Patients with hypertension, even those with mild elevation of blood pressure, are at increased risk of cardiovascular disease, whether or not symptoms are present. In most countries, as many as 15% to 25% of the adult population are found at screening to have raised blood pressure; about two thirds of them have mild elevation of blood pressure. However, blood pressure is not persistently raised in all, and not all need to be treated with antihypertensive drugs.

The present guidelines for the management of hypertension concentrate on mild hypertension, as this condition often presents a diagnostic and therapeutic problem, and evidence for benefit in treating more severe hypertension is clear. Emphasis is also placed on systolic blood pressure as a criterion for decision making and on hypertension in the elderly, another condition in which careful judgment is necessary. Information is provided on useful methods for diagnostic evaluation and the assessment of cardiovascular risk. Additional information is provided on nondrug measures as well as drug treatment of hypertension and on the correction of treatment of hypertension and on the correction of other major risk factors for cardiovascular disease (see Table 1).

In preparing these guidelines, the World Health Organization/International Society of Hypertension (WHO/ISH) Subcommittee has been keenly aware that marked differences exist among individual patients with similar levels of hypertension and that these differences have important implications for decisions about treatment. Hypertensive patients differ with respect to age, blood pressure elevation, organ damage, and concomitant risk factors and diseases, and they live in societies in which cardiovascular risk and economic resources also differ widely. Accordingly, guidelines should not be conceived as rigid constraints to the practicing doctor’s decisions. Rather, guidelines should provide extensive, critical, and well-balanced information on benefits and limitations of the various diagnostic and therapeutic interventions so that the physician can exert the most careful judgment in individual cases. Although the most reliable information is provided by large randomized trials, these trials have their own limitations, and not all aspects of the management of hypertension have been nor can be determined by the results of randomized trials. Scientifically sound interpretation and cautious extrapolation of existing data can also be used to influence clinical decision making.

Assessment of Cardiovascular Risk in Patients With Hypertension

There is a continuum of cardiovascular risk associated with the level of blood pressure: the higher the blood pressure, the higher the risk of both stroke and coronary events.1 The dividing line between "normotension" and "hypertension" is arbitrary. The current definition is that this line is the level of blood pressure above which intervention has been shown to reduce the risk.2 It is well established that lowering of even mildly elevated pressures reduces cardiovascular morbidity and mortality. However, a decision to intervene should not depend on blood pressure alone.

Indeed, among individuals with mild hypertension, the risk of serious cardiovascular disease is also determined by a variety of factors other than the level of blood pressure. These include increasing age, male gender, previous cardiovascular events, target organ damage such as left ventricular hypertrophy or renal disease, smoking, diabetes, dyslipidemia (high total and low-density lipoprotein cholesterol and low high-den- sity lipoprotein cholesterol), central obesity, and seden- tary lifestyle (see Table 2). The presence of one or more of these factors may be a more important determinant of risk than a mild increase in the level of blood pressure. Because the absolute benefits of antihypertensive treatment will be determined by the absolute risk of cardiovascular disease (ie, greater benefits among those at higher risk), each of these factors should be assessed before a decision is made about treatment.

The absolute risk of serious cardiovascular disease varies greatly among individuals with mild hypertension. At one extreme, in elderly patients with a history of previous cardiovascular disease, at least 3 to 5 in every 100 patients will suffer a further serious event each
year.4–7 At the other extreme, in young individuals with no other risk factors, fewer than 1 in every 1000 will suffer a serious event each year.69 Although antihypertensive treatment will reduce risks in both of these patient populations, it may take some decades for clinical benefits to become apparent in young patients at low initial risk.

The absolute risk of cardiovascular disease in mild hypertension may also vary substantially from one geographic region to another. Some of the regional variation in the risk of stroke and coronary events may be accounted for by regional differences in the prevalence of the risk factors listed above. However, other evidence indicates that some regional differences cannot be accounted for by differences in established risk factors. Of particular note are the high rates of stroke in China and Russia. In these populations, stroke incidence is four times that of the United States and Western Europe, but average population blood pressures are only slightly different. For this reason, the treatment of mild hypertension in these populations may yield particularly large absolute benefits.

<table>
<thead>
<tr>
<th>TABLE 1. Highlights of the 1993 Guidelines for the Management of Mild Hypertension</th>
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<td><strong>New sections on</strong></td>
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<td>— Hypertension in the elderly</td>
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<td>— Assessment of cardiovascular risk</td>
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<td>— Cost-effectiveness</td>
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<td>— Issues needing further research</td>
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<td>— First-line drugs</td>
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<td>— Correction of other major risk factors</td>
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**Definition and Classification of Hypertension**

**Blood Pressure Measurement**

Blood pressure is generally measured by the indirect method with a mercury sphygmomanometer. Before measurement begins, the patient should be seated for several minutes in a quiet room; the chair should provide comfortable back support. The arm muscles should be relaxed and the forearm supported with the cubital fossa at heart level (fourth intercostal space). Blood pressure may also be measured with the patient supine and standing, and in each position the arm should be supported at heart level. A cuff of suitable size is applied evenly to the exposed upper arm. Care should be taken to avoid tight sleeves. The standard cuff available in many countries may be too small. A cuff for adults must have a bladder 13 to 15 cm wide and 30 to 35 cm long so as to encircle the average arm. Larger cuffs are needed for fat arms and smaller ones for children. The cuff is rapidly inflated until the manometer reading is approximately 30 mm Hg above the level at which the pulse disappears and then slowly deflated at approximately 2 mm Hg/s. During this time, the Korotkoff sounds are auscultated through a stethoscope placed over the brachial artery.

