		Orthostatic hypotension
Angiotensin II antagonists	ACE inhibitor cough	Heart failure	Pregnancy Bilateral renal artery stenosis Hyperkalaemia	

<sup>a</sup>Grade 2 or 3 atrioventricular block; <sup>b</sup>grade 2 or 3 atrioventricular block with verapamil or diltiazem; <sup>c</sup>verapamil or diltiazem. ACE, angiotensin converting enzyme;

Fig. 1



1. TOD - Target Organ Damage (previous WHO Stage 2 hypertension)[6].

2. ACC - Associated Clinical Conditions including clinical cardiovascular disease and renal disease (previous WHO Stage 3 hypertension)[6].

*ACE inhibitors.* ACE inhibitors are safe and effective in lowering blood pressure and they are now much less expensive than when first introduced. ACE inhibitors

are particularly effective in reducing morbidity and mortality in heart failure [153] and in retarding the progression of renal disease in patients with insulin-

dependent diabetes mellitus, especially in the presence of proteinuria [154]. Their most common adverse effect is a dry cough and their most serious adverse effect is very rare but life-threatening occurrence of angioedema [155]. They are often less effective in black patients.

*Calcium antagonists.* All subgroups of calcium antagonists are effective and well tolerated in lowering blood pressure. They are of demonstrated benefit for the prevention of stroke in elderly patients with systolic hypertension. The evidence about the effects of calcium antagonists on cardiovascular disease events is discussed in detail in the sections on Interventions to reduce cardiovascular risk in hypertensive patients (p.152) and Special populations (p.173). Long-acting calcium antagonists are preferred and rapid-onset short-acting calcium antagonists should be avoided. Calcium antagonists are particularly recommended for elderly patients with systolic hypertension [78] and for black patients. Adverse effects include tachycardia, flushing, ankle oedema and (with verapamil) constipation.

*Angiotensin II antagonists.* Angiotensin II receptor antagonists are the latest major group of antihypertensive drugs to become generally available. They have many features in common with ACE inhibitors, including particular value in patients with heart failure. There is still no reliable evidence of their effects on cardiovascular risk in patients with hypertension. However, they have few side effects, which may encourage adherence to therapy and appear to offer one advantage over ACE inhibitors; that is the absence of cough as a side effect [156].

*$\alpha$ -Blockers.*  $\alpha$ -Blockers are safe and effective in lowering blood pressure [157]. There is still no evidence about their effects on cardiovascular risk in hypertensive subjects. Their main side effect is postural hypotension which may be a particular problem in elderly patients. Assessment of standing blood pressure is essential. These drugs may have advantages in subjects with dyslipidaemia or glucose intolerance.

*Other drugs.* A number of centrally acting drugs are also available. Some of these are new, such as the imidazoline receptor stimulants (agonists), rilmenidine and moxonidine, and others much older, such as reserpine, methyldopa and clonidine. Methyldopa has a well-documented and continuing place in the treatment of hypertension in pregnancy (see section on Pregnancy, p.173) [158]. However, the side-effects profile of centrally acting agents is generally less favourable than that of the other main classes of available drugs. Where consideration of cost-effectiveness favours the use of reserpine in low-income populations, the doses used should be much lower than those used in earlier times.

### **Box 11 Monotherapy versus combination therapy**

#### **Drug monotherapy**

When drugs from the main classes available are used as monotherapy at the recommended doses, they produce very similar blood pressure reductions. In general, the sizes of the blood pressure reductions increase with the initial level of blood pressure, but typically the placebo-adjusted reductions average about 4–8% for both systolic and diastolic blood pressure. Thus for patients with blood pressures of about 160/95 mmHg, the usual reduction produced by monotherapy would be about 7–13 mmHg systolic and 4–8 mmHg diastolic. Clearly, for many patients with hypertension, such reductions in blood pressure would not restore optimal or even nonhypertensive blood pressure levels.

#### **Drug combination therapy**

Combination therapy of several of the available drug classes has been shown to produce blood pressure reductions that are greater than those produced by any group of individual agents used alone. The Hypertension Optimal Treatment (HOT) study [84], in which blood pressure was lowered to below 90 mmHg in over 90% of patients, demonstrated that combination therapy was necessary in 70% of participants. Combinations with fully additive hypotensive effects will deliver blood pressure reductions that are around twice as great as those obtained with a single drug, of the order of 8–15%, or 12–22 mmHg systolic and 7–14 mmHg diastolic for patients with blood pressure of 160/95 mmHg.

#### **Effective drug combinations**

- Diuretic and  $\beta$ -blocker.
- Diuretic and angiotensin converting enzyme (ACE) inhibitor (or angiotensin II antagonists).
- Calcium antagonist (dihydropyridine) and  $\beta$ -blocker.
- Calcium antagonist and ACE inhibitor.
- $\alpha$ -Blocker and  $\beta$ -blocker.

