The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V)

THIS FIFTH Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure—published on the 20th anniversary of the National High Blood Pressure Education Program—aims to contribute to progress in the primary prevention and control of high blood pressure. Like its predecessors, this document builds on the available scientific evidence regarding the detection, evaluation, and treatment of hypertension. More information is available today to guide clinicians and community programs in preventing and managing this important public health problem. However, this increase in information makes clinical choices increasingly complex. Thus, the need for consensus becomes even more important.

The purpose of this report is to guide practicing physicians and other health professionals in their care of hypertensive patients and health professionals participating in the many community high blood pressure control programs.

This report has several new features:

- Prevalence, awareness, treatment, and control rates for high blood pressure are reported from the 1988 to 1991 National Health and Nutrition Examination Survey (NHANES III). These are the first new data in more than a decade in this area.
- A new classification schema of blood pressure that includes systolic as well as diastolic levels is proposed to help convey the impact of high blood pressure risk for cardiovascular disease. Many believe the previously used classification, particularly the term *mild hypertension*, sounded complacent and lacked sufficient emphasis and urgency.
- An expanded section on primary prevention translates a growing body of knowledge about preventing the disease into recommendations for action.
- The list of agents that are suitable for initial monotherapy has been expanded—from diuretics, β-blockers, calcium antagonists, and angiotensin-converting enzyme inhibitors—to include the α_1-receptor blockers and the α-β-blocker.
- Because diuretics and β-blockers are the only classes of drugs that have been used in long-term controlled clinical trials and shown to reduce morbidity and mortality, they are recommended as first-choice agents unless they are contraindicated or unacceptable, or unless there are special indications for other agents.
- Information on special populations and situations has been expanded and now includes recommendations regarding hypertension in women, isolated systolic hypertension in older persons, cyclosporine, shock-wave lithotripsy, cocaine, and erythropoietin.
- Pharmacologic tables have been updated and include new drugs, recommendations for reduced doses, drug-drug interactions, and drugs to be used in hypertensive crises.
- The term *life-style modifications* is used, instead of *nonpharmacologic therapy*, as a treatment modality for prevention and management of high blood pressure.
- A figure describing a new treatment algorithm and new tables describing the manifestations of target-organ disease (TOD) and situations where ambulatory blood

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pressure monitoring might be useful are included.

The National High Blood Pressure Education Program Coordinating Committee will release additional publications expanding on these guidelines as new information becomes available.

SECTION 1: INTRODUCTION

Since the inception of the National High Blood Pressure Education Program in 1972, remarkable progress has been made in detecting, treating, and controlling hypertension. In the last two decades, the number of hypertensive subjects aware of their condition has increased dramatically. In addition, the percentage of hypertensive patients taking medication and controlling their condition has also improved substantially[1,2] (**Table 1**). Concomitantly, notable and sustained declines in cardiovascular mortality have occurred among all adult population strata. During the last two decades, the mortality from the number 1 cause of death, coronary heart disease, has decreased about 50%, and that from stroke has fallen by 57% (National Center for Health Statistics data calculated by National Heart, Lung, and Blood Institute staff) (**Figures 1 through 3**). Because high blood pressure is one of the major risk factors for coronary heart disease (CHD) and the most important risk factor for the cerebrovascular diseases, it is a reasonable inference that progress in the detection, treatment, and control of hypertension has contributed substantially to these mortality declines.

SECTION 2: CLINICAL EVALUATION AND PUBLIC HEALTH ASPECTS OF HIGH BLOOD PRESSURE

As many as 50 million Americans have elevated blood pressure (systolic blood pressure [SBP] of 140 mm Hg or greater and/or diastolic blood pressure [DBP] of 90 mm Hg or greater) or are taking antihypertensive medication. This estimate is derived from a random sample of American adults (National Health and Nutrition Examination Survey III), plus extrapolations from large data sets on the young applied to the 1990 census population and represents a decrease in the number of hypertensive subjects reported one decade ago (National Health and Nutrition Examination Survey II).

The prevalence of high blood pressure increases with age, is greater for blacks than for whites, and in both races is greater in less educated than more educated people. It is especially prevalent and devastating in lower socioeconomic groups. In young adulthood and early middle age, high blood pressure prevalence is greater for men than for women; thereafter, the reverse is true. Blacks and whites in the southeastern United States have a greater prevalence of high blood pressure and greater stroke death rates than do blacks and whites in other areas of the country.[3] Nonfatal and fatal cardiovascular diseases (CVDs)—including CHD and stroke—as well as renal disease and all-cause mortality increase progressively with higher levels of both SBP and DBP. These relationships are strong, continuous, graded, consistent, independent, predictive, and etiologically significant. In the general population, risks are lowest for adults with an average SBP less than 120 mm Hg and an average DBP less than 80 mm Hg. Higher levels of either SBP or DBP or both together are associated with increased risks of morbidity, disability, and mortality. At every level of DBP, risks are greater with higher levels of SBP. Recent data underscore the importance of attention to SBP, as well as to DBP, in diagnosis and therapy.

The National High Blood Pressure Education Program Coordinating Committee

Member Organizations

American Academy of Family Physicians, American Academy of Insurance Medicine, American Academy of Ophthalmology, American Academy of Physician Assistants, American Association of Occupational Health Nurses, American College of Cardiology, American College of Chest Physicians, American College of Occupational and Environmental Medicine, American College of Physicians, American College of Preventive Medicine, American Dental Association, American Diabetes Association, American Dietetic Association, American Heart Association, American Hospital Association, American Medical Association, American Nurses' Association Inc, American Optometric Association, American Osteopathic Association, American Pharmaceutical Association, American Podiatric Medical Association, American Public Health Association, American Red Cross, American Society of Hospital Pharmacists, American Society of Hypertension, Association of Black Cardiologists, Citizens for Public Action on High Blood Pressure and Cholesterol Inc, International Society on Hypertension in Blacks, National Black Nurses' Association Inc, National Heart, Lung, and Blood Institute Ad Hoc Committee on Minority Populations, National Hypertension Association Inc, National Kidney Foundation, National Medical Association, National Optometric Association, National Stroke Association, Society for Nutrition Education.

Federal Agencies

Agency for Health Care Policy and Research, Health Care Financing Administration, Health Resources and Services Administration, National Center for Health Statistics, Centers for Disease Control, National Heart, Lung, and Blood Institute, National Institute of Diabetes and Digestive and Kidney Diseases, Veterans Affairs.

Aware: % of				
	51	64	(54) 73	(65) 84
	98	34	(33) 58	(49) 73
	16	20	(11) 34	(21) 55

*Defined as 160/95 mm Hg or more on one occasion or reported currently taking antihypertensive medication. Numbers in parentheses are percentages at 140/90 mm Hg or more.

†Source, National Health and Nutrition Examination Survey I.[1]

‡Source, National Health and Nutrition Examination Survey II.[2]

§Source: National Health and Nutrition Examination Survey III (unpublished data provided by the Centers for Disease Control, National Center for Health Statistics).

In both middle-aged and older persons, increases in CVD are associated with elevated SBP, not only when DBP is also high but when DBP is normal—the entity of isolated systolic hypertension.

New Classification of High Blood Pressure

Table 2 provides a new classification of adult blood pressure based on impact on risk. The traditional terms *mild hypertension* and *moderate hypertension* failed to convey the major impact of high blood pressure on risk of CVD. High-normal blood pressure is included as a category because persons with SBP and/or DBP in these ranges are at increased risk of developing definite high blood pressure and of experiencing nonfatal and fatal cardiovascular events, compared with otherwise similar persons with lower blood pressures. Individuals with high-normal blood pressure should be monitored frequently and counseled in regard to life-style measures that can reduce their blood pressure, although pharmacologic therapy is rarely if ever needed.[4,5]

The new classification presented in Table 2 describes stages of blood pressure. All stages of hypertension are associated with increased risk of nonfatal and fatal CVD events and renal disease. The higher the blood pressure, the greater the risk. High blood pressure stage 1, previously termed *mild*, is the most common form of high blood pressure in the adult population and is therefore responsible for a large proportion of the excess morbidity, disability, and mortality attributable to hypertension. All stages of hypertension warrant effective long-term therapy.

Cardiovascular risks relate to blood pressure elevation, dyslipidemia, cigarette use, diabetes mellitus, physical inactivity, and obesity. Detection and treatment of cardiovascular risk factors are key to treating persons with high blood pressure. Risks of CVD at any level of high blood pressure are increased severalfold for persons with target-organ disease (TOD), as described in **Table 3**.

Detection and Confirmation

Hypertension control begins with detection and requires continued surveillance. Health care professionals are strongly encouraged to measure blood pressure at each patient visit.

Measurement. Hypertension should not be diagnosed on the basis of a single measurement. Initial elevated readings should be confirmed on at least two subsequent visits during one to several weeks (unless SBP is 210 mm Hg or greater and/or DBP is 120 mm Hg or greater), with average levels of DPB of 90 mm Hg or greater and/or SBP of 140 mm Hg or greater required for diagnosis (**Table 4**).

Blood pressure should be measured in such a manner that values obtained are representative of patients' usual levels. The following techniques are recommended.

- Patients should be seated with their arm bared, supported, and at heart level. They should not have smoked or ingested caffeine within 30 minutes before measurement.
- Measurement should begin after 5 minutes of rest.
- The appropriate cuff size must be used to ensure an accurate measurement. The bladder should nearly (at least 80%) or completely encircle the arm.
- Measurements should be taken with a mercury sphygmomanometer, a recently calibrated aneroid manometer, or a calibrated electronic device.
- Both SBP and DBP should be recorded. The disappearance of sound (phase V) should be used for the diastolic reading.
- Two or more readings separated by 2 minutes should be averaged. If the first two readings differ by more than 5 mm Hg, additional readings should be obtained.

Patients should be informed and taught the meaning of their blood pressure readings and advised of the need for periodic remeasurement. Table 4 provides follow-up advice based on the *initial* set of blood pressure measurements. For more information regarding blood pressure measurement, refer to the American Heart Association's "Recommendations for Human Blood Pressure Determination by Sphygmomanometers"[6] and the Amer-

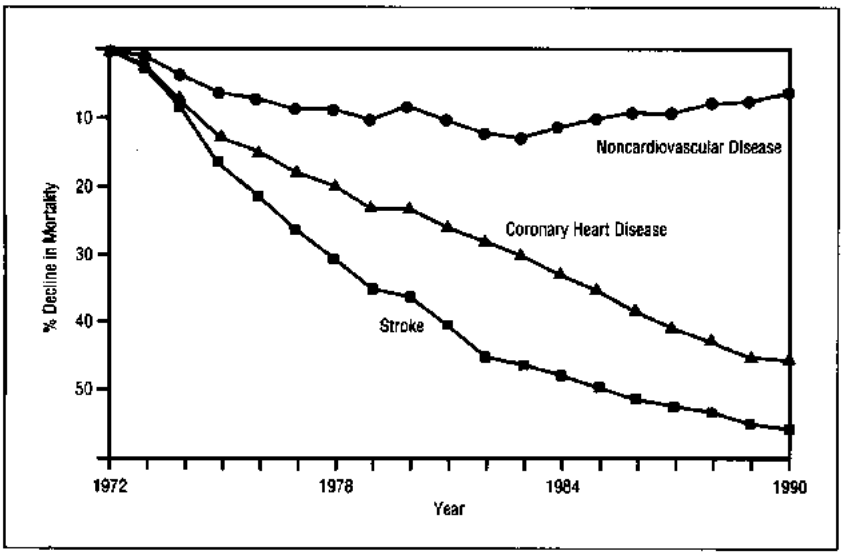


Figure 1. *Decline in age-adjusted mortality since 1972. Data for 1990 are provisional. Source: National Center for Health Statistics data calculated by the National Heart, Lung, and Blood Institute.*

ican Society of Hypertension's "Recommendations for Routine Blood Pressure Measurement by Indirect Cuff Sphygmomanometry."[7]

Confirmation and Follow-up. Repeated blood pressure measurements will determine whether initial elevations persist and require close observation or prompt attention, or whether they have returned to normal and need only periodic remeasurement. Initial blood pressure readings that are markedly elevated (ie, a DBP of ≥120 mm Hg or an SBP of ≥210 mm Hg) or are associated with evidence of TOD may require immediate drug therapy. The timing of subsequent readings should be based on the initial blood pressure (Table 4) as well as previous diagnosis and treatment of CVD and risk factors.