The pressure at which the sounds are first heard is the systolic pressure; the diastolic pressure is the pressure at which the sounds disappear (phase V). Most of the major studies have used the latter point, ie, disappearance of sounds; the use of muffling of sounds (phase IV) gives significantly higher diastolic pressure values and is to be avoided. The systolic and diastolic pressures should be measured at least twice over a period of no less than 3 minutes; both should be recorded and the mean value for both should be used. It is also recommended that on the first visit the blood pressure should be measured in both arms. Measurement with patients in the standing position should also be performed when postural hypotension is suspected and in the elderly, in whom this condition may be more common.

“White coat” hypertension or effect is a condition in which blood pressure is elevated in the presence of a doctor but falls when the subject leaves the medical environment. Measurement by nurses or trained nonmedical staff may reduce but not necessarily abolish the white coat effect.10 How the white coat effect can be precisely defined is controversial, however. Calculations on the basis of the difference between blood pressure measured in the doctor’s office and home blood pressure or daytime ambulatory blood pressure (see below) are questionable because this difference may depend on many more factors than just an alerting reaction. It is not known whether the white coat effect is an innocent phenomenon. Indeed, it has been suggested that subjects showing a more marked difference between clinic and home blood pressure measurements may be at somewhat higher cardiovascular risk; they often have other concomitant risk factors.11 It is important, however, to recognize the condition to avoid unnecessary treatment in many subjects.

Semiautomatic and automatic devices for blood pressure measurement at home and for prolonged (24 hours or more) ambulatory blood pressure monitoring are now available.12 It should be stressed that all these devices should be tested for accuracy and reliability.
against the standard methods according to strict protocols. Ambulatory devices should be tested in ambulatory conditions. Home blood pressure has the potential advantage of providing more numerous measurements and in a quieter setting than blood pressure measurement in the doctor’s office. Ambulatory blood pressure monitoring is an interesting research technique used to investigate blood pressure variability, behavioral influences on arterial pressure, and the time course of the effects of antihypertensive therapy. It is also used, as are home blood pressure readings, to provide a supplementary source of information for diagnostic and therapeutic decisions. Home and ambulatory blood pressure values, however, cannot be equated to readings taken by the conventional method in the clinic by physicians or nurses. There is evidence, supported by a recent population survey, that both home and ambulatory blood pressure values averaged over 24 hours are several millimeters of mercury lower than values measured in the clinic. Prognostic standards with regard to the level of blood pressure to be treated have been based on prospective studies relating casual or clinic blood pressure to morbidity and mortality. No prospective studies are available providing prognostically valuable standards for home or ambulatory blood pressures. Therefore, it is likely that therapeutic decisions based on clinic blood pressure will differ from those based on home or ambulatory blood pressure measurements. For the time being, the latter measurements should be used only in selected cases to complement the blood pressure values measured by the physician.

**Definition of Mild Hypertension Based on Diastolic Blood Pressure**

Diastolic blood pressure has generally been used to define mild hypertension. This choice is somewhat arbitrary but is supported by the fact that diastolic blood pressure has been used as the criterion for inclusion in most randomized therapeutic trials, including those on mild hypertension. Mild hypertension in adults can be defined as a persistent resting level of diastolic blood pressure (phase V) between 90 and 105 mm Hg. "Borderline" hypertension (diastolic blood pressure of 90 to 95 mm Hg) accounts for approximately half of mildly hypertensive patients. Community screening has shown that up to 20% of the population aged 50 years or older have diastolic pressures within the mild hypertension range at the time of screening measurement. With repeated measurements over periods of up to 3 to 6 months, the diastolic pressure of almost half of the subjects within the mild hypertension range falls to levels below this range. People whose resting values of diastolic blood pressure remain persistently at or above 90 mm Hg after repeated measurements are at increased risk of cardiovascular mortality and morbidity, and the risk clearly increases with the height of the diastolic blood pressure. Between 12% and 15% of such patients will develop moderate or severe hypertension (diastolic blood pressure >105 mm Hg) within 3 to 5 years, with a worse prognosis, whereas the remaining patients will stay within the mild range. The risk of stroke is increased in patients with mild hypertension, and drug treatment has been clearly shown to reduce risk by 35% to 40%. In populations with high plasma lipid levels, the major cause of cardiovascular mortality and morbidity in patients with mild hypertension is usually ischemic heart disease. Lowering of blood pressure with drugs also reduces the risk of nonfatal myocardial infarction and death from ischemic heart disease by approximately 15% to 20%, but the size of the benefit obtained with the treatments so far tested in controlled clinical trials appears to be slightly smaller than that expected from a long-term decrease in blood pressure of the same magnitude.

In practice, when the initial diastolic pressure averages between 90 and 105 mm Hg, measurements should be repeated on at least two more occasions during the next 4 weeks. With repeated measurements, both systolic and diastolic pressures often fall substantially. Therefore, before labeling a subject as hypertensive and deciding to initiate medical treatment, a physician must identify those patients with sustained high or increasing blood pressure.

All patients should be given advice to modify their lifestyle, as appropriate, by stopping smoking, reducing obesity, limiting alcohol and dietary saturated fat, and engaging in regular mild dynamic exercise. This advice should form a very important part of the strategies to reduce blood pressure and improve cardiovascular health. Salt restriction may also assist in lowering blood pressure. Management decisions should be made after discussion with the patient and his or her family outlining the risks and benefits of various intervention strategies.

Practical guidelines for defining and managing mild hypertension are illustrated in the Figure. At 4 weeks from initial measurements, (1) patients in whom dia-
systolic blood pressures fall below 90 mm Hg within 4 weeks should have further measurements at 3-month intervals for a year. (2) If the diastolic blood pressure remains between 90 and 105 mm Hg, appropriate nondrug treatment for all patients (see below) should be instituted and the blood pressure monitored on several occasions during the following 3 months.