Effective drug combinations utilize drugs from different classes in order to obtain the additive hypotensive effect that comes from combining drugs with different primary actions, while minimizing the compensations that limit the fall in blood pressure. Combinations of limited value generally result from combining drugs that work through similar mechanisms so that their hypotensive actions may be less than additive, or drugs that have similar side effects so that the risk of adverse effects is increased.

The older vasolidator agents such as hydralazine are also widely used in some regions of the world. How-

ever, the side effects of direct vasodilators such as hydralazine and minoxidil (tachycardia, headache and sodium and water retention) make them less suitable for use as first-line drugs.

#### **Patient education and compliance with therapy**

Good communication between the physician and the patient lies at the core of the successful management of hypertension. Since the treatment of hypertension is for life, it is essential that the physician establish a good relationship with the patient, provide the patient with information, both verbal and written, and answer any questions the patient may have. Good information about blood pressure and high blood pressure, about risks and prognosis, about the expected benefits of treatment and about the risks and side effects of treatment will be essential for satisfactory life long control of hypertension.

Failure to establish effective communications and relations will generally lead to poor adherence to antihypertensive therapy and unsatisfactory control of the raised blood pressure. The magnitude of this problem is reflected in population surveys that have demonstrated that hypertension is either untreated or inadequately controlled in around 70–75% of patients worldwide.

One of the best ways to improve adherence to therapy is to involve the patient in making decisions about treatment strategies. Another approach may be to use clinical pharmacists to inform the patient on the use of medications, and on side effects. Well trained clinic nurses will also contribute a great deal to improve compliance with therapy, as will other health professionals such as dieticians and trained counsellors who are experienced in the implementation of lifestyle measures.

Other measures that may help include the use of home blood pressure measurement and the involvement of the patient's family in the therapeutic plan.

#### **Refractory hypertension**

Hypertension may be termed refractory, when a therapeutic plan that has included attention to lifestyle measures and the prescription of combination drug therapy in adequate doses has failed to lower SBP/DBP below 140/90 mmHg in patients with classical essential hypertension, or below 140 mmHg SBP in patients with isolated systolic hypertension. In these situations, referral to a specialist should be considered.

There are many causes for resistance to treatment, as illustrated in Box 12 below, including apparent causes such as isolated office (white-coat) hypertension and the failure to use an appropriately large cuff in a patient

#### **Box 12 Causes of refractory hypertension**

- Unsuspected secondary cause (NB: renal and endocrine).
- Poor adherence to therapeutic plan.
- Continued intake of drugs that raise blood pressure (NB: nonsteroidal anti-inflammatory drugs, but see section on Clinical history, p.159).
- Failure to modify lifestyle including.
  - weight gain;
  - heavy alcohol intake (NB: binge drinking).
- Volume overload due to:
  - inadequate diuretic therapy;
  - progressive renal insufficiency; or
  - high sodium intake.

#### **Causes of spurious refractory hypertension**

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

with a very fat arm. One of the most important causes of refractory hypertension may be poor compliance or adherence to therapy and in this situation, after all else fails, it can be very helpful to suspend all drug therapy while continuing to monitor blood pressure frequently. A fresh start with a new regimen may help break a vicious cycle.

#### **Other drug treatment**

Since the aim of treatment is the reduction of the total cardiovascular risk, it is at least as important to treat the other risk factors and clinical conditions present in the individual hypertensive patient. This means the physician should either refer the patient to appropriate clinics and specialists, or institute an appropriate regimen of lifestyle factors and drug treatment for associated conditions such as diabetes mellitus, hypercholesterolaemia, CHD, cerebrovascular disease or renal disease.

#### **Antiplatelet therapy**

The use of aspirin, and of some other antiplatelet agents, has been well documented to reduce the risk of fatal and nonfatal coronary events, of stroke and of cardiovascular death in patients with established coronary or cerebrovascular disease [100]. In the light of the results of the HOT study [84], it is reasonable to recommend the use of low-dose aspirin in hypertensive patients whose blood pressure has been rigorously controlled, who are at high risk of CHD and who are not particularly at risk of bleeding from the gastro-intestinal tract or from other sites.

**Cholesterol-lowering therapy**

Cholesterol reduction with a variety of agents has been shown to reduce the risks of initial and recurrent CHD events among patients with a wide range of initial cholesterol levels [26,42,94–97]. Trials of HMG CoA reductase inhibitors, conducted primarily among patients with CHD, have also reported reductions in stroke risk [26,94–97]. The relative effects of cholesterol-lowering therapy appear to be similar in those with or without hypertension. In these circumstances, the use of cholesterol-lowering therapy can be recommended for hypertensive patients who have elevated cholesterol or who are for other reasons at high risk of CHD.