Home Measurement and Ambulatory Automatic Monitoring of Blood Pressure

Blood pressure measurements obtained in the health care setting may not reflect a patient's usual or average blood pressure. With the use of inexpensive manual or semiautomatic devices, blood pressure monitoring at home and/or work (by the patient, family, or friends) is often helpful in evaluating the severity of hypertension and judging the effectiveness of therapy. Each device must be calibrated initially and then at least yearly. Each user must be carefully instructed in the technique of measurement and rechecked periodically.

Fully automatic, lightweight, portable, unobtrusive blood pressure recording devices are now available that can measure and store blood pressure and heart rate data for 24 hours or longer. Clinical situations for which noninvasive ambulatory blood pressure monitoring may be useful are shown in **Table 5**.[8] There is increasing evidence that damage to target organs (heart, kidney, brain, and large arteries) correlates better with out-of-office measurements, including those by ambulatory blood pressure monitoring, than with office measurements.[9-11] While ambulatory blood pressure monitoring is a unique tool for research and for extended assessment of particular hypertensive patients with special clinical problems, it is not necessary for the routine diagnosis and treatment of most patients.

Evaluation

Clinical examination of patients with confirmed hypertension should help answer the following questions.

1. Does the patient have primary or secondary (possibly reversible) hypertension?
2. Is TOD present?
3. Are cardiovascular risk factors present in addition to high blood pressure?

Examination should seek to eliminate the possibility of rare secondary hypertension.[12] Physical findings suggestive of secondary hypertension include abdominal or flank masses (polycystic kidneys); abdominal bruits, particularly those that lateralize or have a diastolic component (renovascular disease); delayed or absent femoral arterial pulses and decreased blood pressure in lower extremities compared with the upper extremities (aortic coarctation); truncal obesity with purple striae (Cushing's syndrome); and tachycardia, tremor, orthostatic hypotension, sweating, and pallor (pheochromocytoma). Additional diagnostic procedures may be indicated to seek causes of secondary hypertension, particularly in patients (1) whose age, history, physical examination results, severity of hypertension, or initial laboratory findings suggest secondary hypertension; (2) whose blood pressures are responding poorly to drug therapy; (3) with well-controlled hypertension whose blood pressures begin to increase; (4) with accelerated or malignant hypertension; and (5) with sudden onset of hypertension.

The remainder of the clinical evaluation primarily addresses TOD and other cardiovascular risk factors. Such information, along with degree of blood pressure elevation, will determine absolute risk level and, therefore, how aggressively blood pressure should be reduced.

Medical History

A medical history should include the following:

- Family history of high blood pressure, premature CHD, stroke, CVD, diabetes mellitus, and dyslipidemia
- Patient history or symptoms of cardiovascular, cerebrovascular, or renal disease; diabetes mellitus; dyslipidemia; or gout
- Known duration and levels of el-

evated blood pressure
- History of weight gain, leisure-time physical activities, and smoking or other tobacco use
- Dietary assessment, including sodium intake, alcohol use, and intake of cholesterol and saturated fats
- Results and side effects of previous antihypertensive therapy
- Symptoms suggesting secondary hypertension
- Psychosocial and environmental factors (eg, family situation, employment status and working conditions, educational level) that may influence blood pressure control

Clinicians should obtain a history of all prescribed and over-the-counter medications. Some medications can raise blood pressure and/or interfere with the effectiveness of antihypertensive drugs. These drugs include, but are not limited to, oral contraceptives, steroids, nonsteroidal anti-inflammatory drugs, nasal decongestants and other cold remedies, appetite suppressants, cyclosporine, erythropoietin, tricyclic antidepressants, and monoamine oxidase inhibitors.

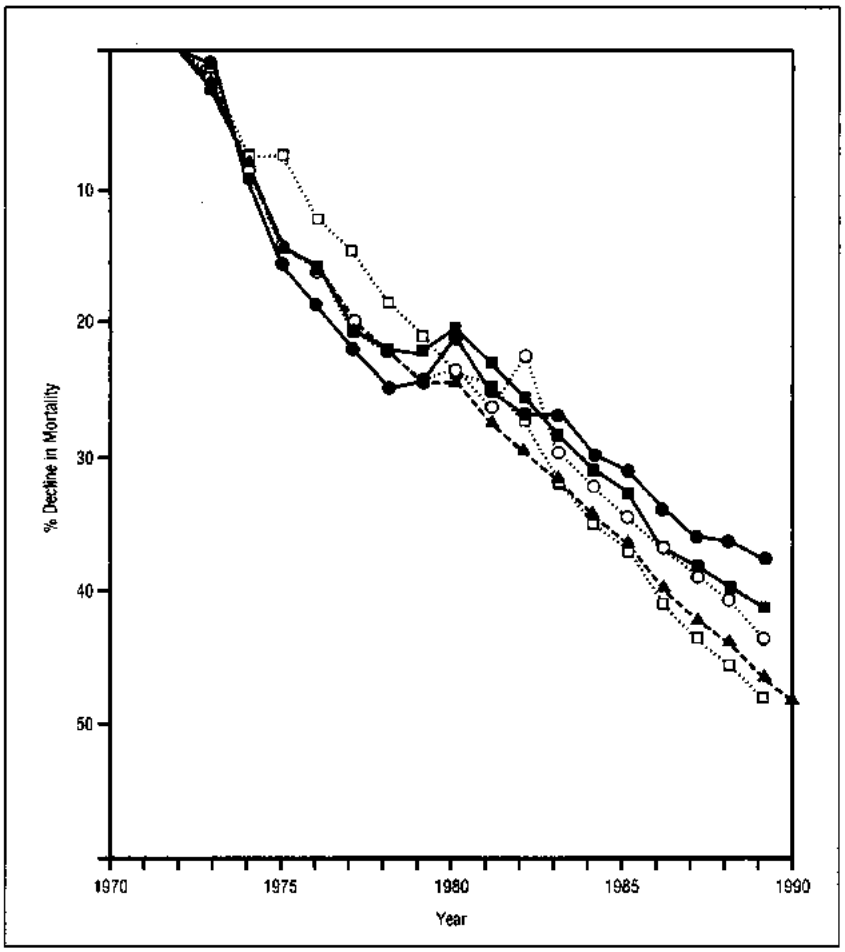


Figure 2. *Decline in age-adjusted mortality for coronary heart disease by race and sex since 1972. Triangles indicate total; solid squares, black men; solid circles, black women; open squares, white men; and open circles, white women. Data for 1990 are provisional. Race/sex data for 1990 were not yet available. Source: National Center for Health Statistics data calculated by the National Heart, Lung, and Blood Institute.*

Physical Examination

The initial physical examination should include the following:
- Two or more blood pressure measurements separated by 2 minutes with the patient either supine or seated, and after standing for at least 2 minutes
- Verification in the contralateral arm (if values are different, the higher value should be used)
- Measurement of height and weight
- Funduscopic examination (with pupil dilatation if necessary) for arteriolar narrowing, arteriovenous nicking, hemorrhages, exudates, or papilledema
- Examination of the neck for carotid bruits, distended veins, or an enlarged thyroid gland
- Examination of the heart for increased rate, increased size, precordial heave, clicks, murmurs, arrhythmias, and third (S_3) and fourth (S_4) heart sounds
- Examination of the abdomen for bruits, enlarged kidneys, masses, and abnormal aortic pulsation
- Examination of the extremities for diminished or absent peripheral arterial pulsations, bruits, and edema
- Neurologic assessment

Laboratory Tests and Diagnostic Procedures

A few laboratory tests should be performed routinely before therapy is initiated. These include urinalysis; complete blood cell count, blood glucose (fasting, if possible), potassium, calcium, creatinine, uric acid, cholesterol (total and high-density lipoprotein) and triglyceride levels (an automated blood chemistry study is usually less expensive); and electrocardiography. Some of these tests are needed for determining severity of CVD and possible causes of hypertension. Others relate to cardiovascular risk factors or provide baseline values for judging biochemical effects of therapy. Other tests—such as urinary microalbumin determination, assessment of caridac anatomy and function by echocardiography, and plasma renin/urinary sodium determination—are additional measures occasionally useful in assessing cardiovascular status in selected cases.

From the history, physical examination results, and findings on laboratory tests, an assessment of absolute risk should be made. Tables, formulas, and various computer software to calculate CVD risks by means

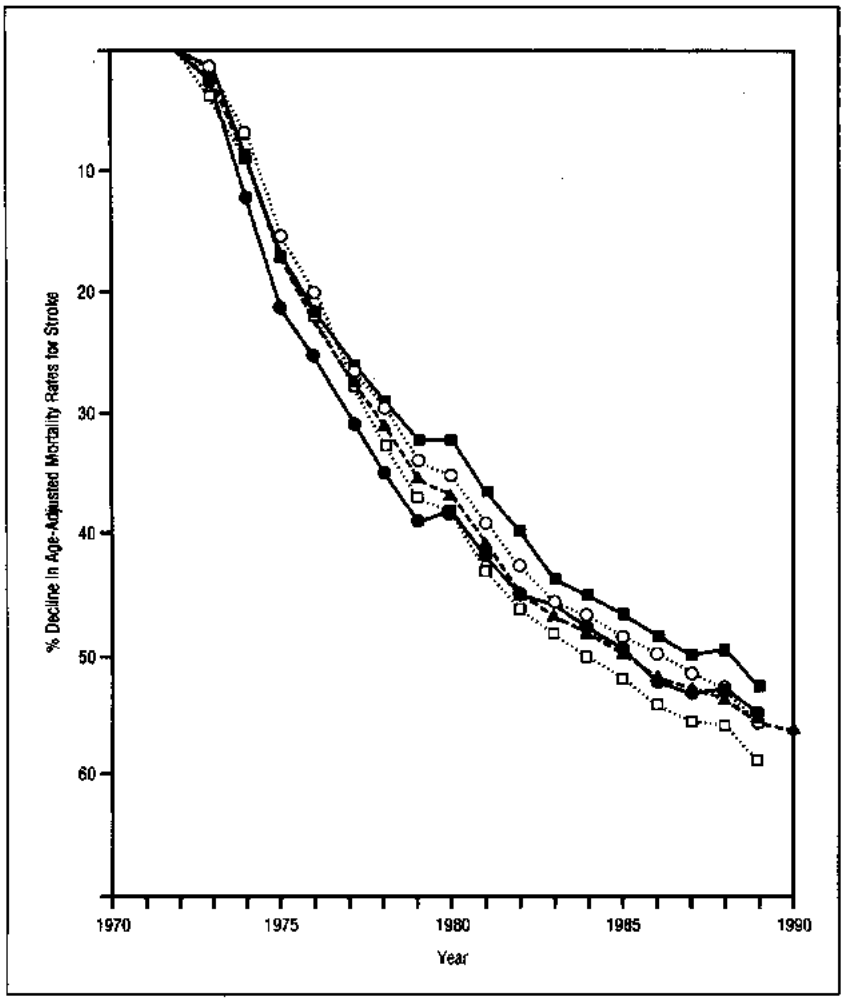


Figure 3. *Decline in age-adjusted mortality for stroke by race and sex since 1972. Triangles indicate total; solid squares, black men; solid circles, black women; open squares, white men; and open circles, white women. Data for 1990 are provisional. Race/sex data for 1990 were not yet available. Source: National Center for Health Statistics data calculated by the National Heart, Lung, and Blood Institute.*

of data from epidemiologic studies are available.[13]

Primary Prevention of High Blood Pressure

Primary prevention of hypertension can be accomplished by application of interventions to the general population (population strategy) with the objective of achieving a downward shift in the distribution of blood pressure. This approach can be complemented by special attempts to lower blood pressure among those who are most likely to develop hypertension (targeted strategy). The latter include persons with high-normal blood pressure, a family history of hypertension, and one or more of the several life-style factors that are important contributors to age-related increases in blood pressure. These life-style factors include a high sodium intake, an excessive consumption of calories, physical inactivity, excessive alcohol consumption, and a low intake of potassium. They form the basis for intervention strategies that have shown promise in the prevention of high blood pressure.[4] The evidence is less convincing for stress management and for supplementation with calcium, magnesium, fish oils, or fiber, and for alteration in macronutrient consumption. In many instances, however, the data are insufficient to make a final judgment on the potential role of these factors in the primary prevention of hypertension.