After the first 3-month period, (3) drug treatment should be instituted if the diastolic blood pressure is 100 mm Hg or above. (4) If the diastolic blood pressure is 95 to 100 mm Hg, nondrug measures should be reinforced and drug treatment considered, especially when other cardiovascular risk factors are present. (5) If the diastolic blood pressure remains between 90 and 95 mm Hg, nondrug measures should be reinforced and long-term observation of the patient continued.

After a second 3-month period, (6) drug treatment should be instituted even when other cardiovascular risk factors are absent if the diastolic blood pressure is 95 mm Hg or above. (7) Patients whose diastolic pressure remains between 90 and 95 mm Hg after prolonged observation also have an increased risk of cardiovascular disease. This is more marked when systolic blood pressure is also elevated; in elderly people, smokers, diabetics, and individuals with raised plasma lipids or left ventricular hypertrophy; and in those with a family history of cardiovascular disease. Drug treatment should be considered for such patients who are at higher risk. Lower-risk individuals, if not treated with drugs, should be further assessed at about 3-month intervals, and appropriate nondrug measures should be maintained or reinforced.

Definition of Mild Hypertension Based on Systolic Blood Pressure

Although most of the randomized therapeutic trials on mild hypertension have defined and treated patients on the basis of diastolic blood pressure values only, evidence is mounting that systolic blood pressure values should also be taken into account in defining and managing mild hypertension. Indeed, cardiovascular risk is as strongly associated with systolic as with diastolic values, with no evidence of a threshold below which a decrease in systolic pressure does not reduce risk. Furthermore, some of the intervention studies on mild hypertension indicate that cardiovascular risk factors are present. (8) If the diastolic blood pressure is 100 mm Hg or above.

Isolated systolic hypertension in elderly people is often beyond the mild hypertension range. In adults younger than 60 years of age, although there is little direct evidence of benefit from treating isolated systolic hypertension (which is also infrequent at this age), it seems reasonable to consider drug therapy in subjects with systolic blood pressure values persistently equal to or above 160 mm Hg even if diastolic values are below 90 mm Hg, particularly when other risk factors are present.

Classification of Hypertension

As mentioned at the beginning of this article, the risk associated with raised blood pressure increases progressively throughout the entire range of blood pressure values, and the dividing line between “normotension” and “hypertension” is arbitrary. However, the considerations made in the preceding sections of this article allow an operational classification of hypertension to be made. This classification is illustrated in Table 3 as a practical guide to management. As previously mentioned, the term “mild hypertension” refers to individuals with either diastolic blood pressure in the range of 90 to 105 mm Hg or systolic blood pressure in the range of 140 to 180 mm Hg. The term “borderline hypertension” is used in the subgroup of mildly hypertensive subjects with diastolic blood pressures between 90 to 95 mm Hg or systolic blood pressures between 140 and 160 mm Hg. The term mild is used to convey the information that the blood pressure is mildly elevated, but it does not imply that the absolute risk of cardiovascular disease is always mildly elevated. For instance, in an individual at high risk for stroke or myocardial infarction, mild hypertension may considerably aggravate this risk, and the reduction of even mildly elevated blood pressure is likely to result in large benefits. The same
considerations apply to patients with diabetic nephropathy. Furthermore, the population burden due to mild hypertension is markedly elevated because of the high prevalence of mild hypertension.

Isolated systolic hypertension is a comprehensive term indicating all patients with systolic blood pressures equal to or greater than 140 mm Hg and diastolic blood pressures less than 90 mm Hg. As the benefits of treating isolated systolic hypertension have so far been shown for patients with systolic blood pressure levels of 160 mm Hg and above, the subjects with systolic blood pressure values between 140 and 160 mm Hg and diastolic pressures below 90 mm Hg can be classified as having "borderline" isolated systolic hypertension. Classifying subjects with diastolic blood pressures between 85 and 89 mm Hg or systolic blood pressures between 130 and 139 mm Hg as "high normal" individuals does not appear justified at the moment and carries the risk of labeling a very large number of subjects. As cardiovascular risk is associated with blood pressure levels in a continuous way, it appears reasonable that, beyond the range of mild hypertension, the risk of hypertension is indicated by reporting the actual values of systolic and diastolic blood pressures. As suggested in the 1978 WHO Expert Report, the term "stage" is better used to indicate the absence, presence, or severity of complications than to substitute for blood pressure values (Table 4).

Table 3. Classification of Hypertension by Blood Pressure Level

<table>
<thead>
<tr>
<th>Classification</th>
<th>Systolic (mm Hg)</th>
<th>Diastolic (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotension</td>
<td>&lt;140</td>
<td>&lt;90</td>
</tr>
<tr>
<td>Mild hypertension</td>
<td>140-160</td>
<td>90-105</td>
</tr>
<tr>
<td>Subgroup: borderline hypertension</td>
<td>140-160</td>
<td>90-95</td>
</tr>
<tr>
<td>Moderate and severe hypertension*</td>
<td>≥180</td>
<td>≥105</td>
</tr>
<tr>
<td>Isolated systolic hypertension (ISH)</td>
<td>≥140</td>
<td>&lt;90</td>
</tr>
<tr>
<td>Subgroup: borderline ISH</td>
<td>140-160</td>
<td>&lt;90</td>
</tr>
</tbody>
</table>

*Risk to be indicated by reporting the actual values of systolic and diastolic blood pressures.