**Follow-up**

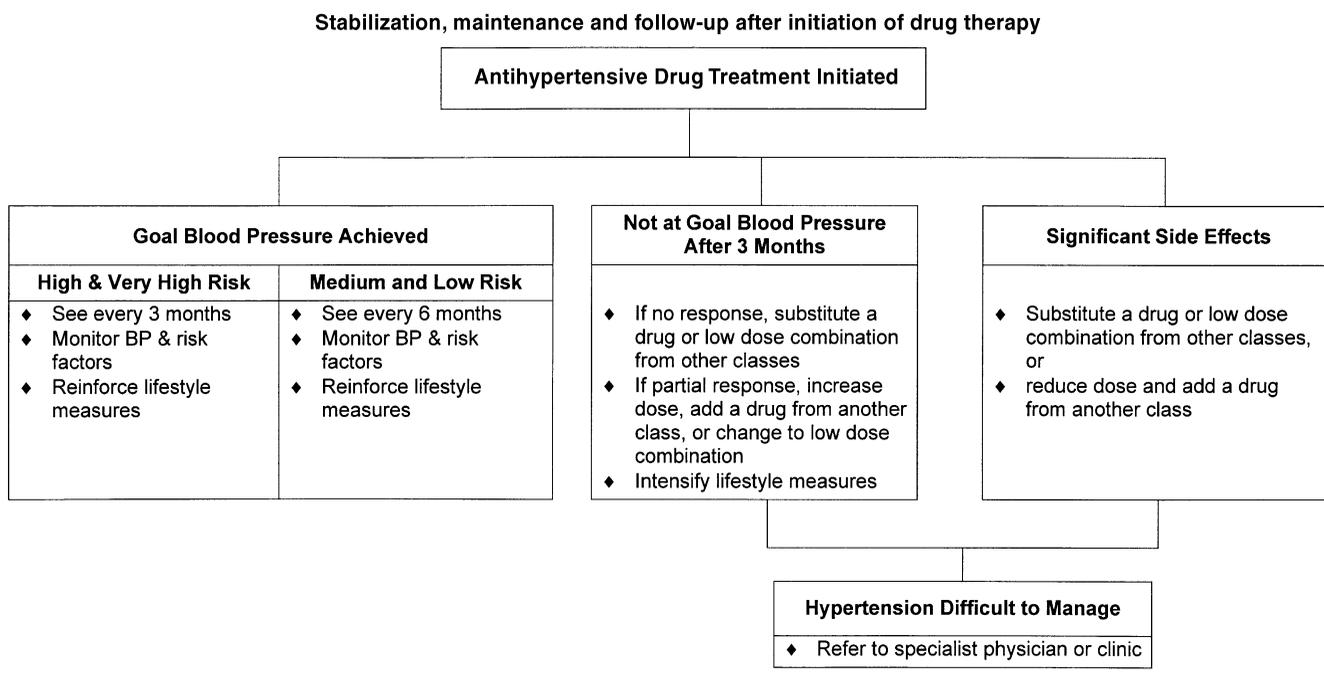
During the period of evaluation and stabilization of treatment, patients need to be seen at frequent intervals to monitor the changes in blood pressure and in the other risk factors and clinical conditions present, and to observe the effects of treatment. Follow-up visits should be used to establish good relations with the patient and to educate the patient on the nature of the condition of hypertension and of the other risk factors or disorders present. The patient should understand why control of hypertension is important, and that treatment should generally continue for a lifetime. The acceptance and implementation of changes in lifestyle in particular, need satisfactory explanation and

reinforcement. For successful drug therapy, it is important to explain the possible adverse effects and emphasize the need for regular medication, with early reporting of any side effects.

The frequency of visits will depend on the overall risk category of the patient as well as on the level of blood pressure (Fig. 2). 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. 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 progres-

Fig. 2



sive reduction in the dose or number of drugs used, particularly among patients strictly observing lifestyle (nondrug) measures. Such attempts to 'step down' treatment should be accompanied by careful continued supervision of the blood pressure.

Since a hypertensive patient is typically treated for decades, it is likely that the treatment regimen, including the choice of drugs, will undergo multiple changes. It is therefore advisable for all hypertensive patients to keep a record of all treatments used and of their outcomes, and it is the responsibility of doctors and health services to maintain adequate records of treated hypertensive patients and to make them readily available.

## Special populations

### Ethnic minorities and high-risk regions

The prevalence of hypertension and the incidence of blood pressure-related cardiovascular disease vary considerably between ethnic groups and geographic regions. Ethnic minority groups in many Western populations frequently have higher rates of hypertension [60,159,160], as well as higher rates of major cardiovascular events. The pattern of cardiovascular disease within minority ethnic groups appears to vary by region. For example, in some, but not all, African-American populations, renal failure [62] and stroke [61] are particularly prevalent. In South Asian populations of the United Kingdom, CHD, stroke and renal failure rates are all high [63], whereas in Canada, the rates among South Asians are similar to or lower than those in Caucasians [64].