Intervention programs conducted in community-based and practice-based settings indicate that the desired life-style changes are potentially feasible. Achievement of the intervention goals has, however, been constrained by a number of societal barriers, including a lack of satisfactory food substitutes and the absence of a national campaign to foster adoption of the population-based and targeted intervention strategies necessary to prevent high blood pressure. The National High Blood Pressure Education Program is well positioned to provide leadership for such a campaign. Goals of the campaign should include promotion of foods that are lower in sodium and calorie content and higher in potassium content, and promotion of physical activity and moderation in alcohol consumption. To reach these goals, public education to underscore the importance of life-style factors in the development of hypertension, as well as enhanced education and support of health care providers to encourage and facilitate their active participation, will be necessary. Objectives for national change in the prevalence of factors that increase the public's risk of developing high blood pressure should be established, where they do not yet exist. Finally, additional attention needs to be focused on research questions related to the prevention of high blood pressure. Although primary prevention of hypertension is challenging, the potential for benefit makes this an important national goal for the next decade.

Community Programs for Blood Pressure Control

Community screening activities are important for population subgroups at especially high risk for developing CVD and with limited access to

medical care. Community programs may be an important strategy for primary prevention of hypertension and for monitoring the progress and promoting adherence of hypertensive persons already receiving therapy.

Ideally, community programs are encouraged to include as many of the following as their resources will allow.

- Detection, education, and referral for other cardiovascular risk factors
- Multiple strategies to improve treatment adherence, including public, patient, and professional education activities incorporating culturally sensitive approaches[14] as well as environmental supports, such as informative food labeling, heart-healthy menus in restaurants, and safe trails for walking and biking
- Multiple sites to reach all segments of the population, including all health care settings, schools, worksites, churches, community centers, supermarkets, and pharmacies
- Extensive use of media promotion in conjunction with these activities[15-17]
- Multiple targets, including individuals and groups with increased cardiovascular risk factors as well as those with "normal" risk factor levels who need education and support to continue to practice preventive behaviors, such as weight control, exercise, and good nutrition[4]

In the absence of resources for comprehensive efforts, community programs are encouraged to begin modest activities with expansion to more comprehensive programs when possible. Community programs are most effective when they work with clinicians and other health care providers. This coordination occurs only if clinicians are aware of and support the community programs. Advisory boards or community high blood pressure councils can facilitate cooperation among professional agencies, local health departments, voluntary health agencies, hospitals, industry, and other interest groups. These boards or councils can help identify community problems, resources, priorities, solutions to problems, and methods of evaluating program effectiveness.[18] Such community involvement fosters a sense of ownership and acceptance of responsibility for the community's health problems and their solutions.

Cost of Care

Lifelong antihypertensive therapy represents a significant component of the nation's financial commitment to health. Drug costs can amount to 70% to 80% of total expenditure for treating hypertension.[19] Thus, for individual as well as societal reasons, minimizing cost must be an essential component of the health care provider's responsibility.[20] Interventions should be commensurate with the risk and potential for benefit in each case. Determinants of cost include the following:

- **Initial Evaluation.** Beyond history and physical examination, laboratory evaluations should be done only to the extent necessary to guide individual clinical practice.
- **Follow-up Visits.** The goal of antihypertensive care is to prevent CVD. Frequency of visits and intensity of evaluation and treatment should be the minimum sufficient to achieve and maintain control of blood pressure and other major risk factors and to contain progression of vascular disease.
- **Drugs.** Newer classes of antihypertensive drugs are up to 30 times more expensive than generic diuretics and β-blockers.[20] However, the use of diuretics and β-blockers requires additional surveillance and measurement of changes in blood biochemical and lipid levels that will somewhat increase the cost of their use. Regardless of which drug is chosen, drug dosages and associated costs may be reduced with appropriate patient education/counseling for diet and weight control. In addition, the cost of drugs may be reduced by prescribing scored tablets containing twice the prescribed dosage, when available, and dividing the tablet to achieve the appropriate dose.
- **Confirmation Strategy.** A strategy that reduces the number of individuals initially identified as having stage 1 hypertension and needing long-term drug therapy can lead to a substantial reduction in health care costs. Patient self-monitoring of blood pressure and ambulatory blood pressure monitoring may prove to be useful and cost-effective in assisting the cli-

Table 2. Classification of Blood Pressure for Adults Aged 18 Years and Older*

Category	Systolic, mm Hg	Diastolic, mm Hg
Normal†	<130	<85
High normal	130-139	85-89
Hypertension‡		
Stage 1 (mild)	140-159	90-99
Stage 2 (moderate)	160-179	100-109
Stage 3 (severe)	180-209	110-119
Stage 4 (very severe)	≥210	≥120

*Not taking antihypertensive drugs and not acutely ill. When systolic and diastolic pressures fall into different categories, the higher category should be selected to classify the individual's blood pressure status. For instance, 160/92 mm Hg should be classified as stage 2, and 180/120 mm Hg should be classified as stage 4. Isolated systolic hypertension is defined as a systolic blood pressure of 140 mm Hg or more and a diastolic blood pressure of less than 90 mm Hg and staged appropriately (eg, 170/85 mm Hg is defined as stage 2 isolated systolic hypertension).

In addition to classifying stages of hypertension on the basis of average blood pressure levels, the clinician should specify presence or absence of target-organ disease and additional risk factors. For example, a patient with diabetes and a blood pressure of 142/94 mm Hg, plus left ventricular hypertrophy should be classified as having "stage 1 hypertension with target-organ disease (left ventricular hypertrophy) and with another major risk factor (diabetes)." This specificity is important for risk classification and management.

†Optimal blood pressure with respect to cardiovascular risk is less than 120 mm Hg systolic and less than 80 mm Hg diastolic. However, unusually low readings should be evaluated for clinical significance.

‡Based on the average of two or more readings taken at each of two or more visits after an initial screening.

Table 3. Manifestations of Target-Organ Disease

Organ System	Manifestations
Cardiac	Clinical, electrocardiographic, or radiologic evidence of coronary artery disease; left ventricular hypertrophy or "strain" by electrocardiography or left ventricular hypertrophy by echocardiography; left ventricular dysfunction or cardiac failure
Cerebrovascular	Transient ischemic attack or stroke
Peripheral vascular	Absence of 1 or more major pulses in extremities (except for dorsalis pedis) with or without intermittent claudication; aneurysm
Renal	Serum creatinine ≥130 μmol/L (1.5 mg/dL); proteinuria (1+ or greater); microalbuminuria
Retinopathy	Hemorrhages or exudates, with or without papilledema

nician in making an appropriate diagnosis.[21] These strategies may identify patients with normal blood pressure outside the office and thereby limit the number requiring treatment; however, controlled clinical trials need to be done to substantiate this.[22]

SECTION 3: TREATMENT

Goal

The goal of treating patients with hypertension is to prevent morbidity and mortality associated with high blood pressure and to control blood pressure by the least intrusive means possible. This should be accomplished by achieving and maintaining SBP below 140 mm Hg and DBP below 90 mm Hg, while concurrently controlling other modifiable cardiovascular risk factors. Further reduction to levels of 130/85 mm Hg may be pursued, with due regard for cardiovascular function, especially in older persons. How far the DBP should be reduced below 85 mm Hg is unclear.[23]

Life-style Modification

Life-style modifications previously referred to as *nonpharmacologic therapy*—which include weight reduction, increased physical activity, and moderation of dietary sodium and alcohol intake—are used as definitive or adjunctive therapy for hypertension.[24,25] Physicians should vigorously encourage their patients to adopt these life-style modifications. They offer some hope for prevention of the disease.[4,26-28] They are effective in lowering the blood pressure of many people who follow them, and they can also reduce other risk factors for premature CVD. Their capacity to reduce morbidity or mortality in those with elevated blood pressure has not been conclusively documented. However, because of their ability to improve the cardiovascular risk profile, life-style modification interventions, properly used, offer multiple benefits at little cost and with minimal risk. Even when not adequate in themselves to control hypertension, they may reduce the number and doses of antihypertensive medications needed to manage the condition.[29] Life-style modifications are particularly helpful in the large proportion of hypertensive patients who have additional risk factors for premature CVD, especially dyslipidemia or diabetes.[30]

Tobacco Avoidance. Although unrelated to hypertension, cigarette smoking is a major risk factor for CVD, and avoidance of tobacco is essential. Everyone, especially hypertensive patients, should be strongly advised not to smoke. Repetitive counseling, including referral to effective smoking cessation programs, should be provided. Those who continue to smoke may not receive the full degree of protection against CVD from antihypertensive therapy.[31,32] The nicotine patch or nicotine chewing gum in conjunction with patient counseling may assist the clinician in promoting smoking cessation. Smoking cessation information is available from voluntary health associations and the National Heart, Lung, and Blood Institute Information Center (PO Box 30105, Bethesda, MD 20824-0105).

Weight Reduction. Excess body weight is correlated closely with increased blood pressure. The deposition of excess fat in the upper part of the body (truncal or abdominal), as evidenced by an increased waist-to-hip ratio above 0.85 in women and 0.95 in men, has also been correlated with hypertension, dyslipidemia, diabetes, and increased coronary heart disease mortality.[33]

Weight reduction reduces blood pressure in a large proportion of hypertensive individuals who are more than 10% above ideal weight.[34] A re-

Table 4. Recommendations for Follow-up Based on Initial Set of Blood Pressure Measurements for Adults

Initial Screening Blood Pressure, mm Hg*		
Systolic	Diastolic	Follow-up Recommended†
<130	<85	Recheck in 2 y
130-139	85-89	Recheck in 1 y‡
140-159	90-99	Confirm within 2 mo
160-179	100-109	Evaluate or refer to source of care within 1 mo
180-209	110-119	Evaluate or refer to source of care within 1 wk
≥210	≥120	Evaluate or refer to source of care immediately

**If the systolic and diastolic categories are different, follow recommendation for the shorter-time follow-up (eg, 160/85 mm Hg should be evaluated or referred to source of care within 1 month).*

†The scheduling of follow-up should be modified by reliable information about past blood pressure measurements, other cardiovascular risk factors, or target-organ disease.

‡Consider providing advice about life-style modifications (see text, section 3).

Table 5. Situations in Which Automated Noninvasive Ambulatory Blood Pressure Monitoring Devices May Be Useful

"Office" or "white-coat" hypertension; blood pressure repeatedly elevated in office setting but repeatedly normal out of office
Evaluation of drug resistance
Evaluation of nocturnal blood pressure changes
Episodic hypertension
Hypotensive symptoms associated with antihypertensive medications or autonomic dysfunction
Carotid sinus syncope and pacemaker syndromes*

*Along with electrocardiographic monitoring.

duction in blood pressure usually occurs early during a weight loss program, often with as small a weight loss as 4.5 kg.[35] Weight reduction in overweight hypertensive patients enhances the blood pressure–lowering effect of concurrent antihypertensive agents and can significantly reduce concomitant cardiovascular risk factors.