As cardiovascular risk is associated with blood pressure levels in a continuous way, it appears reasonable that, beyond the range of mild hypertension, the risk of hypertension is indicated by reporting the actual values of systolic and diastolic blood pressures. As suggested in the 1978 WHO Expert Report, the term "stage" is better used to indicate the absence, presence, or severity of complications than to substitute for blood pressure values (Table 4).

Evaluation

A complete history and physical examination are essential for the evaluation of hypertension. Factors of significance include a family history of hypertension, diabetes, hyperlipidemia, ischemic heart disease, or stroke; a personal history of symptoms suggestive of ischemic heart disease, cardiac failure, or transient cerebral ischemic episodes; a history of kidney disease, diabetes, or bronchospasm; previous measurements of blood pressure; and details of lifestyle, educational level, and sociological factors. Smoking and alcohol consumption should be carefully quantitated. Weight gain since early adult life can provide a useful index of excess body fat. Patients should be questioned on the ingestion of prohypertensive substances or drugs, notably oral contraceptives, nonsteroidal anti-inflammatory drugs, licorice, cocaine, etc. Attention should be paid to the possible use of erythropoietin, cyclosporine, or steroids for concomitant diseases. Physical examination should include measurement of weight and height, evaluation of heart size, examination of optic fundi, and evidence of arterial disease in the carotid, renal, and peripheral arteries. Certain minimum investigations should be performed in all patients: analysis for blood, protein, and glucose in the urine; microscopic examination of the urine; estimations of plasma potassium, creatinine, total and high-density lipoprotein cholesterol, uric acid, and blood glucose; and an electrocardiogram. Echocardiography is widely used in assessing left ventricular mass. The quality of its results depends on the patient's morphology and the operator's training, and its cost-effectiveness in the evaluation of mildly hypertensive subjects has not been investigated. Nonetheless, the important prognostic role of left ventricular hypertrophy has made echocardiography a frequent component of the diagnostic workup of the hypertensive patient, particularly in those cases in which evaluation of left ventricular mass and geometry may help the physician decide about initiation of treatment. Ultrasound is also useful in evaluating carotid and abdominal aortic walls and renal morphology. In selected cases, further investigations should be carried out to exclude curable causes of hypertension. The cost of investigations should be considered when a decision is made for a given patient.

Treatment: General Concepts

Effects of Antihypertensive Treatment on the Risks of Cardiovascular Events

Randomized controlled trials have shown that in patients with mild hypertension, lowering of blood pressure with antihypertensive drugs decreases morbidity and mortality from cardiovascular disease. On average, a reduction of 5 to 6 mm Hg in diastolic blood pressure (and of 10 mm Hg in systolic blood pressure) reduced stroke risk by about a third and the risk of coronary events by about a sixth. It is likely, however, that the benefits of antihypertensive therapy have been underestimated by most of the randomized controlled trials for at least three reasons: (1) in many trials of active versus placebo treatment, there has been extensive crossover of patients from placebo to active treatment; (2) in several trials, low-risk patients were preferentially included; and (3) most trials have been relatively short-term (3 to 5 years' duration), and the full effects of blood pressure reduction, on coronary events in particular, may take a decade or more to become manifest. Because the absolute risk of coronary events in young patients is low, the initial goals of treatment are to prevent the progression of disease processes such as left ventricular hypertrophy and, possibly, atherosclerosis rather than discrete events.
Factors Influencing Initiation of Treatment

Diasstolic and systolic blood pressure values are important for initiation of treatment, and it should be stressed here that, whenever blood pressure values above the mild hypertension range (i.e., systolic 180 and diastolic 105 mm Hg or above; see Table 3) are measured, a decision to treat with drugs should be made after a shorter observation period than the one suggested for mild hypertension in the Figure. However, several factors other than diastolic and systolic blood pressures and age may influence the decision to begin drug treatment.

Gender. Premenopausal women are at a 50% lower risk of cardiovascular disease than men of the same age,3 and the absolute benefit of treatment is less conspicuous in this group of women than in men, unless other risk factors are present. Furthermore, hypertension appears to be frequently underdiagnosed and undertreated in men.25

Cardiovascular complications. Clinical, echocardiographic, or radiological evidence of left ventricular hypertrophy is a predictor of a substantially higher incidence of morbid events27,28 and is therefore a clear indication to begin treatment. Clinical, echocardiographic, or angiographic evidence of ischemic heart disease in hypertensive patients requires lowering of blood pressure in addition to treatment of the underlying disorder. A history of cerebrovascular disease (e.g., transient cerebral ischemia or stroke, especially cerebral or subarachnoid hemorrhage) is also a clear indication for the initiation of treatment. It has not been fully proved, however, that antihypertensive therapy can prevent the recurrence of strokes. The presence and nature of cardiovascular complications may also influence the choice of treatment.

Renal disease. Raised serum creatinine and proteinuria are predictors not only of renal impairment but also of a higher incidence of cardiovascular events.29 If either is present, drug treatment should be started. In patients with chronic renal failure, particularly those with diabetic nephropathy, even blood pressure values in the borderline range represent a considerable risk and must be lowered by drugs.

Diabetes. Diabetes and hypertension are frequent concomitant diseases, and hypertension is a potent additional risk factor in diabetes and vice versa. The presence of microalbuminuria is an early indicator of this increase in risk.30 There is good evidence that treatment of high blood pressure or even lowering normal blood pressure in diabetic patients reduces microalbuminuria, slows the decline in renal function, and delays the development of diabetic nephropathy.31 Therefore, the presence of diabetes (both insulin-dependent and non-insulin-dependent forms) in patients with mild hypertension is a clear indication that antihypertensive treatment should be begun. In these patients, particular attention should also be paid to accompanying disorders of lipid metabolism.