The pattern of cardiovascular disease in ethnic majority groups also varies considerably between geographic regions. For example, in many Eastern Asian populations, stroke (particularly haemorrhagic stroke) is relatively common whereas CHD is relatively uncommon compared with that seen in Western populations [7]. However, the proportional relationships of blood pressure with specific cardiovascular disease risks in Chinese and Japanese populations appears to be very similar to those observed in North American and European populations. The higher incidence of haemorrhagic stroke in Eastern populations appears to reflect, at least in part, a particularly strong association of this type of stroke with blood pressure [7]. In other large non-Western populations such as those of sub-Saharan Africa, stroke and renal disease appear to predominate among cardiovascular diseases [5].

The available data provide no reason to believe that the relative effects of lowering blood pressure on specific disease risks will vary importantly between ethnic groups or regions, although there may be lesser effects of some specific agents (e.g. ACE inhibitors) in specific ethnic groups (e.g. African-Americans). How-

ever, because ethnicity and geographic region are such important determinants of absolute risk, it is likely that the absolute effects of treatment will vary markedly between ethnic groups and geographic regions. For example, among individuals with similar levels of blood pressure, the absolute risk of cardiovascular disease will tend to be higher in individuals of South Asian descent in the United Kingdom or African-Americans in the United States compared with Caucasians in the same populations. Therefore, it could be expected that absolute treatment benefits conferred by any given reduction in blood pressure would also be greater in these groups.

The absolute benefits of blood-pressure-lowering therapy may be particularly great in groups in which there are high risks of events that are very strongly blood pressure-related (e.g. stroke or renal failure). Such populations include many of those in the Eastern Asian region and sub-Saharan Africa as well as African American populations in the United States. The rates both of stroke and of CHD are high in Eastern Europe, Russia and the Baltic states [65], suggesting that the absolute effects of treatment in populations from these regions are also likely to be particularly large. Some ongoing randomized controlled trials will provide evidence about the comparative absolute benefits of blood pressure lowering treatments in such diverse populations [161].

For regions in which healthcare resources are particularly scarce, investment in population-based primary prevention strategies may yield the largest dividend. The most cost-effective hypertension treatment programmes will involve the use of the lowest cost drugs (e.g. diuretics, reserpine,  $\beta$ -blockers, generic formulations of ACE inhibitors, angiotensin II antagonists, calcium antagonists and other generic agents) in the highest risk groups. The selective treatment of patients with pre-existing cardiovascular or renal disease (irrespective of hypertension severity) or with severe hypertension (SBP > 180 mmHg or diastolic > 110 mmHg) will result in the greatest ratio of events prevented to numbers of patients treated.

### Pregnancy

Hypertension in pregnancy is usually defined either by an absolute level of blood pressure (e.g. 140/90 mmHg or greater) or by a rise in blood pressure from pre-conception or first trimester levels (e.g. SBP blood pressure rise  $\geq$  25 mmHg and/or DBP rise  $\geq$  15 mmHg) [162,163]. Hypertension in pregnancy is typically classified as: chronic (essential or secondary hypertension); *de novo* (pre-eclampsia or gestational hypertension); or pre-eclampsia superimposed on chronic hypertension. Pre-eclampsia is a multisystem disorder in which raised blood pressure is but one sign. The

major maternal abnormalities occur in kidneys, liver, brain and coagulation systems. Impaired uteroplacental blood flow may cause fetal growth retardation or intrauterine death.

It is generally agreed that blood pressures greater than about 170/110 mmHg should be lowered to protect the mother against risk of stroke or eclampsia. However, there is less agreement about the value of treatment for lower levels of blood pressure. The drugs that are most widely used to lower blood pressure acutely in pregnancy include nifedipine, labetalol and hydralazine [158]. Magnesium sulphate may produce some blood-pressure-lowering effects but is generally inadequate to treat severe hypertension in pregnancy. The drugs most widely used for chronic treatment of raised blood pressure in pregnancy include:  $\beta$ -blockers, in particular oxprenolol, pindolol and atenolol (associated with fetal growth retardation when used long-term throughout pregnancy); labetalol; methyldopa; prazosin; hydralazine; nifedipine and isradipine. Antihypertensive agents that are generally avoided during pregnancy include ACE inhibitors, which are associated with fetal growth retardation, oligohydramnios, neonatal renal failure and possibly abnormal fetal morphology (fetal hypotensive syndrome), and angiotensin II receptor antagonists, the effects of which may be similar to those of ACE inhibitors. Diuretics are also used infrequently because of concerns that they may further reduce the already compromised plasma volume, although they have been shown to be effective in randomized controlled trials [164].