Therefore, all hypertensive patients who are above their ideal weight should initially be placed on an individualized, monitored weight reduction program involving caloric restriction and increased caloric expenditure by regular physical activity. In overweight patients with stage 1 hypertension, an attempt to control blood pressure with weight loss and other life-style modifications should be tried for at least 3 to 6 months before initiating pharmacologic therapy. If pharmacologic therapy is needed, the weight loss program should continue to be pursued vigorously. While recidivism is common and can be discouraging, the long-term goal of attenuating age-related weight gain should be kept in mind.

Moderation of Alcohol Intake. Excessive alcohol intake can raise blood pressure and cause resistance to antihypertensive therapy.[36] A detailed history of current alcohol consumption should be elicited. Hypertensive patients who drink alcohol-containing beverages should be counseled to limit their daily intake to 1 oz of ethanol (2 oz of 100-proof whiskey, 8 oz of wine, or 24 oz of beer). Significant hypertension may develop during withdrawal from heavy alcohol consumption, but the pressor effect of alcohol withdrawal reverses a few days after alcohol consumption is reduced.[37]

Physical Activity. Regular aerobic physical activity, adequate to achieve at least a moderate level of physical fitness, may be beneficial for both prevention and treatment of hypertension. It can also enhance weight loss and functional health status and reduce the risk of CVD and all-cause mortality.[38] Sedentary and unfit normotensive individuals have a 20% to 50% increased risk of developing hypertension during follow-up when compared with their more active and fit peers.[39]

Regular aerobic physical activity can reduce SBP in hypertensive patients by approximately 10 mm Hg.[40] Effective lowering of blood pressure can be achieved with only moderately intense physical activity (40% to 60% of maximum oxygen consumption). Therefore, physical activity need not be complicated or expensive; for most sedentary patients, such moderate activity as 30 to 45 minutes of brisk walking three to five times per week will be beneficial. The majority of patients with uncomplicated hypertension can safely increase their level of physical activity without an extensive medical or physical fitness evaluation. Patients with known cardiac disease or other serious health problems need a more thorough examination, often including an electrocardiogram-monitored exercise test, and may need to be referred to medically supervised rehabilitative exercise programs.

Moderation of Dietary Sodium. Epidemiologic observations and clinical trials support an association between dietary sodium intake and blood pressure. On the basis of linear regression analysis, within populations, a 100-mmol/d–lower average sodium intake was associated with a 2.2–mm Hg–lower SBP in 10 000 people[41] and a 5– to 10–mm Hg–lower SBP in several other studies involving 47 000 participants.[42] Furthermore, a 100-mmol/d–lower sodium intake was associated with a 9–mm Hg attenuation of the rise of SBP between the ages of 25 and 55 years.[43]

Multiple therapeutic trials document a reduction of blood pressure in response to reduced sodium intake. In short-term trials, moderate sodium restriction in hypertensive individuals on average has been shown to reduce SBP by 4.9 mm Hg and DBP by 2.6 mm Hg.[44] In trials involving people aged 50 to 59 years and lasting 5 weeks or longer, a 50-mmol/d reduction of sodium intake was associated with an average of a 7–mm Hg reduction in SBP in hypertensive persons and a 5–mm Hg reduction in normotensive people.[45]

The impact of dietary sodium on blood pressure depends on the provision of sodium as the chloride salt. Individuals vary in their blood pressure response to changes in dietary sodium chloride.[46] Blacks, older people, and patients with hypertension are more sensitive to changes in dietary sodium chloride.[47,48]

Because the average American

Table 6. Life-style Modifications for Hypertension Control and/or Overall Cardiovascular Risk

Lose weight if overweight
Limit alcohol intake to ≤1 oz/d of ethanol (24 oz of beer, 8 oz of wine, or 2 oz of 100-proof whiskey)
Exercise (aerobic) regularly
Reduce sodium intake to less than 100 mmol/d (<2.3 g of sodium or approximately <6 g of sodium chloride)
Maintain adequate dietary potassium, calcium, and magnesium intake
Stop smoking and reduce dietary saturated fat and cholesterol intake for overall cardiovascular health; reducing fat intake also helps reduce caloric intake—important for control of weight and type II diabetes

consumption of sodium is in excess of 150 mmol/d, moderate dietary sodium chloride reduction to a level of less than 100 mmol/d (approximately < 6 g of sodium chloride or < 2.3 g of sodium per day) is recommended. With appropriate counseling, this is an achievable diet. Blood pressure may be controlled by this degree of sodium chloride restriction in some patients with stage 1 hypertension; in those patients who still need drug therapy, the medication requirements may be decreased.

Potassium. A high dietary potassium intake may protect against developing hypertension,[48] and potassium deficiency may increase blood pressure and induce ventricular ectopy.[49] Therefore, normal plasma concentrations of potassium should be maintained, preferably from food sources. If hypokalemia occurs during diuretic therapy, additional potassium may be needed from potassium-containing salt substitutes, potassium supplements, or use of a potassium-sparing diuretic. Potassium chloride supplements and potassium-sparing diuretics must be used with caution in patients susceptible to hyperkalemia.

Calcium. In many but not all epidemiologic studies, there is an inverse association between dietary calcium and blood pressure. Calcium deficiency is associated with an increased prevalence of hypertension, and a low calcium intake may amplify the effects of a high sodium intake on blood pressure.[50] An increased calcium intake may lower blood pressure in some patients with hypertension, but the overall effect is minimal, and there is no way to predict which patients will benefit.[51] Therefore, there is currently no rationale for recommending calcium intakes in excess of the recommended daily allowance of 20 to 30 mmol (800 to 1200 mg) in an attempt to lower blood pressure.

Magnesium. There is suggestive evidence of an association between lower dietary magnesium intake and higher blood pressures. However, there are currently no convincing data to justify recommending an increased magnesium intake in an effort to lower blood pressure.

Other Dietary Factors. *Dietary Fats.* In randomized controlled studies, diets varying in total fat and proportions of saturated to unsaturated fats have had little, if any, effect on blood pressure.[52] Although large amounts of omega-3 fatty acids may lower blood pressure,[53] they may be associated with multiple adverse effects and are not recommneded for treatment or prevention of high blood pressure. Nevertheless, dyslipidemia is a major independent risk factor for coronary artery disease; therefore, dietary and, if necessary, drug therapy for dyslipidemia is an important adjunct to the antihypertensive regimen.

Caffeine. Caffeine may acutely raise the blood pressure, but tolerance to this pressor effect rapidly develops. Therefore, unless cardiac or other forms of excessive sensitivity to caffeine are present, no limitation of consumption of caffeine-containing beverages is needed.

Dietary Carbohydrates and Protein. No consistent effects on blood pressure have been demonstrated in controlled tnals of varying proportions of carbohydrate or protein in the diet.

Garlic or Onion. No effects on blood pressure of increased amounts of garlic or onion have been found in controlled trials.

Relaxation and Biofeedback. Stress can raise blood pressure acutely and may contribute to the cause of hypertension, but the role of stress management techniques in treating patients with elevated blood pressure is uncertain. Relaxation therapies and biofeedback have been studied in short-term and long-term controlled trials with little effect beyond that seen in the control groups. Therefore, although stress management is an appealing concept, the available literature does not support the use of relaxation therapies for definitive therapy or prevention of hypertension.[4,54]

Summary. **Table 6** summarizes those life-style modifications useful in treating hypertensive patients. The modifications also may be useful in preventing blood pressure from rising and protecting cardiovascular health in those with high-normal blood pressure.

Pharmacologic Treatment

The decision to initiate pharmacologic treatment in individual patients requires consideration of several factors: severity of blood pressure elevation, TOD, and presence of other conditions and risk factors.

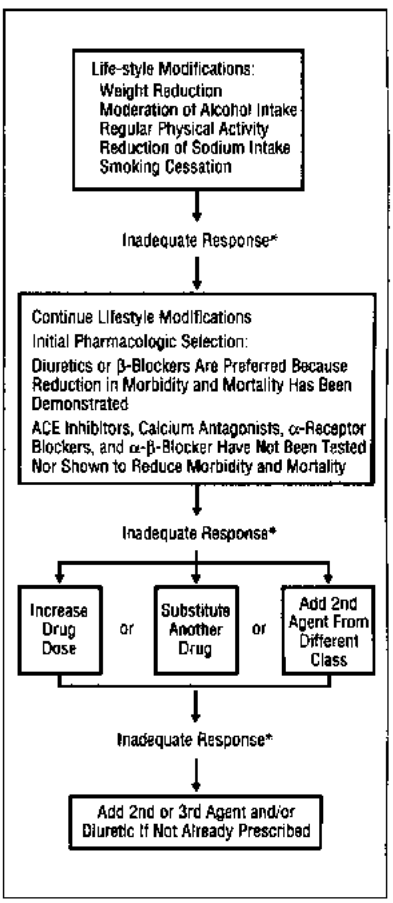


Figure 4. *Treatment algorithm. Asterisk indicates that response means the patient achieved goal blood pressure or is making considerable progress toward this goal. ACE indicates angiotensin-converting enzyme.*

Table 7. Antihypertensive Agents*

Type of Drug	Usual Dosage Range, Total mg/d†	Frequency, Times/d	Mechanisms	Comments
Initial Antihypertensive Agents				
Diuretics				For thiazide and loop diuretics, lower doses and dietary counseling should be used to avoid metabolic changes
Thiazides and related agents			Decreased plasma volume and decreased extracellular fluid volume; decreased cardiac output initially, followed by decreased total peripheral resistance with normalization of cardiac output; long-term effects include slight decrease in extracellular fluid volume	More effective antihypertensive than loop diuretics except in patients with serum creatinine ≥221 μmol/L (2.5 mg/dL)
Bendroflumethiazide	2.5-5	1		Hydrochlorothiazide or chlorthalidone is generally preferred; used in most clinical trials
Benzthiazide	12.5-50	1		
Chlorothiazide	125-500	2		
Chlorthalidone	12.5-50	1		
Cyclothiazide	1.0-2	1		
Hydrochlorothiazide	12.5-50	1		
Hydroflumethiazide	12.5-50	1		
Indapamide	2.5-5	1		
Methyclothiazide	2.5-5	1		
Metolazone	0.5-5	1		
Polythiazide	1.0-4	1		
Quinethazone	25.0-100	1		
Trichlormethiazide	1.0-4	1		
Loop diuretics			See thiazides	Higher doses of loop diuretics may be needed for patients with renal impairment or congestive heart failure
Bumetanide	0.5-5	2		Ethacrynic acid is only alternative for patients with allergy to thiazide and sulfur-containing diuretics
Ethacrynic acid	25.0-100	2		
Furosemide	20.0-320	2		
Potassium sparing			Increased potassium resorption	Weak diuretics
Amiloride	5-10	1 or 2		Used mainly in combination with other diuretics to avoid or reverse hypokalemia from other diuretics
Spironolactone	25-100	2 or 3	Aldosterone antagonist	Avoid when serum creatinine ≥221 μmol/L (2.5 mg/dL)
Triamterene	50-150	1 or 2		May cause hyperkalemia, and this may be exaggerated when combined with ACE inhibitors or potassium supplements
Adrenergic Inhibitors				
β-Blockers				
Atenolol	25-100‡	1	Decreased cardiac output and increased total peripheral resistance; decreased plasma renin activity; atenolol, betaxolol, bisoprolol and metoprolol are cardioselective	Selective agents will also inhibit β_2-receptors in higher doses, eg; all may aggravate asthma
Betaxolol	5-40	1		
Bisoprolol	5-20	1		
Metoprolol	50-200	1 or 2		
Metoprolol (extended release)	50-200	1		
Nadolol	20-240‡	1		
Propranolol	40-240	2		
Propranolol (long acting)	60-240	1		
Timolol	20-40	2		
β-Blockers with ISA				
Acebutolol	200-1200‡	2	Acebutolol is cardioselective	No clear advantage for agents with ISA except in those with bradycardia who must receive a β-blocker; they produce fewer or no metabolic side effects
Carteolol	2.5-10‡	1		
Penbutolol	20-80‡	1		
Pindolol	10-60‡	2		
α-β-Blocker				
Labetalol	200-1200	2	Same as β-blockers, plus α_1-blockade	Possibly more effective in blacks than other β-blockers
				May cause postural effects; titration should be based on standing blood pressure
α_1-Receptor blockers				
Doxazosin	1.0-16	1	Block postsynaptic α_1-receptors and cause vasodilation	All may cause postural effects; titration should be based on standing blood pressure
Prazosin	1.0-20	2 or 3		
Terazosin	1.0-20	1		