Other cardiovascular risk factors. Continued cigarette smoking, elevated fasting glucose, elevated serum total cholesterol, and low high-density lipoprotein cholesterol all markedly increase the cardiovascular risk associated with high blood pressure3 and increase the absolute benefit of blood pressure lowering. Therefore, the presence of one or more of these risks should influence the decision toward early drug treatment and the intensive use of appropriate nondrug measures and may also influence the choice of the antihypertensive drugs.

Family history. A family history of hypertension or of premature stroke, heart disease, or sudden cardiac death should influence the decision toward early drug treatment.

Low-income populations. A decision to initiate drug treatment and, more broadly, the range of actions desirable for hypertension control will vary with a population's resources, constraints, mortality structure, and the resulting health care priorities. In developing countries, costs may make it difficult to extend all choices of diagnostic procedures and drug therapies to all individuals with mild hypertension. Advice on modification of lifestyle should be of particular benefit in such circumstances before resorting to drug therapy. Although individualized counseling and structured programs (see below) will be difficult to provide in most developing countries, population-based initiatives to reduce average blood pressure levels would be worthwhile. In low-income societies, it is a realistic approach to train auxiliaries for measuring blood pressure and for simple urine testing, as well as to follow a less rigorous evaluation schedule. Although higher-risk individuals should be treated pharmacologically, careful choice of drugs with increased emphasis on cost-effectiveness becomes particularly important with growing economic constraints. It is as important in low-income as in affluent populations to increase the public's awareness of the hazards of hypertension, measure blood pressure at every opportunity, regularly monitor hypertensive individuals, and educate the population about factors that may raise blood pressure or aggravate existing hypertension. Political and public education is particularly important in reducing tobacco dependency and promoting the production and marketing of healthy food. Indeed, the medical practitioner has a responsi-
Hypertension in the Elderly

In absolute terms, hypertension represents a much greater risk of cardiovascular events in the elderly than in younger people. In Western populations, among those with mild hypertension the 10-year risk of a major cardiovascular event ranges from less than 1% in individuals aged 25 to 34 years to more than 30% in those aged 65 to 74 years. Correspondingly, numerous intervention trials have shown that the absolute benefit of antihypertensive therapy is particularly high in the elderly.

In addition to the results of the European Working Party on High Blood Pressure in the Elderly (EWPHE) trial published in 1985, which clearly demonstrated the beneficial effect of antihypertensive medication in the elderly, the results of three prospective placebo-controlled therapeutic trials in elderly hypertensive patients were reported in 1991 and 1992. All demonstrated significant reduction of cardiovascular morbidity or mortality. The Systolic Hypertension in the Elderly Program (SHEP) specifically examined the value of antihypertensive treatment in elderly men and women (≥60 years) with isolated systolic hypertension (systolic blood pressures of 160 to 219 mm Hg and diastolic blood pressures below 90 mm Hg); highly significant reductions in fatal and nonfatal cardiovascular events were observed. The Swedish Trial in Old Patients with Hypertension (STOP-Hypertension) evaluated active antihypertensive therapy versus placebo in “old elderly” patients (aged 70 to 84 years) with systolic blood pressures of 160 to 230 mm Hg and diastolic blood pressures of 90 to 120 mm Hg or systolic blood pressures equal to or below 230 mm Hg and diastolic blood pressures of 105 to 120 mm Hg. Fatal and nonfatal strokes were reduced by 47%, all “primary end points” (ie, fatal and nonfatal stroke, fatal and nonfatal myocardial infarction, and other cardiovascular death) by 40%, and total mortality by 43%; all changes were statistically highly significant. The Medical Research Council trial in older adults (aged 65 to 74 years) with systolic blood pressures of 160 to 209 mm Hg and diastolic blood pressures below 115 mm Hg showed a 25% reduction in stroke mortality and morbidity and a 17% reduction in all cardiovascular events, both of which were significant. From the results of all these trials, it is obvious that antihypertensive therapy in elderly patients with hypertension, be it isolated systolic or combined systolic and diastolic, provides relative benefits, in terms of percent reduction in cardiovascular morbidity and mortality, that are of at least the same magnitude (approximately 20% to 50%) as the benefits of treatment in young and middle-aged hypertensive patients. Furthermore, because the cardiovascular event incidence is high in the elderly, the same relative reduction in risk as in younger patients provides a greater absolute benefit in this age group. In all trials, with the single exception of the Medical Research Council trial, benefit ranges between one event prevented each year for every 35 treated patients and one event prevented for every 90 treated patients. Old age, therefore, renders antihypertensive therapy particularly beneficial. According to the STOP-Hypertension study, significant benefits are also seen in the “old elderly” without any clear upper limit of age. In the oldest patients, however, caution is needed in the use of drugs, especially if other medications are also prescribed for associated diseases. It should also be remembered that in elderly patients the blood pressure elevation can often be controlled by low-dose medication. Bearing in mind these precautions, antihypertensive therapy can be instituted in the elderly along the same general guidelines as in young and middle-aged patients.

Goal of Treatment

Because the relation between blood pressure and cardiovascular risk is continuous, it seems appropriate for the goal of treatment to be the maximum tolerated blood pressure reduction. There is very good evidence from epidemiologic studies that, within the “normal” range of both systolic and diastolic blood pressures, the lower the blood pressure, the lower the risks of both stroke and coronary events. The claim that lowering diastolic blood pressure below 85 mm Hg, at least in particular groups of patients (such as those with ischemic heart disease), raises the risk above that associated with a more moderate blood pressure reduction is unproved but is currently being tested by a randomized trial. Until such evidence becomes available, it may be worth recalling that the safety of blood pressure reduction even at very low initial blood pressure levels has been indicated by the results of trials in patients with congestive heart failure or after myocardial infarction who have been treated with angiotensin converting enzyme inhibitors or β-blockers. Furthermore, patients in the SHEP study with an average initial diastolic blood pressure of 77 mm Hg exhibited substantial benefits with further lowering of diastolic blood pressure.