Lowering blood pressure is only one aspect of the management of pre-eclampsia. Management ideally involves a multidisciplinary team. Maternal and fetal monitoring are essential for the detection of signs of advancing pre-eclampsia or of impending fetal demise and, thereby, the need for delivery, which remains the definitive management for pre-eclampsia. Aspirin has not been shown to be effective in preventing pre-eclampsia [165]. Oral calcium supplementation is not of benefit as prophylaxis against pre-eclampsia in calcium-replete populations, but although evidence is limited, it is generally agreed that dietary calcium intake should be increased to recommended levels in populations with low calcium diets.

#### **Very elderly**

The results of randomized trials provide clear evidence of the benefits and safety of antihypertensive treatment in patients across a wide age range up to about 80 years [166]. These trials have not provided any clear evidence of differential proportional effects of therapy in younger and older patients, although the absolute effects are typically greater in older individuals because of their higher risk of cardiovascular events [70].

Benefits of treatment have been demonstrated among older patients with classical hypertension (raised SBP and DBP), as well as among older patients with isolated systolic hypertension (raised SBP alone).

However, most of the completed studies have included too few patients above this age to provide reliable evidence of benefits or safety. Among the trials reported to date, the oldest average age of patients was in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension) [167]. In that study, which demonstrated a marked reduction in cardiovascular events among patients assigned active treatment, participants were aged between 70 and 84 years at enrolment (mean 76 years). However, the number of patients in that study above age 80 years was too small for reliable conclusions to be drawn about the effects of treatment on cardiovascular disease risk in this subgroup. In the Syst-Eur trial of treatment for isolated systolic hypertension among patients aged 60 years or older, there was no clear evidence of an association between older age and the size of the treatment effects on combined fatal or nonfatal cardiovascular events, although there was a trend towards a lesser effect on fatal events with increasing age [168].

Because of the absence of direct evidence about the effects of blood pressure lowering in the very elderly, and the limited prognostic relevance of blood pressure levels when measured at very old ages, there is uncertainty about the value of antihypertensive treatment for patients over the age of 80 years. A large-scale randomized controlled trial has recently been initiated to assess the potential benefits of treatment of hypertension in very old patients. The Hypertension in the Very Old Trial (HYVET) is currently recruiting hypertensive patients aged over 80 years [161]. Patients are randomized to receive either a diuretic-based regimen, a calcium antagonist-based regimen, or no treatment. In addition to this study, several other ongoing trials involving a broader patient group are recruiting some patients older than 80 years. The results of these trials should eventually provide reliable evidence about the effects of blood-pressure-lowering therapy in this very-high-risk population.

#### **Co-existing cerebrovascular or cardiac disease** **Cerebrovascular disease**

Individuals with a history of stroke or TIA have very high risks of further cerebrovascular events. Among such patients, the typical stroke rate is 4% or more per year. Individuals with a history of ischaemic stroke or TIA also have high risks of CHD events. The risks of recurrent cerebrovascular events (as well as initial CHD events) appear to be directly related to levels of blood pressure [12–14]. Consequently, even modest reduction

in blood pressure among such patients could confer worthwhile reductions in the absolute risk of cardiovascular events. In trials among stroke survivors with hypertension, blood-pressure-lowering therapy produced a 29% (SD 9) reduction in stroke risk and a trend towards a reduction in CHD events [169]. The proportional reduction in stroke risk was similar to that observed in patients without stroke; however, the absolute benefits were several times greater. In the three trials of blood-pressure-lowering agents among patients with a broad range of blood pressures at entry, the effects of treatment were less clear, although there was still a suggestion of benefit [12]. The remaining uncertainty about the benefits of treatment for a broad range of patients with cerebrovascular disease should be resolved by the Perindopril Protection against Recurrent Stroke Study (PROGRESS), a trial of ACE inhibitor-based therapy in patients with a history of stroke or TIA [170].