(Continued)

Table 7. Antihypertensive Agents* (cont)

Type of Drug	Usual Dosage Range, Total mg/d†	Frequency, Times/d	Mechanisms	Comments
Initial Antihypertensive Agents				
ACE inhibitors				
Benazepril	10.0-40‡	1 or 2	Block formation of angiotensin II, promoting vasodilation and decreased aldosterone; also increased bradykinin and vasodilatory prostaglandins	Diuretic doses should be reduced or discontinued before starting ACE inhibitors whenever possible to prevent excessive hypotension Reduce dose of those drugs marked with double dagger in patients with serum creatinine ≥221 μmol/L (2.5 mg/dL) May cause hyperkalemia in patients with renal impairment or in those receiving potassium-sparing agents Can cause acute renal failure in patients with severe bilateral renal artery stenosis or severe stenosis in artery to solitary kidney
Captopril	12.5-150‡	2		
Cilazapril	2.5-5.0	1 or 2		
Enalapril	2.5-40‡	1 or 2		
Fosinopril	10.0-40	1 or 2		
Lisinopril	5.0-40‡	1 or 2		
Perindopril	1.0-16‡	1 or 2		
Quinapril	5.0-80‡	1 or 2		
Ramipril	1.25-20‡	1 or 2		
Spirapril	12.5-50	1 or 2		
Calcium antagonists			Block inward movement of calcium ion across cell membranes and cause smooth-muscle relaxation	
Diltiazem	90-360	3		These agents also block slow channels in heart and may reduce sinus rate and produce heart block
Diltiazem (sustained release)	120-360	2		
Diltiazem (extended release)	180-360	1		
Verapamil	80-480	2		
Verapamil (long acting)	120-480	1 or 2		
Dihydropyridines				Dihydropyridines are more potent peripheral vasodilators than diltiazem and verapamil and may cause more dizziness, headache, flushing, peripheral edema, and tachycardia
Amlodipine	2.5-10	1		
Felodipine	5-20	1		
Isradipine	2.5-10	2		
Nicardipine	60-120	3		
Nifedipine	30-120	3		
Nifedipine (GITS)	30-90	1		
Supplemental Antihypertensive Agents				
Centrally acting α_2-agonists				
Clonidine	0.1-1.2	2	Stimulate central α_2-receptors that inhibit efferent sympathetic activity	Clonidine patch is replaced once/wk None of these agents should be withdrawn abruptly; avoid in patients who do not adhere to treatment
Clonidine (patch)§	0.1-0.3	1 weekly		
Guanabenz	4-64	2		
Guanfacine	1-3	1		
Methyldopa	250-2000	2		
Peripheral-acting adrenergic antagonists				
Guanadrel	10-75	2	Inhibits catecholamine release from neuronal storage sites	May cause serious orthostatic and exercise-induced hypotension
Guanethidine	10-100	1		
Rauwolfia alkaloids				
Rauwolfia serpentina	50-200	1	Depletion of tissue stores of catecholamines	
Reserpine	0.05‖-0.25	1		
Direct vasodilators				
Hydralazine	50-300	2-4	Direct smooth-muscle vasodilation (primarily arteriolar)	Hydralazine is subject to phenotypically determined metabolism (acetylation) For both agents, should treat concomitantly with diuretic and β-blocker due to fluid retention and reflex tachycardia
Minoxidil	2.5-80	1 or 2		

**In all patients, life-style modifications should also be advised (Table 6). ACE indicates angiotensin-converting enzyme; ISA, intrinsic sympathomimetic activity; and GITS, gastrointestinal therapeutic system.*

†The lower dose indicated is the preferred initial dose, and the higher dose is the maximum daily dose. Most agents require 2 to 4 weeks for complete efficacy, and more frequent dosage adjustments are not advised except for severe hypertension. The dosage range may differ slightly from the recommended dosage in the Physicians' Desk Reference *or package insert.*

‡Indicates drugs that are excreted by the kidney and require dosage reduction in the presence of renal impairment (serum creatinine ≥221 μmol/L ≥2.5 mg/dL).

§Weekly patch is 1, 2, 3, equivalent to 0.1 to 0.3 mg/d.

‖A 0.1-mg dose may be given every other day to achieve this dosage.

Table 8. Antihypertensive Drug Therapy: Individualization Based on Special Considerations (Guidelines for Selecting Initial Therapy)*

Clinical Situation	Preferred	Requires Special Monitoring	Relatively or Absolutely Contraindicated
Cardiovascular			
Angina pectoris	β-Blockers, calcium antagonists	...	Direct vasodilators
Bradycardia/heart block, sick sinus syndrome	...	...	β-blockers, labetalol, verapamil, diltiazem
Cardiac failure	Diuretics, ACE inhibitors	...	β-Blockers, calcium antagonists, labetalol
Hypertrophic cardiomyopathy with severe diastolic dysfunction	β-Blockers, diltiazem, verapamil	...	Diuretics, ACE inhibitors, α_1-blockers, hydralazine, minoxidil
Hyperdynamic circulation	β-Blockers	...	Direct vasodilators
Peripheral vascular occlusive disease	...	β-Blockers	...
After myocardial infarction	Non-ISA β-blockers	...	Direct vasodilators
Renal			
Bilateral renal arterial disease or severe stenosis in artery to solitary kidney	...	...	ACE inhibitors
Renal insufficiency			
Early (serum creatinine, 130-221 μmol/L [1.5-2.5 mg/dL])	...	...	Potassium-sparing agents, potassium supplements
Advanced (serum creatinine, ≥221 μmol/L [≥2.5 mg/dL])	Loop diuretics	ACE inhibitors	Potassium-sparing agents, potassium supplements
Other			
Asthma/COPD	...	...	β-Blockers, labetalol
Cyclosporine-associated hypertension	Nifedipine, labetalol	Verapamil,† nicardipine,† diltiazem†	...
Depression	...	α_2-Agonists	Reserpine
Diabetes mellitus			
Type I (insulin dependent)	...	β-Blockers	...
Type II	...	β-Blockers, diuretics	...
Dyslipidemia	...	Diuretics, β-blockers	...
Liver disease	...	Labetalol	Methyldopa
Vascular headache	β-Blockers	...	...
Pregnancy			
Preeclampsia	Methyldopa, hydralazine	...	Diuretics, ACE inhibitors
Chronic hypertension	Methyldopa	...	ACE inhibitors

*ACE indicates angiotensin-converting enzyme; ISA, intrinsic sympathomimetic activity; and COPD, chronic obstructive pulmonary disease.
†Can increase serum levels of cyclosporine.

Efficacy. Reducing blood pressure with drugs clearly decreases the incidence of cardiovascular mortality and morbidity.[55,56] Protection has been demonstrated for stroke, coronary events, congestive heart failure, progression to more severe hypertension, and all-cause mortality. Meta-analysis of 14 randomized trials indicated a 42% reduction in stroke from a 5– to 6–mm Hg lowering of DBP.[55] This reduction in stroke rate was highly consistent with long-term observational studies that predicted 35% to 40% reductions with this blood pressure difference. The same long-term analyses predicted a 20% to 25% reduction in the rate of CHD; however, the observed reduction from the 14 pooled trial results was 14% during periods of 4 to 6 years. Several explanations but little conclusive evidence have been presented to account for the less than expected reduction in CHD events in these trials.[55] This meta-analysis did not include new data from three recent clinical trials on hypertension control in older persons. The Systolic Hypertension in the Elderly Program,[57] the Swedish Trial in Old Patients With Hypertension,[58] and the Medical Research Council Trial[59] demonstrated a 27%, 13%, and 19% reduction in CHD events, respectively.

Stage 1 and Stage 2 Hypertension. If blood pressure remains at or above 140/90 mm Hg during a 3- to 6-month period despite vigorous encouragement of life-style modifications, antihypertensive medications should be started, especially in individuals with TOD and/or other known risk factors for CVD. In the absence of TOD and other major risk factors, some physicians may elect to withhold antihypertensive drug therapy from patients with DBP in the 90– to 94–mm Hg range and SBP in the 140–to 149–mm Hg range. In these patients, careful follow-up is indicated at 3- to 6-month intervals be-