On the basis of available evidence, it would seem desirable to achieve blood pressures on the order of at least 120 to 130/80 mm Hg in young patients with mild hypertension. In elderly patients with elevation of both systolic and diastolic blood pressures it would seem desirable to lower blood pressure to below 140/90 mm Hg, and in patients with isolated systolic hypertension the goal of treatment should be to achieve a systolic blood pressure of at least 140 mm Hg if this is tolerated. When home or ambulatory blood pressure measurements are used to help in the evaluation of blood pressure achieved by treatment, it should be remembered that blood pressure values provided by these methods are on the average several millimeters of mercury lower than clinic blood pressures; therefore, treatment goal blood pressure when assessed by these techniques should be set at a lower level to avoid undertreatment.

Modes of Treatment

Nonpharmacologic Interventions

Several nonpharmacologic interventions are recommended for the primary prevention of hypertension and other cardiovascular diseases and have been the object of a recent joint WHO/ISH document on this issue.

These interventions have also been shown to lower blood pressure in patients with mild hypertension. As discussed in the document mentioned above, weight reduction in overweight subjects, reduction of alcohol
consumption to no more than 20 to 30 g of ethanol per day, regular mild (not strenuous) exercise in sedentary subjects (such as walking, jogging, cycling, or swimming), and sodium chloride restriction to no more than 5 g/day at least in some patients are effective in lowering blood pressure. It is known, however, that these lifestyle modifications are difficult to apply at large, that compliance to such recommendations is poor in the long term, and that the ability of nonpharmacologic interventions to reduce mortality and morbidity in hypertension has not been proved directly. Nevertheless, it appears reasonable to advise that efforts to lower blood pressure by lifestyle modifications should normally precede any decision about the necessity of drug treatment for mild hypertension. It should be remembered that some of these measures may take several months to become fully effective. If a decision is made to begin drug treatment, a structured program of nonpharmacologic intervention remains an important component of the overall therapeutic program, even in patients with initial blood pressure above the mild hypertension range, in whom drug requirements may be consequently reduced.

Control of Associated Risks

Tobacco. All the large-scale trials of treatment of mild hypertension have confirmed that treated hypertensive patients who smoke tobacco have a greater incidence of both stroke and coronary heart disease than equally treated hypertensive patients who do not smoke. It is likely that the pressor effect of smoking has been underestimated by the usual recommendation of avoiding smoking before blood pressure is measured. Repeated advice as to how to discontinue smoking is therefore of major importance and will need to be coupled with particular efforts to prevent consequent weight gain. Intensive advice programs, supported when necessary by a pharmacologic treatment of nicotine addiction, are more effective than haphazard admonitions.

Lipids. Because high serum cholesterol levels and diabetes also unfavorably influence the long-term prognosis of hypertensive people, nutritional counseling and, when appropriate, drug treatment are indicated to control these risk factors. If dietary measures are to be successful, a careful follow-up should be instituted. Increased physical activity is also likely to reduce the risk of cardiovascular disease, so this is appropriate in mildly hypertensive patients.

Oral contraceptive pills and hormone replacement therapy. Alternative methods of contraception should be considered for hypertensive women in place of estrogen and progesterone-containing oral contraceptives, as these substances may raise blood pressure as well as carry other cardiovascular risks.

Hormone replacement therapy is being increasingly used to prevent osteoporosis in postmenopausal women. There is evidence that replacement with estrogen alone reduces coronary risk but less evidence for this with combined estrogen/progesterone therapy. Such combinations are generally recommended for women with an intact uterus to protect against uterine malignancy. There is no contraindication to the use of hormone replacement therapy in hypertension, but blood pressure should be monitored more frequently because it is not yet clear whether hypertensive responses may occur in some women.

It should also be emphasized that the nonpharmacologic interventions described in the above sections, whether or not they lower blood pressure, can reduce the overall risk of cardiovascular disease and significantly contribute to global health care.

Antihypertensive Drugs

Randomized trials of antihypertensive treatment have shown the benefits of lowering blood pressure, and although most of these trials have used diuretics, centrally acting drugs, vasodilators, and/or β-blockers, often in combination, no evidence is so far available that benefits are due to any particular class of antihypertensive agents rather than to the lowering of blood pressure per se. Also, in several of the recent trials of antihypertensive treatment in the elderly, as many as 60% to 70% of the patients on active treatment received a combination of two or more drugs, and the real evidence provided by these trials is about the benefit of lowering blood pressure.

Several classes of drugs can be recommended as first-line treatment of mild sustained hypertension. In order of proved benefit based on mortality and morbidity studies, they are (1) diuretics, (2) β-blocking drugs, and (3) angiotensin-converting enzyme inhibitors, calcium antagonists, and α-adrenergic receptor-blocking drugs.

The average blood pressure fall induced in groups of patients by each of the different categories of drugs is similar, but there are large variations in the fall induced in the individual patient. The appropriate choice of a particular class of antihypertensive drug for a patient may also be determined by the individual's other characteristics because of such extensive differences in the risk profile and in side effects in different patients.

The choice of the initial drug therapy of an individual hypertensive patient is a challenge for the physician and should not be restricted, on theoretical or economic grounds, to any one or two of the various classes of drugs that have been tested so far, although it is also the physician's responsibility to give due consideration to the cost of drugs.