#### **Coronary heart disease**

Individuals with a history of CHD have very high risks of further CHD events. Among patients with a history of myocardial infarction or unstable angina, the risk of CHD death or nonfatal myocardial infarction is 5% or more per year. Once again, the risk of these recurrent events appears to be directly related to the level of blood pressure [13]. There are few data available about the effects of blood pressure lowering in hypertensive patients with CHD. However, many of the more common blood pressure lowering drugs have been assessed in broader groups of patients with CHD, albeit with objectives other than reduction of blood pressure.  $\beta$ -Blockers have been shown to reduce the risks of both re-infarction and cardiovascular death by about a quarter in patients with myocardial infarction [171]. Overall there is no clear evidence from clinical trials that calcium antagonists reduce recurrent CHD events outcomes, but there are suggestive, though not definitive, data demonstrating a reduced risk of myocardial infarction in patients treated with verapamil or diltiazem, and an increased risk in patients treated with immediate release nifedipine [86]. Ongoing studies of verapamil, diltiazem and longer-acting dihydropyridine calcium antagonists in hypertensive and nonhypertensive patients with CHD should provide clearer evidence about the effects of these agents on recurrent CHD risk [161]. Several large trials of ACE inhibitors in patients with heart failure or left ventricular dysfunction have provided evidence of a reduction of about one-fifth in the risk of myocardial infarction or sudden death [172]. In both the trials of  $\beta$ -blockers and the trials of ACE inhibitors, the magnitude of the effects on CHD events appears greater than that which would be expected from the blood pressure lowering alone and seems likely to reflect, at least in part, other cardioprotective effects of these agents. The remaining

uncertainty about the effects of ACE inhibitors on CHD events among high risk patients without heart failure or left ventricular dysfunction should be resolved by the Heart Outcome Prevention Evaluation (HOPE) study [173].

#### **Congestive heart failure**

Patients with congestive heart failure are at particularly high risk of death from cardiovascular disease. There are few data available about the effects of blood pressure lowering specifically among hypertensive patients with heart failure. However, the effects of various blood-pressure-lowering drugs have been assessed in a broad range of patients with heart failure. Several large trials of ACE inhibitors in patients with heart failure or left ventricular dysfunction have provided evidence of a reduction in mortality of about one-sixth and somewhat larger reductions in heart failure-related morbidity [153]. Recent evidence also indicates that  $\beta$ -blockers reduce the risk of cardiovascular death and the need for hospital admission by about a quarter in patients with heart failure, a group for which  $\beta$ -blockers were previously thought to be contraindicated [151]. Trials of calcium antagonists in patients with heart failure have produced no evidence of beneficial effects of treatments with these agents.

#### **Renal disease**

Hypertension is both a cause and a consequence of renal disease, and irrespective of aetiology, hypertension is a major determinant of renal disease progression [174]. Malignant or accelerated hypertension, renal artery stenosis and athero-embolic disease are all important causes of renal disease secondary to hypertension. The role of less severe blood pressure elevations in the genesis of renal failure is less clear, although there is strong evidence of a role for such blood pressure elevations in some populations, such as African-Americans [62]. Primary renal parenchymal disease has been observed to be responsible for 3–4% of hypertension in some populations, and renovascular disease in around 1% [11]. Most (80–90%) patients presenting to renal replacement programmes are hypertensive, but patients presenting with the combination of hypertension and renal impairment require definition of macroscopic and/or microscopic renal and/or renovascular anatomy before hypertension can be regarded as the cause of the renal impairment. Diabetic nephropathy, hypertensive nephropathy and primary glomerulonephritis are the three most common causes of end-stage renal failure worldwide. Other important aetiologies include reflux nephropathy, polycystic kidney disease, analgesic nephropathy and secondary glomerulonephritis.

Irrespective of whether hypertension causes renal disease or vice versa, it is clear that hypertension is a

major determinant of progression of renal disease and the risk of end-stage failure [11,175]. There is also some evidence that any familial tendency to hypertension will increase the prevalence of renal failure in patients with primary renal disorders [176] or with diabetes [177]. There is little evidence from randomized trials in hypertensive patients to show that treatment modifies the slight risk of developing renal failure, but more compelling evidence that blood pressure control will slow progression in patients with renal failure [178]. There has been much interest in the question of whether some classes of antihypertensive agents, in particular ACE inhibitors, retard progression of renal disease over and above their effects on blood pressure lowering [179] but this remains unproven. Evidence from the Modification of Diet in Renal Disease Study (MDRDS) suggests that more aggressive blood pressure lowering should be pursued in patients with chronic renal failure and proteinuria. Lower blood pressure targets have been proposed for patients with proteinuria of  $> 1$  g/day (125/75 mmHg) than for patients with lesser proteinuria (130/80 mmHg) [180].