Table 9. Selected Drug Interactions With Antihypertensive Therapy*

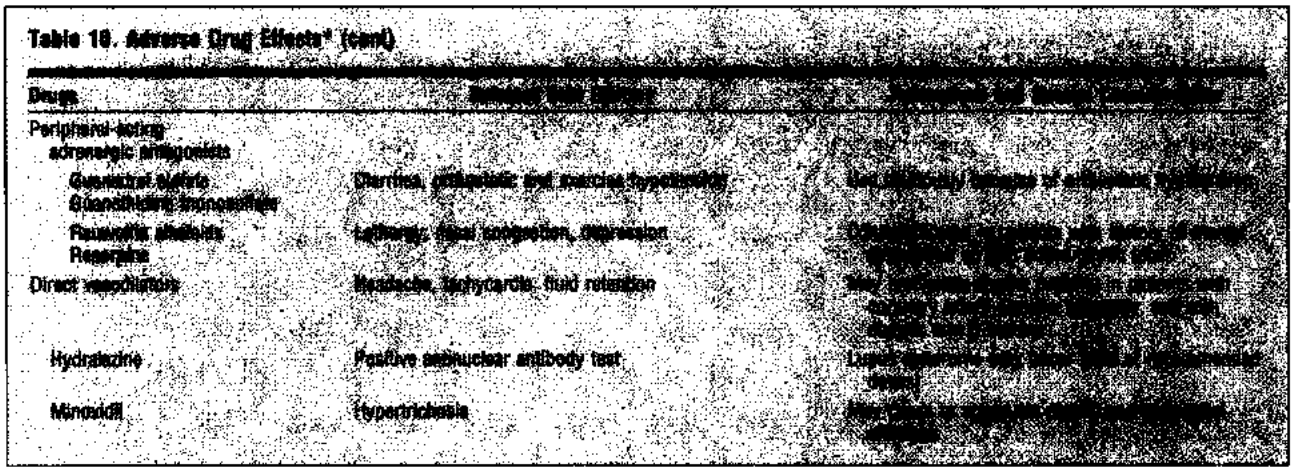
- Diuretics
  - Possible situations for decreased antihypertensive effects
    - Cholestyramine and colestipol decrease absorption
    - NSAIDs (including aspirin and over-the-counter ibuprofen) may antagonize diuretic effectiveness
  - Possible situations for increased antihypertensive effects
    - Combinations of thiazides (especially metolazone) with furosemide can produce profound diuresis, natriuresis, and kaliuresis in renal impairment
  - Effects of diuretics on other drugs
    - Diuretics can raise serum lithium levels and increase toxic effects by enhancing proximal tubular resorption of lithium
    - Diuretics may make it more difficult to control dyslipidemia and diabetes
- β-Blockers
  - Possible situations for decreased antihypertensive effects
    - NSAIDs may decrease effects of β-blockers
    - Rifampin, smoking, and phenobarbital decrease serum levels of agents primarily metabolized by liver due to enzyme induction
  - Possible situations for increased antihypertensive effects
    - Cimetidine may increase serum levels of β-blockers that are primarily metabolized by liver due to enzyme inhibition
    - Quinidine may increase risk of hypotension
  - Effects of β-blockers on other drugs
    - Combinations of diltiazem or verapamil with β-blockers may have additive sinoatrial and atrioventricular node depressant effects and may also promote negative inotropic effects on failing myocardium
    - Combination of β-blockers and reserpine may cause marked bradycardia and syncope
    - β-Blockers may increase serum levels of theophylline, lidocaine, and chlorpromazine due to reduced hepatic clearance
    - Nonselective β-blockers prolong insulin-induced hypoglycemia and promote rebound hypertension due to unopposed α stimulation; all β-blockers mask adrenergically mediated symptoms of hypoglycemia and have potential to aggravate diabetes
    - β-Blockers may make it more difficult to control dyslipidemia
    - Phenylpropanolamine (which can be obtained over the counter in cold and diet preparations), pseudoephedrine, ephedrine, and epinephrine can cause elevations in blood pressure due to unopposed α-receptor–induced vasoconstriction
- ACE inhibitors
  - Possible situations for decreased antihypertensive effects
    - NSAIDs (including aspirin and over-the-counter ibuprofen) may decrease blood pressure control
    - Antacids may decrease the bioavailability of ACE inhibitors
  - Possible situations for increased antihypertensive effects
    - Diuretics may lead to excessive hypotensive effects (hypovolemia)
  - Effect of ACE inhibitors on other drugs
    - Hyperkalemia may occur with potassium supplements, potassium-sparing agents, and NSAIDs
    - ACE inhibitors may increase serum lithium levels
- Calcium antagonists
  - Possible situations for decreased antihypertensive effects
    - Serum levels and antihypertensive effects of calcium antagonists may be diminished by these interactions: rifampin-verapamil; carbamazepine-diltiazem and verapamil; phenobarbital and phenytoin-verapamil
  - Possible situations for increased antihypertensive effects
    - Cimetidine may increase pharmacologic effects of all calcium antagonists due to inhibition of hepatic metabolizing enzymes resulting in increased serum levels
  - Effects of calcium antagonists on other drugs
    - Digoxin and carbamazepine serum levels and toxic effects may be increased by verapamil and possibly by diltiazem
    - Serum levels of prazosin, quinidine, and theophylline may be increased by verapamil
    - Serum levels of cyclosporine may be increased by diltiazem, nicardipine, and verapamil; cyclosporine dose may need to be decreased
- α-Blockers
  - Possible situations for increased antihypertensive effects
    - Concomitant antihypertensive drug therapy (especialy diuretics) may increase chance of postural hypotension
- Sympatholytics
  - Possible situations for decreased antihypertensive effects
    - Tricyclic antidepressants may decrease effects of centrally acting and peripheral norepinephrine depleters
    - Sympathomimetics, including over-the-counter cold and diet preparations, amphetamines, phenothiazines, and cocaine, may interfere with antihypertensive effects of guanethidine and guanadrel
    - Severity of clonidine withdrawal reaction can be increased by β-blockers
    - Monoamine oxidase inhibitors may prevent degradation and metabolism of norepinephrine released by tyramine-containing foods and may cause hypertension; they may also cause hypertensive reactions when combined with reserpine or guanethidine
  - Effects of sympatholytics on other drugs
    - Methyldopa may increase serum lithium levels

**This table does not include all potential drug interactions with antihypertensive drugs. NSAID indicates nonsteroidal anti-inflammatory drug; ACE, angiotensin-converting enzyme.*

Table 10. Adverse Drug Effects*

Drugs	Selected Side Effects†	Precautions and Special Considerations
Diuretics‡		
Thiazides and related diuretics	Hypokalemia, hypomagnesemia, hyponatremia, hyperuricemia, hypercalcemia, hyperglycemia, hypercholesterolemia, hypertriglyceridemia, sexual dysfunction, weakness	Except for metolazone and indapamide, ineffective in renal failure (serum creatinine ≥221 μmol/L [≥2.5 mg/dL]); hypokalemia increases digitalis toxic effect; may precipitate acute gout
Loop diuretics	Same as for thiazides except loop diuretics do not cause hypercalcemia	Effective in chronic renal failure
Potassium-sparing agents	Hyperkalemia	Danger of hyperkalemia in patients with renal failure, in patients treated with ACE inhibitor or with NSAIDs
Amiloride	...	...
Spironolactone	Gynecomastia, mastodynia, menstrual irregularities, diminished libido in males	...
Triamterene	...	Danger of renal calculi
Adrenergic Inhibitors		
β-Blockers‡	Bronchospasm, may aggravate peripheral arterial insufficiency, fatigue, insomnia, exacerbation of CHF, masking of symptoms of hypoglycemia; also, hypertriglyceridemia, decreased high-density lipoprotein cholesterol (except for drugs with ISA); reduces exercise tolerance	Should not be used in patients with asthma, COPD, CHF with systolic dysfunction, heart block (greater than 1st degree), and sick sinus syndrome; use with caution in insulin-treated diabetics and patients with peripheral vascular disease; should not be discontinued abruptly in patients with ischemic heart disease
α-β-Blocker		
Labetalol	Bronchospasm, may aggravate peripheral vascular insufficiency, orthostatic hypotension	Should not be used in patients with asthma, COPD, CHF, heart block (greater than 1st degree), and sick sinus syndrome; use with caution in insulin-treated diabetics and patients with peripheral vascular disease
α_1-Receptor blockers	Orthostatic hypotension, syncope, weakness, palpitations, headache	Use cautiously in older patients because of orthostatic hypotension
ACE inhibitors	Cough, rash, angioneurotic edema, hyperkalemia, dysgeusia	Hyperkalemia can develop, particularly in patients with renal insufficiency; hypotension has been observed with initiation of ACE inhibitors, especially in patients with high plasma renin activity or receiving diuretic therapy; can cause reversible, acute renal failure in patients with bilateral renal arterial stenosis or unilateral stenosis in solitary kidney and in patients with cardiac failure and with volume depletion; rarely can induce neutropenia or proteinuria; absolutely contraindicated in 2nd and 3rd trimesters of pregnancy
Calcium antagonists		
Dihydropyridines Amlodipine Felodipine Isradipine Nicardipine Nifedipine	Headache, dizziness, peripheral edema, tachycardia, gingival hyperplasia	Use with caution in patients with CHF; may aggravate angina and myocardial ischemia
Diltiazem Verapamil	Headache, dizziness, peripheral edema (less common than with dihydropyridines), gingival hyperplasia, constipation (especially verapamil), atrioventricular block, bradycardia	Use with caution in patients with cardiac failure; contraindicated in patients with 2nd- or 3rd-degree heart block, or sick sinus syndrome
Centrally acting α_2-agonists		
Clonidine Guanabenz Guanfacine hydrochloride	Drowsiness, sedation, dry mouth, fatigue, orthostatic dizziness	Rebound hypertension may occur with abrupt discontinuance, particularly with previous administration of high doses or with continuation of concomitant β-blocker therapy
Clonidine patch	Same as for clonidine; localized skin reaction to patch	...
Methyldopa	...	May cause liver damage, fever, and Coombs-positive hemolytic anemia

(Continued)



*See Table 7 for a list of drugs. ACE indicates angiotensin-converting enzyme; NSAID, nonsteroidal anti-inflammatory drug; COPD, chronic obstructive pulmonary disease; ISA, intrinsic sympathomimetic activity; and CHF, congestive heart failure.

†The listing of side effects is not all-inclusive, and clinicians are urged to refer to the package insert for a more detailed listing. Sexual dysfunction, particularly impotence in men, has been reported with the use of all antihypertensive agents. Few data are available on the effect of antihypertensive agents on sexual function in women.

‡Some of the metabolic side effects of diuretics and β-blockers can be minimized by appropriate dietary counseling.

cause blood pressure may rise to higher levels, and cardiac and vascular changes may occur. Clinical trial data strongly suggest that antihypertensive drug therapy should be initiated before the development of TOD.[60]

Initial Drug Therapy. Initial drug therapy is monotherapy for stage 1 and Stage 2 hypertension, ie, start with a single drug. Because diuretics and β-blockers have been shown to reduce cardiovascular morbidity and mortality in controlled clinical trials, these two classes of drugs are preferred for initial drug therapy[61] (**Figure 4**). The alternative drugs—calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, α_1-receptor blockers, and the α-β blocker—are equally effective in reducing blood pressure.[24] Although these alternative drugs have potentially important benefits, they have not been used in long-term controlled trials to demonstrate their efficacy in reducing morbidity and mortality and therefore should be reserved for special indications or when diuretics and β-blockers have proved unacceptable or ineffective. There is an urgent need to evaluate the effectiveness of ACE inhibitors, calcium antagonists, and α_1-receptor blockers in reducing long-term cardiovascular morbidity and mortality.

Other factors that should be considered in the selection of drugs are the cost of medication, metabolic and subjective side effects, and drug-drug interactions (see section 4).

Supplemental antihypertensive agents, such as the direct-acting smooth-muscle vasodilators, the α_2-agonists, and the peripherally acting adrenergic neuron antagonists, are not well suited for initial monotherapy. The direct-acting smooth-muscle vasodilators (eg, hydralazine, minoxidil) often induce reflex sympathetic stimulation of the cardiovascular system and fluid retention. The α_2-agonists and peripherally acting adrenergic antagonists produce annoying side effects in a large number of patients.

The antihypertensive drugs are listed in **Table 7**.

Special Considerations. Also to be considered in the selection of initial therapy are demographic characteristics, concomitant diseases that may be beneficially or adversely affected by the antihypertensive agent chosen (**Table 8**), and the use of other drugs that may lead to drug interactions (**Table 9**).[62-64]

Demographics. In general, blacks are more responsive to diuretics and calcium antagonists than to β-blockers or ACE inhibitors. Older persons with hypertension are generally responsive to all classes of drugs. Gender has not been found to determine drug responsiveness. In any event, gender, age, or race does not provide sufficient reason to avoid any drug class, particularly if it is needed for other therapeutic benefits, because efficacy differences can usually be overcome with the addition of a diuretic or another agent.

Concomitant Diseases and Therapies. Antihypertensive drugs may worsen some diseases while improving others (Table 9). For example, β-blockers may worsen asthma, diabetes, and peripheral ischemia, but they may improve angina pectoris, certain cardiac dysrhythmias, and migraine headaches, and they have proved to prolong life after myocardial infarction. Selection of an antihypertensive agent that also treats a coexisting disease may simplify therapeutic regimens and reduce costs.

Quality of Life. Antihypertensive drugs may cause undesirable symptoms (**Table 10**). For example, many of these agents may impair sexual function, centrally acting drugs may impair mental acuity, and β-blockers may reduce exercise tolerance.

Physiologic and Biochemical Measurements. Some clinicians have found certain physiologic and biochemical

Table 11. Causes of Lack of Responsiveness to Therapy

- Nonadherence to therapy
  - Cost of medication
  - Instructions not clear and/or not given to patient in writing
  - Inadequate or no patient education
  - Lack of involvement of patient in treatment plan
  - Side effects of medication
  - Organic brain syndrome (eg, memory deficit)
  - Inconvenient dosing
- Drug-related causes
  - Doses too low
  - Inappropriate combinations (eg, 2 centrally acting adrenergic inhibitors)
  - Rapid inactivation (eg, hydralazine)
  - Drug interactions
    - Nonsteroidal anti-inflammatory drugs
    - Oral contraceptives
    - Sympathomimetics
    - Antidepressants
    - Adrenal steroids
    - Nasal decongestants
    - Licorice-containing substances (eg, chewing tobacco)
    - Cocaine
    - Cyclosporine
    - Erythropoietin
- Associated conditions
  - Increasing obesity
  - Alcohol intake more than 1 oz/d of ethanol
- Secondary hypertension
  - Renal insufficiency
  - Renovascular hypertension
  - Pheochromocytoma
  - Primary aldosteronism
- Volume overload
  - Inadequate diuretic therapy
  - Excess sodium intake
  - Fluid retention from reduction of blood pressure
  - Progressive renal damage
- Pseudohypertension

measurements (eg, body weight, heart rate, plasma renin activity, resting electrocardiographic tracing, and hemodynamic measures) to be helpful in choosing specific therapy.