Finally, we should bear in mind that the "hard" evidence of benefit (risk ratios for mortality, stroke, and coronary events) has been obtained largely over a relatively short time (of about 2.5 years to the terminating event). Such end points may not be relevant for younger patients with hypertension, who may have decades of treatment ahead of them. For such patients, a reduction in progression of cardiovascular lesions may be of greater relevance.
recent trials of antihypertensive therapy in the elderly. Diuretics are also inexpensive, and they are particularly valuable as ancillary treatment to enhance the effectiveness of many other antihypertensive drugs. Combination of diuretics with potassium-sparing drugs or with angiotensin converting enzyme inhibitors may prevent potassium depletion.

β-Adrenergic receptor-blocking drugs. β-Blocking drugs are widely and effectively used to initiate treatment for mild hypertension. β-Blocker-based antihypertensive therapy has been shown to reduce cardiovascular morbidity and mortality. Numerous β-blocking drugs are available, some with cardioselective properties, others with partial agonist activity, and others with α-blocking or vasodilator properties. Although β-blockers have been shown to prevent fatal and nonfatal coronary events in patients with a previous myocardial infarction, they have not been shown to have any consistent advantage over diuretics for the primary prevention of myocardial infarction.

β-Blocking drugs are particularly useful in hypertensive patients with effort angina, tachyarrhythmias, or a past myocardial infarction. They should be avoided in patients with obstructive airways disease, heart failure, and peripheral vascular disease. They have limitations in patients with dyslipidemia or reduced glucose tolerance as well as in athletes or physically active subjects.

Angiotensin converting enzyme inhibitors. Angiotensin converting enzyme inhibitors are effective in lowering blood pressure. They are generally well tolerated and have been shown not to exert untoward effects on serum lipids and glucose homeostasis. Possible adverse effects include persistent cough and, rarely, angioedema. In patients with renovascular disease, deterioration in renal function has been reported. Angiotensin converting enzyme inhibitors should be avoided in women considering childbearing and are definitely contraindicated in the second half of pregnancy, because they may increase fetal and neonatal death. Their safety profile is otherwise good.

Angiotensin converting enzyme inhibitors have been shown to reduce cardiovascular mortality and morbidity, including coronary events, in patients with congestive heart failure and after a myocardial infarction in patients with a reduced ejection fraction. In these patients, a reduction of left ventricular dilatation has also been reported. The ability of angiotensin converting enzyme inhibitors to reduce cardiovascular events in hypertension has not yet been proved in controlled clinical trials.

Calcium antagonists. There are three major classes of calcium antagonists with different characteristics (phenylalkylamine, dihydropyridine, and benzothiazepine derivatives), but all are effective in lowering blood pressure. Troublesome side effects may include initial tachycardia, headache, flushing (especially with fast-acting dihydropyridines), ankle edema, and (with phenylalkylamine derivatives) constipation. With few exceptions, they do not have undesirable metabolic effects and their safety profile in hypertension appears good. However, the safety of dihydropyridines in early pregnancy has not been fully established. In patients with atherosclerotic arterial disease, the calcium antagonists may reduce the development of new plaques, but studies with fast-acting short-duration dihydropyridines have been discouraging in providing evidence of secondary prevention of ischemic heart disease. On the other hand, verapamil and diltiazem have been reported to reduce morbidity and mortality in post-myocardial infarction patients provided that heart failure or left ventricular dysfunction is absent. As with all recent classes of antihypertensive agents, the ability of the calcium antagonists to reduce cardiovascular events in hypertension has not yet been proved in controlled clinical trials.

α-Adrenergic receptor-blocking drugs. α-Adrenergic receptor-blocking drugs effectively reduce blood pressure and have limited side effects. Their dose should be carefully titrated, however, to avoid postural hypotension, a complication particularly undesirable in the elderly. A favorable aspect of this class of drugs is a potential beneficial effect on lipid and glucose homeostasis. As with all newer classes of antihypertensive agents, the ability of the α-blockers to reduce morbidity and mortality has not been proved in controlled clinical trials.

Other classes. Centrally acting drugs are also effective antihypertensive agents and have been used for many years. Although mostly in association with diuretics, they have been used in several controlled clinical trials that have proved the ability of antihypertensive therapy to reduce cardiovascular events. In particular, methyldopa remains an important, well-validated agent to effectively treat hypertension in pregnancy. The side-effect profile of centrally acting drugs, however, is less favorable than for the antihypertensive agents previously mentioned. If consideration of cost-effectiveness should favor the use of centrally acting drugs, such as reserpine, in low-income populations, it is recommended that they be used in much lower doses than commonly prescribed in earlier years.

Direct vasodilators, such as hydralazine and minoxidil, are also quite effective in lowering blood pressure, but some of their side effects (tachycardia, headache, sodium and water retention) make it difficult to use them as monotherapy.

Combination of drugs. If monotherapy with a compound of any of the five major pharmacologic classes mentioned above has been found ineffective in lowering blood pressure in a given patient, it is reasonable to substitute the first drug with a compound belonging to a different class. If a single drug has been partly effective, it may be preferable to add a small dose of a second drug rather than to increase the dose of the first. Effective combinations use compounds from different drug groups. This permits the addition of different primary actions while minimizing the homeostatic compensations that limit the fall in pressure. Combination therapy also minimizes side effects by encouraging the use of drugs in low doses. An additive effect has been shown when combining (1) a diuretic with a β-blocker, an angiotensin converting enzyme inhibitor, or an α-blocker; (2) a β-blocker with an α-blocker or a dihydropyridine calcium antagonist; or (3) an angiotensin converting enzyme inhibitor with a calcium antagonist.