#### Diabetes mellitus

The prevalence of hypertension is 1.5 to 2 times greater in patients with diabetes mellitus compared with matched nondiabetic individuals [181]. Type 1 diabetes mellitus is associated with hypertension only when albuminuria and early nephropathy develop, but type 2 diabetes mellitus may be associated with hypertension at or even preceding diagnosis [182]. Type 2 diabetes and hypertension are associated with an insulin-resistant state (syndrome X) characterized by hyperinsulinaemia, dyslipidaemia and obesity [183], but a causal relationship between insulin resistance and hypertension has not yet been established [184]. The co-existence of diabetes mellitus and hypertension is important, as they are multiplicative risk factors for macrovascular and microvascular disease, resulting in increased risks of cardiac death, CHD, congestive heart failure, cerebrovascular disease and peripheral vascular disease [182,185]. Macrovascular complications account for the majority of deaths in the diabetic population and the absence of hypertension is associated with long-term survival [186]. Microvascular disease resulting in diabetic nephropathy and retinopathy leads to significant morbidity and mortality. The progressive decline in glomerular function that is seen in diabetic patients with hypertension, especially those with albuminuria, can be slowed with antihypertensive treatment [187]. ACE inhibitors have been shown to slow the rate of decline in renal function and reduce the risk of dialysis in normotensive type 1 diabetic subjects with proteinuria [154]. Hypertension is also associated with an increased incidence of diabetic retinopathy [188] and treatment with ACE inhibitors has been shown to

reduce the progression of retinopathy in normotensive type 1 diabetic subjects [189].

Nonpharmacological interventions such as weight loss have been shown to improve insulin resistance and blood pressure in hypertensive diabetic patients [190] and similar lifestyle modifications are recommended for the initial treatment of hypertension and diabetes mellitus individually or when these diseases co-exist. Pharmacological treatment of hypertension in diabetic patients can potentially differ from that in the nondiabetic because of differing effects on lipid profiles, insulin sensitivity and glucose metabolism [191]. Diuretics and  $\beta$ -blockers are reported to reduce insulin sensitivity and increase triglyceride levels. However, diuretic-based regimens have been shown to reduce cardiovascular events in diabetic patients with hypertension [182].  $\beta$ -Blockers potentially mask hypoglycaemic awareness, but in practice this is not a major contraindication considering the clear evidence of benefits of  $\beta$ -blockers in diabetic patients after myocardial infarction [192]. ACE inhibitors and calcium antagonists are thought not to alter insulin sensitivity or lipid profiles, but the CAPPP study has recently reported that hypertensive patients assigned captopril-based therapy had a lower risk of developing diabetes than did patients assigned diuretic- or  $\beta$ -blocker-based therapy [81,191]. Recently, the UKPDS (38 and 39) has demonstrated that there were similar benefits of ACE inhibitor- and  $\beta$ -blocker-based therapy for a variety of both macrovascular and microvascular disease outcomes in patients with type 2 diabetes [83,85]. Two small, randomized, controlled trials have reported that ACE inhibitors have a more favourable effect on CHD events compared with calcium antagonists in diabetic patients [193,194]. These results are consistent with either a more favourable effect of ACE inhibitors or, alternatively, an adverse effect of calcium antagonists, on vascular events in hypertensive diabetic patients. However, since these studies were small and their results less than definitive, further evidence is required to determine whether there are true differences between these drug classes in their effects on macrovascular events.

In the HOT study of calcium-antagonist-based therapy [84], there was evidence that lowering blood pressure to the lowest target level (DBP  $< 80$  mmHg) in diabetic hypertensive patients resulted in lower risks of cardiovascular events. This finding is consistent with evidence from the UKPDS 38, demonstrating that lower achieved SBP/DBP (144/82 mmHg versus 154/87 mmHg) was associated with significantly reduced risks of major macrovascular disease events as well as microvascular disease outcomes [85]. The likelihood that diabetic hypertensive patients will benefit from low target blood pressures is consistent with the

evidence from trials of blood pressure lowering in normotensive diabetic patients with or without renal disease [195].

### **Implementation**

Translating the recommendations of clinical guidelines and the findings from research studies into daily clinical practice remains a daunting challenge, no less in the treatment of hypertension than in other fields. The rule of halves (only half of all hypertensive patients are aware that they have hypertension, only half of those aware are actually on treatment, and only half of those on treatment have their blood pressure well controlled) still applies in many countries around the world, and even the most affluent countries have only doubled the proportion of well-controlled hypertensive patients to approximately one-quarter (see section on Trials of diuretic- and  $\beta$ -blocker-based regimens, p.155). This only serves to emphasize the validity of Alexander Lomas' statement 'Words without action: the production, dissemination and impact of consensus recommendations' [196]. It is now plain that as a stand-alone tool, practice guidelines neither change clinical practice nor affect health outcomes [196–199]. The evidence from many analyses has established that in order to improve physician performance or other health outcomes, it is necessary to put in place a range of measures reaching locally into the practice site and involving local medical practitioners in an active way [196–199]. This is plainly beyond the direct capacity or resources of the WHO–ISH Guidelines Committee, but it is hoped to achieve far greater penetration to medical practitioners through alliances and partnerships with national and regional hypertension societies, leagues against hypertension and hypertension research councils.