Economic Considerations. The cost of therapy may be a barrier to controlling hypertension. Treatment costs include not only the price of drugs but also the expense of routine or special laboratory tests, supplemental therapies, office visits, and time lost from work for visits to physicians' offices.

Dosage and Follow-up. The lowest dosage listed in Table 7 should be selected to protect the patient from adverse effects, although it may not immediately control the blood pressure. If blood pressure remains uncontrolled, the lowest dose should be given for several weeks before it is increased to the next dosage level. It must be recognized that it may take months to control hypertension adequately while avoiding adverse effects of therapy. Most antihypertensive medications can be given once or twice daily, and this should be the goal so as to improve patient adherence. Adherence improves substantially as prescribed dose frequency decreases.[65]

If, after 1 to 3 months, the response to initial therapy is inadequate, the patient is not experiencing significant side effects, and adherence to therapy is adequate, three options for subsequent therapy should be considered (see Figure 4 for treatment algorithm):

- Increase the dose of the first drug to or toward maximal levels (see Table 7).
- Substitute an agent from another class.
- Add a second drug from another class.

Combining antihypertensive drugs with different modes of action will often allow smaller doses of drugs to be used to achieve control, thereby minimizing the potential for dose-dependent side effects. If a diuretic is not chosen as the first drug, it will be useful as a second-step agent because its addition usually enhances the effects of other agents. If addition of a second agent produces satisfactory blood pressure control, an attempt to withdraw the first agent may be considered, because monotherapy with virtually all agents provides blood pressure control for at least half of all patients.

Before proceeding to each successive treatment step, clinicians should address possible reasons for lack of responsiveness to therapy, including those listed in **Table 11**.

After blood pressure is reduced to goal level and maintenance doses of antihypertensive drugs are stabilized, substituting comparable combination tablets may simplify patients' regimens and promote adherence to a comprehensive antihypertensive treatment program.

Stage 3 and Stage 4 Hypertension. Although similar general approaches are advocated for all patients with hypertension, modification may be appropriate for those with DBP of 110 mm Hg or higher and/or SBP of 180 mm Hg or higher. Although some patients may respond adequately to only one drug, it is often necessary to add a second or third agent after a short interval if control is not achieved. The intervals between changes in the regimen should be decreased, and the maximum dose of some drugs may be increased. In some patients it may be necessary to start treatment with more than one agent. Patients with average DBP of 120 mm Hg or greater require more immediate therapy and, if significant TOD is present, may require hospitalization and consultation.

Isolated Systolic Hypertension. Isolated systolic hypertension frequently occurs in older persons and is discussed in more detail in the "Hypertension in Older Patients" section (section 4). When isolated systolic hypertension occurs in adolescents and young adults, it often indicates a hyperdynamic circulation and may predict future diastolic elevation. Life-style modifications should be used in an attempt to lower SBP in isolated systolic hypertension. However, when the SBP is consistently 160 mm Hg or greater and the DBP is less than 90 mm Hg despite life-style modification, antihypertensive drug treatment is indicated for older patients and should be considered for younger patients.

Step-Down Therapy. Sound patient treatment should include attempts to

Table 12. Management of Hypertensive Crisis: Emergencies and Urgencies*

Drug	Dose	Onset	Cautions
Parenteral vasodilators			
Sodium nitroprusside	0.25-10 μg/kg per min as IV infusion; maximal dose for 10 min only	Instantaneous	Nausea, vomiting, muscle twitching; with prolonged use may cause thiocyanate intoxication, methemoglobinemia acidosis, cyanide poisoning; bags, bottles, and delivery sets must be light resistant
Nitroglycerin	5-100 μg as IV infusion	2-5 min	Headache, tachycardia, vomiting, flushing, methemoglobinemia; requires special delivery system due to drug binding to PVC tubing
Diazoxide	50-150 mg as IV bolus, repeated, or 15-30 mg/min by IV infusion	1-2 min	Hypotension, tachycardia, aggravation of angina pectoris, nausea and vomiting, hyperglycemia with repeated injections
Hydralazine	10-20 mg as IV bolus 10-40 mg IM	10 min 20-30 min	Tachycardia, headache, vomiting, aggravation of angina pectoris
Enalaprilat	0.625-1.25 mg every 6 h IV	15-60 min	Renal failure in patients with bilateral renal artery stenosis, hypotension
Parenteral adrenergic inhibitors			
Phentolamine	5-15 mg as IV bolus	1-2 min	Tachycardia, orthostatic hypotension
Trimethaphan camsylate	1-4 mg/min as IV infusion	1-5 min	Paresis of bowel and bladder, orthostatic hypotension, blurred vision, dry mouth
Labetalol	20-80 mg as IV bolus every 10 min; 2 mg/min as IV infusion	5-10 min	Bronchoconstriction, heart block, orthostatic hypotension
Methyldopate	250-500 mg as IV infusion every 6 h	30-60 min	Drowsiness
Oral agents			
Nifedipine (not extended release)	10-20 mg PO, repeat after 30 min	15-30 min	Rapid, uncontrolled reduction in blood pressure may precipitate circulatory collapse in patients with aortic stenosis
Captopril	25 mg PO, repeat as required	15-30 min	Hypotension, renal failure in bilateral renal artery stenosis
Clonidine	0.1-0.2 mg PO, repeated every hour as required to a total dose of 0.6 mg	30-60 min	Hypotension, drowsiness, dry mouth
Labetalol	200-400 mg PO, repeat every 2-3 h	30 min-2 h	Bronchoconstriction, heart block, orthostatic hypotension

**It is sometimes appropriate to administer a diuretic agent with any of these drugs. IV indicates intravenous; IM, intramuscular; PO, orally; and PVC, polyvinyl chloride.*

decrease the dosage or number of antihypertensive drugs while maintaining life-style modifications. In general, complete cessation of an antihypertensive treatment program is not indicated. However, after blood pressure has been effectively controlled for 1 year and at least four visits, it may be possible to reduce antihypertensive drug therapy in a deliberate, slow, and progressive manner. Step-down therapy is especially successful in patients who are also following life-style treatment recommendations: a higher percentage maintain normal blood pressure levels with less or no medication.[28] Patients whose drugs have been discontinued should have regular follow-up because blood pressure usually rises again to hypertensive levels, sometimes months or years after discontinuance, especially in the absence of sustained improvements in life-style.

J-Curve Hypothesis. Concerns have been raised that lowering DPB too much may increase the risk of coronary disease possibly by lowering diastolic perfusion pressure in the coronary circulation—the so-called J-curve hypothesis.[23,66] This concern may be more relevant to hypertensive patients with preexisting coronary disease. No data support a similar relationship of blood pressure reduction to adverse effects on cerebral or renal function. Regardless of the presence or absence of a J-curve, available evidence supports the reduction of DBP and SBP at all ages to the levels achieved in clinical trials—usually less than 90 mm Hg in DBP, and 140 to 160 mm Hg in isolated systolic hypertension.

Resistant Hypertension. Hypertension should be considered resistant if the blood pressure in a patient who is adherent to treatment cannot be reduced to less than 160/100 mm Hg by an adequate and appropriate triple-drug regimen prescribed in nearly maximal doses when the pretreatment blood pressure was greater than 180/115 mm Hg. If the pretreatment blood pressure was less than 180/115 mm Hg, resistance should

be defined as failure to achieve normotension (<140/90 mm Hg) on a similar regimen. An adequate and appropriate regimen should include at least three different pharmacologic agents, including a diuretic plus two of the following classes of drugs: β-adrenergic blocker or another antiadrenergic agent, direct vasodilator, calcium antagonist, or ACE inhibitor.

For older patients with isolated systolic hypertension, resistance in a patient who is adherent to treatment is defined as failure of an adequate triple-drug regimen to reduce SBP to less than 170 mm Hg if pretreatment SBP was greater than 200 mm Hg or to less than 160 mm Hg and by at least 10 mm Hg if pretreatment SBP was 160 to 200 mm Hg.

If goal blood pressure cannot be achieved without intolerable side effects, even suboptimal reduction of blood pressure will contribute to decreased morbidity and mortality.

Hypertensive Crises: Emergencies and Urgencies. Hypertensive emergencies are those situations that require immediate blood pressure reduction (not necessarily to normal ranges) to prevent or limit TOD. Examples include hypertensive encephalopathy, intracrancial hemorrhage, acute left ventricular failure with pulmonary edema, dissecting aortic aneurysm, eclampsia or severe hypertension associated with pregnancy, unstable angina pectoris, and acute myocardial infarction. Hypertensive urgencies are those situations in which it is desirable to reduce blood pressure within 24 hours. Hypertensive urgencies include accelerated or malignant hypertension without severe symptoms or progressive target-organ complications and severe perioperative hypertension. Drugs available and their routes of administration are listed in **Table 12**.[67]

Although most hypertensive emergencies are treated initially with parenteral administration of an appropriate agent, oral administration of selected agents may also be associated with rapid reduction in blood pressure. There is no clearly defined clinical advantage for sublingual over oral administration of nifedipine or captopril.

When treating the hypertensive urgency or emergency, it is desirable to choose agents that enable a controlled reduction in blood pressure during 30 minutes to several hours. Elevated blood pressure alone, in the absence of symptoms or evident TOD, rarely requires emergency therapy. The risks of overly aggressive intervention in any hypertensive crisis must always be considered. Even the administration of oral agents for hypertensive urgencies has resulted in myocardial ischemia and cerebral hypoperfusion.

Long-term Adherence to Therapy

Follow-up Visits. Achieving and maintaining target blood pressure with the lowest possible dosage of medication requires ongoing patient follow-up and may involve dosage adjustments. Patients with stage 1 hypertension without TOD should generally be seen within 1 to 2 months after the initiation of therapy to determine the adequacy of blood pressure control, the degree of patient adherence, and the presence of adverse effects. Associated medical problems, including TOD, other major risk factors, and laboratory test abnormalities, will also play a part in determining the frequency of patient follow-up. Once the blood pressure is stabilized, follow-up at 3- to 6-month intervals (depending on the patient's status) is generally appropriate. Monitoring should include blood pressure measurements in the supine or sitting positions and after standing quietly for 2 minutes. Patient education should be an important feature of follow-up visits.

Planned Patient Education Programs. Poor adherence to long-term treatment, both life-style modifications and pharmacologic therapy, has been identified as the major reason for inadequate control of high blood pressure. Planned patient education programs may significantly improve adherence to treatment schedules, improve blood pressure control, and decrease hypertension-related morbidity and mortality.[68] Combinations of patient education intervention strategies are likely to achieve the greatest improvement in long-term adherence and are usually aimed at improving patient understanding of specific therapies and treatment goals, correcting misconceptions, adjusting the therapeutic interventions to patients' life-styles, and enhancing family or other social support.

Strategies to Improve Adherence to Therapy and Control of High Blood Pressure. The choice and application of specific strategies will depend on individual patient characteristics, severity of specific diseases, and comorbidities. It is not expected that all strategies would be applied any one time, nor to all patients, as the priority of strategies should be developed on an individual basis. Review of patient progress and effectiveness of the approaches at follow-up visits is recommended. With time, the patient's needs may change and behavioral and pharamcologic approaches may need to be altered. The following outlines a series of strategies to enhance adherence to treatment. They are designed to provide guidance at the initial as well as follow-up visits.