To achieve the full goal of antihypertensive treatment in all hypertensive patients (ie, the maximum tolerated reduction in blood pressure), two-drug and sometimes three-drug combinations frequently may be required. For reasons of convenience, cost, and increased patient...
compliance, preparations that combine two drugs in a single tablet or capsule may be appropriate for many hypertensive patients once the need and dose for constituent drugs have been established.

**Follow-up**

During the stabilization period of treatment, patients need to be seen at regular intervals until blood pressure levels are satisfactorily controlled. The main task of doctors during follow-up is to ensure that the target systolic and diastolic blood pressures are reached and maintained and that other risk factors are controlled. Gradual and careful lowering of blood pressure will minimize side effects and complications and will improve compliance. Sometimes, telling a patient that he or she has hypertension ("labeling") may be followed by anxiety or mood changes. Additional support, eg, reassurance about prognosis, stress on the ability to lead a normal active life, and explanation of any new symptoms that may appear, is therefore particularly important. Self-measurement of blood pressure may be helpful to ensure compliance. After stabilization of blood pressure, follow-up visits at intervals of 3 to 6 months may be adequate.

During each visit, blood pressure should be measured and side effects monitored, including a careful assessment of the patient’s quality of life. Whenever possible, close contact with the patient’s family is helpful. During follow-up visits, nonpharmacologic measures, particularly cessation of smoking, control of serum cholesterol and weight, moderation of alcohol intake, and institution of physical exercise, should be reinforced. Pharmacologic therapy should be reconfirmed or readjusted. In cases resistant to therapy, further etiologic investigation should be performed. Depending on the drugs used, appropriate laboratory investigations should be performed at regular intervals.

As a rule, antihypertensive therapy should be maintained indefinitely. Cessation of therapy in patients who had been correctly diagnosed as hypertensive (see criteria above and the Figure) is usually followed, sooner or later, by return of blood pressure to pretreatment levels. Nevertheless, after prolonged blood pressure control it may be possible to attempt a careful progressive reduction in the dose or number of drugs used, especially in patients strictly observing nondrug treatment. Attempts to step down treatment should be accompanied, however, by careful, continued supervision of blood pressure.

A hypertensive patient is typically treated for several decades, and during that period major changes in the available drugs occur and new practical issues arise. It is likely that under the influence of pharmacologic progress as well as habits, advertisements, or economic considerations, a patient’s treatment will undergo multiple changes. It is in the interest of every patient that physicians carefully document all drugs to which the patient has been exposed for many years, in conjunction with a careful analysis of their efficacy, clinical tolerability, and biochemical effects. It also is the responsibility of both doctors and health services to make the history of a treated hypertensive patient easily available.

**Cost-effectiveness**

The cost-effectiveness of treating hypertension varies markedly with the degree of cardiovascular risk in various subgroups of patients with hypertension. Cost-effectiveness is more apparent in elderly subjects and in patients with previous cardiovascular disease, in whom the benefit is realized within a shorter time span than it is in younger patients, in whom the benefit is delayed for many years during which the costs of management accumulate. On the other hand, the costs of treating cardiovascular complications of hypertension such as stroke make the treatment of hypertension a very cost-effective process in high-risk groups, in whom the incidence of stroke is reduced by more than 40%.

Although the costs of relatively expensive diagnostic procedures and drugs are readily justified in high-risk groups, the practicing physician should give careful consideration to the costs associated with the investigation and treatment of patients with mild hypertension without associated risk factors. Primary prevention of hypertension and strategies based on changing the lifestyle of the whole population may offer the most cost-effective means of reducing the morbidity and mortality associated with mild hypertension. The effectiveness of these approaches in primary prevention requires further validation.

**Further Research**

Many issues require resolution, and some are being addressed by major studies already in progress. The question of goal blood pressures and the "J curve" is being addressed by the Hypertension Optimal Treatment (HOT) study. Evidence for reduction of morbidity and mortality by the newer classes of antihypertensive drugs is clearly needed and is currently being addressed by the STOP-Hypertension III" and Syst-Eur" studies in the elderly. A major study in middle-aged subjects comparing the benefits of the newer agents with those provided by diuretics and β-blockers may also be desirable.

In young and middle-aged subjects with mild hypertension, in whom the short-term incidence of cardiovascular events is rather low, trials monitoring progression and regression of organ damage (such as left ventricular hypertrophy, carotid artery wall media-intima thickness and plaques, proteinuria, and microalbuminuria) may also provide relevant information on the comparative effectiveness of various classes of antihypertensive agents. A related issue is whether the reversal of organ damage, in particular left ventricular hypertrophy, is accompanied by a commensurate reduction in cardiovascular risk. It would also be important to investigate whether combining antihypertensive and antiplatelet therapies can further reduce cardiovascular events in hypertensive patients (as is being studied in the HOT trial) and whether combining antihypertensive and lipid-lowering treatments can help to reduce the progression of atherosclerosis. Another important issue concerns the potential benefit of lowering blood pressure in subjects with blood pressure below 140/90 mm Hg but with other factors that markedly increase risk (diabetes, previous transient ischemic attack, nephropathies, etc). Methods for optimizing the choice of antihypertensive drugs for each individual patient need
to be improved, and research on the effectiveness of different methods of hypertensive management should be promoted in different countries and populations.

More data are clearly needed on the prognostic significance of blood pressure values obtained by ambulatory blood pressure monitoring or by self-measurements taken at home or at work. The quantification and prognostic significance of white coat hypertension should be addressed. Finally, developments in genetic research may help to further clarify which hypertensive patients are at particular risk of developing cardiovascular disease and events and to indicate the subjects in greatest need of preventive therapy.

The Guidelines Subcommittee plans to assess diffusion, understanding, acceptance, and implementation of these guidelines.

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