These Guidelines, which are being published in specialist medical journals, will be accompanied by a much briefer companion set of *Practice Guidelines* intended for translation into many languages and distribution to local medical practitioners in many countries. The presidents of the leagues and societies affiliated with the International Society of Hypertension and the World Hypertension League have agreed to assist in forming national alliances with government agencies, with professional medical associations and colleges and with public education groups in order to develop action programs for the implementation of the recommendations in these guidelines. The WHO–ISH Guidelines can serve as a model and a stimulus for the development of custom-built national recommendations, adapted to suit the local cultural, economic and social realities. It is hoped that such modified recommendations could be embedded in an implementation plan that reaches local medical practitioners and local communities alike. Such programmes could embrace both the clinical strategies set out in these pages, and the

mass strategies necessary for hypertension control at the population level.

### **Future research**

#### **Blood pressure and cardiovascular disease in developing countries**

There is a pressing need for observational epidemiological studies as well as randomized controlled trials in populations from Asia, Africa and Latin America, so as to provide direct evidence about the risks associated with blood pressure and other risk factors, and to determine the effects of blood-pressure-lowering treatments in patients from these large populations. The detection and quantification of any regional differences that may have relevance for decisions about the strategies adopted for both prevention and treatment of cardiovascular diseases [7]. Importantly, such research would obviate the need to extrapolate from research conducted in other geographically and ethnically distinct populations.

#### **Alternative blood pressure measurements and arterial distensibility**

Reliable data are urgently needed on the prognostic significance of blood pressure values obtained by ambulatory blood pressure monitoring or by self-measurement, particularly at home. In this regard, the prognostic significance of isolated clinic (white-coat) hypertension also needs clarification. Further trials of ambulatory blood pressure measurement-guided treatment versus standard therapy would also be of value. More research is also required to determine the independent prognostic relevance of the various other indices of blood pressure and arterial distensibility that have been developed. This includes further investigation of pulse pressure in comparison with mean arterial pressure, DBP and SBP. It should also include investigation of the prognostic relevance of other indices of arterial distensibility and stiffness.

#### **Blood pressure lowering in high-risk patients**

It is essential to continue to extend trials of blood pressure lowering to include high-risk groups with or without hypertension but with other major risk factors for cardiovascular events such as diabetes, renal insufficiency, cerebrovascular disease, CHD, peripheral vascular disease or atrial fibrillation. There is a strong rationale for expecting a wide range of patients, both hypertensive and normotensive, with these conditions to benefit from blood pressure lowering.

#### **More versus less blood pressure lowering**

The results of the UKPDS, together with the subgroup results for patients with diabetes in the HOT study, provide strong evidence that lower blood pressure targets among diabetic patients are associated with important reductions in cardiovascular risk. More re-

search is required to determine whether there are similar advantages of a lower blood pressure target in other high-risk groups. Studies investigating the effects of combination therapy versus monotherapy in patients at high risk of cardiovascular events would be helpful in this regard.

#### **Evaluation of surrogate endpoints**

While there is reasonably good evidence about the independent prognostic significance of left ventricular hypertrophy (assessed by electrocardiogram or echocardiogram), there is a need for better evidence about the prognostic significance of other surrogate endpoints including carotid atherosclerosis, endothelial dysfunction and microalbuminuria (particularly among nondiabetic patients), for the separate risks of stroke and CHD events. Further trials evaluating the effects of blood-pressure-lowering treatments on the risks of cardiovascular events among individuals with these conditions would also be valuable. Furthermore, it would be of particular interest to determine whether different agents producing the same blood pressure reduction are differentially effective in reversing or retarding the progression of these conditions; and, if so, whether this has implications for cardiovascular disease.

#### **Combined interventions for cardiovascular disease prevention**

The causes of cardiovascular disease in hypertensive patients are clearly multifactorial, and there is a strong case for the conduct of factorial randomized trials investigating the separate and joint effects of blood-pressure-lowering treatments and other intervention modalities. For example, in active- or placebo-controlled trials of new blood-pressure-lowering agents, it would be of value to include factorial assignment to such interventions as cholesterol lowering, folic acid (for homocysteine lowering) and/or antioxidant vitamins

#### **Effects of new blood-pressure-lowering agents**

There are many ongoing trials of the new classes of blood-pressure-lowering agents, and more will be required as new drugs are developed. Most of the ongoing studies are head-to-head comparisons of older and newer agents in which the advantages and disadvantages of one or other treatment may be modest and difficult to detect. Another approach that is more likely to produce evidence of clear benefits is to randomize patients to new treatments or to placebo against a background of treatment with standard therapy. In this way the full effects of any new treatment will be demonstrated (i.e. the combined effects of blood-pressure-lowering plus any independent protective effects).

#### **Genetically targeted blood-pressure-lowering therapy**

Despite the limited success of efforts to date, research is still required to identify both genetic factors that

may be predictive of cardiovascular disease events, particularly in younger individuals, and genetic factors that may predict response to blood-pressure-lowering treatment.

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