Educate about conditions and treatment

- Assess patient's understanding and acceptance of the diagnosis and expectations of being in care
- Discuss patient's concerns and clarify misunderstandings
- Inform patient of blood pressure level
- Agree with patient on a goal blood pressure
- Inform patient about recommended treatment and provide specific written information
- Elicit concerns and questions and provide opportunities for patient

to state specific behaviors to carry out treatment recommendations

Emphasize need to continue treatment, that patient cannot tell if blood pressure is elevated, and that control does not mean cure

Individualize the regimen

- Include patient in decision making
- Simplify the regimen
- Incorporate treatment into patient's daily life-style
- Set, with the patient, realistic short-term objectives for specific components of the treatment plan
- Encourage discussion of side effects and concerns
- Encourage self-monitoring
- Minimize cost of therapy
- Indicate you will ask about adherence at next visit
- When weight loss is established as a treatment goal, discourage quick weight loss regimens, fasting, and unscientific methods, since these are associated with weight cycling, which may increase cardiovascular morbidity and mortality

Provide reinforcement

- Provide feedback regarding blood pressure level
- Ask about behaviors to achieve blood pressure control
- Give positive feedback for behavioral and blood pressure improvement
- Hold exit interviews to clarify regimen
- Make appointment for next visit before patient leaves the office
- Use appointment reminders and contact patients to confirm appointments
- Schedule more frequent visits to counsel nonadherent patients
- Contact and follow up patients who missed appointments
- Consider clinician-patient contracts

Promote social support

- Educate family members to be part of the blood pressure control process and provide daily reinforcement
- Suggest small group activities to enhance mutual support and motivation

Collaborate with other professionals

- Draw on complementary skills and knowledge of nurses, pharmacists, dietitians, optometrists, dentists, and physician assistants
- Refer patients for more intensive counseling.

SECTION 4: SPECIAL POPULATIONS AND SITUATIONS

Hypertension in African-Americans and Other Racial and Ethnic Minorities

The frequency of hypertension in African-Americans is among the highest in the world,[41] and hypertension is the major health problem of adult African-Americans. Blacks develop hypertension at an earlier age; and, at any decade of life, hypertension is more severe in blacks than in whites. As much as 30% of all deaths in hypertensive black men and 20% of all deaths in hypertensive black women may be attributable to high blood pressure.[69] This earlier onset, higher prevalence, and greater severity of hypertension in blacks than in whites is accompanied by a 1.3-fold greater rate of nonfatal stroke, a 1.8-fold greater rate of fatal stroke, a 1.5-fold greater rate of heart disease deaths,[70] and a fivefold greater rate of end-stage renal disease.[71]

Available evidence indicates that, at similar starting blood pressure levels, blacks will achieve similar overall blood pressure declines and may experience a lower incidence of CVD than whites, when provided equal access to adequate therapy.[72]

Because of the high prevalence of salt sensitivity, obesity, and cigarette smoking in blacks, life-style modifications are particularly important. The control of obesity is of particular importance because blacks have twice the prevalence of non–insulin-dependent diabetes mellitus.

In blacks, diuretics have been proved in controlled trials to reduce hypertensive morbidity and mortality; thus, diuretics should be the agent of first choice in the absence of other conditions that prohibit their use. Monotherapy with β-blockers or ACE inhibitors is less effective in blacks; but calcium antagonists, α_1-receptor blockers, and the α-β-blocker are as effective in blacks as in whites. Because of the greater rate of severe hypertension in blacks, more black patients will require multidrug therapy, and clinicians should not hesitate to use the most powerful agents, including minoxidil, especially in those with impaired renal function.

Little information is available on whether other racial and ethnic groups—including Native Americans, Asians and Pacific Islanders, and Hispanics—respond differently from whites to antihypertensive medications or life-style modifications. Further studies are needed to understand better the factors influencing the control of hypertension in these groups.

Hypertension in Children

According to the "Report of the Second Task Force on Blood Pressure Control in Children—1987,"[73] hypertension in children is defined as average SBP and/or DBP equal to or greater than the 95th percentile for age on at least three occasions (**Table 13**). In many of the childhood cases, significant and severe hypertension may have an identifiable underlying cause. Children who have slight or periodic blood pressure elevation frequently exhibit other risk factors for future CVD that usually persist into adult life and often cluster within families. All clinicians who care for children aged 3 years through adolescence should be encouraged to measure blood pressure once a year, when the child is well.[73] This is es-

Table 13. Classification of Hypertension in the Young by Age Group*

Age Group	[illegible], mm Hg	[illegible], mm Hg	[illegible], mm Hg
Newborns (BBP)			
7 d	...	90-105	≥106
8-30 d	...	104-109	≥110
Infants (≤2 y)			
SBP	104-111	112-117	≥118
DBP	70-73	74-81	≥82
Children			
3-5 y			
SBP	108-115	116-123	≥124
DBP	70-75	76-83	≥84
6-9 y			
SBP	114-121	122-129	≥130
DBP	74-77	78-85	≥86
10-12 y			
SBP	122-125	126-133	≥134
DBP	78-81	82-89	≥90
13-15 y			
SBP	130-135	136-143	≥144
DBP	80-85	86-91	≥92
Adolescents (16-18 y)			
SBP	136-141	142-149	≥150
DBP	84-91	92-97	≥98

*Adapted from the "Report of the Second Task Force on Blood Pressure Control in Children—1987."[73] Note that adult classifications differ. SBP indicates systolic blood pressure; DBP, diastolic blood pressure.

pecially true in children who have a hypertensive parent. Likewise, the parents of children who exhibit elevated pressures should also be screened.

The "Report of the Second Task Force on Blood Pressure Control in Children—1987"[73] offers a comprehensive approach to the detection, evaluation, and treatment of high blood pressure in children. This report provides normative data on blood pressure from more than 70 000 white, black, and Mexican-American children. Table 13 depicts the levels of blood pressure in childhood that have been used to diagnose hypertension. These levels are different from those levels found in adults because percentile levels are used in classification of blood pressure levels in children and adolescents.

Children, like adults, require repeated measurements with proper equipment to determine the level of blood pressure accurately. The widest cuff that will comfortably encircle the arm without covering the antecubital fossa should be used. For infants in whom the accuracy of measurements by auscultation is uncertain, an electronic device using a Doppler technique can be used.

The higher the blood pressure and the younger the child, the greater the possibility of secondary hypertension. Attention should also be given to risk factor assessment, including family history, obesity, diet, and physical activity. In adolescents, the use of alcohol, cocaine, or other addictive substances should be considered as a possible cause of the elevated blood pressure. Laboratory tests for young patients are generally similar to those recommended for adults. However, efforts to arrive at a diagnosis of secondary hypertension should be more thorough in a child.

The underlying cause, severity, or complications of hypertension in children will determine the degree and types of intervention required. Therapy should reduce blood pressure without causing adverse effects that limit adherence or impair normal growth and development. Life-style modifications can be introduced as initial treatments but may be insufficient therapy when there is severe hypertension or when there is a demonstrated cause. Weight reduction in obese children often lowers the blood pressure. Antihypertensive drug therapy should usually be reserved for patients with levels of blood pressure above the 99th percentile or with significantly elevated blood pressure that responds inadequately to life-style modifications or is associated with TOD. As with adults, children with insulin-dependent diabetes mellitus and with primary renal disease may benefit from pharmacologic antihypertensive therapy at any level of hypertension to prevent or delay progression of renal insufficiency. Pharmacologic agents generally used for adults are also effective in young persons.

Uncomplicated elevated blood pressure, by itself, should not be a

reason to restrict asymptomatic children from participating in physical activities, particularly because exercise may both prevent and relieve hypertension. Use of steroid hormones for the purpose of body building should be strongly discouraged.

Hypertension in Women

The long-term and large clinical trials of antihypertensive treatment have included both men and women but have not clearly demonstrated gender differences in blood pressure response and outcomes.[74] Because the rate of cardiovascular events in middle-aged women is much lower than in men, these trials had limited ability to distinguish the degree of benefit from treatments between men and women.[75] Recent trials in older persons reinforce the conclusion to support a similar approach to the management of hypertension in men and women. Therefore, at this time, there are insufficient data to support a different approach to the management of hypertension in women, but further study is warranted.

Hypertension Associated With Oral Contraceptives. Most women taking oral contraceptives experience a small but detectable increase in both SBP and DBP, usually within the normal range.[76] Hypertension has been reported to be two to three times more common in women taking oral contraceptive pills for 5 years or longer than in those not taking oral contraceptives.[77] The risk appears to increase with age, with duration of use, and perhaps with increased body mass. Women aged 35 years and older who smoke cigarettes should be strongly counseled to stop smoking. If they continue to smoke, they should be discouraged from using oral contraceptives, because most of the cardiovascular deaths attributable to oral contraceptive use have been in such women. Since many of the studies of blood pressure and oral contraceptives involved higher doses of both estrogen and progesterone than are presently in use, the current incidence of oral contraceptive–induced hypertension is probably less than reported earlier. Nonetheless, in a small number of patients, oral contraceptives may cause accelerated or malignant hypertension.[78]

The mechanism of the increase in blood pressure remains unclear. If hypertension develops in a woman taking oral contraceptives, it is advisable to stop the use of the pill. The blood pressure will normalize in most cases within a few months. If high blood pressure persists and the risks of pregnancy are considered to be greater than the risks of stage 1 hypertension, and other contraceptive methods are not suitable, it may be necessary to continue the pill in spite of the elevation in blood pressure. Life-style modifications and antihypertensive medication should be used to normalize blood pressure, and patients should be carefully monitored.

Hypertension in Pregnancy. Hypertension during pregnancy may result in life-threatening consequences for both mother and fetus. The National High Blood Pressure Education Program's "Working Group Report on High Blood Pressure in Pregnancy"[79] recommends a simple classification of four diagnostic categories: (1) chronic hypertension, (2) preeclampsia-eclampsia, (3) chronic hypertension with superimposed preeclampsia, and (4) transient hypertension. The report emphasizes the importance of differentiating hypertension that antedates pregnancy from a pregnancy-specific condition that is characterized by poor perfusion of many organs and usually has increased blood pressure as one of its features. In the former condition, elevated blood pressure is the cardinal pathophysiologic feature, whereas in the latter, increased blood pressure is important primarily as a sign of the underlying disorder.

Criteria. The criteria for diagnosing hypertension in pregnancy are SBP increases of 30 mm Hg or greater and DBP increases (Korotkoff phase V) of 15 mm Hg or greater compared with the average of values before 20 weeks' gestation. When previous blood pressures are not known, a reading of 140/90 mm Hg or above is considered abnormal.

Chronic Hypertension. Chronic hypertension is hypertension that is present and observable before pregnancy or that is diagnosed before the 20th week of gestation. The goal of treatment of chronic hypertension in pregnancy is to minimize the short-term risks of elevated blood pressure to the mother while avoiding therapy that compromises fetal well-being. Diuretics or any other antihypertensive drugs except ACE inhibitors may be continued if they were taken before pregnancy. Angiotensin-converting enzyme inhibitors should be avoided because serious neonatal problems, including renal failure and death, have been reported when mothers have taken these agents during the last two trimesters.[80] For women who were not taking antihypertensive therapy when they became pregnant and those whose antihypertensive therapy was stopped in early stages of pregnancy, increased rest or stopping work may be helpful when DBP is between 90 and 100 mm Hg. Moderate sodium restriction should be considered only if it was useful before pregnancy. Antihypertensive drug therapy is reserved for patients with DBP greater than or equal to 100 mm Hg.[79] Aggressive antihypertensive therapy is discouraged because of the concern for maintaining adequate uteroplacental blood flow.

Methyldopa has been most extensively evaluated in pregnancy and is therefore recommended.[81] β-Blockers compare favorably with methyldopa with respect to efficacy and are considered safe in the latter part of pregnancy, but their use early in pregnancy may be associated with growth retardation of the fetus.[82]

Preeclampsia. The pregnancy-specific condition preeclampsia is increased blood pressure accompanied by proteinuria, edema, or both, and, at times abnormalities of coagulation and liver function. Preeclampsia may progress rapidly to a con-

vulsive phase, eclampsia. Preeclampsia occurs primarily in primigravidas and after the 20th week of gestation.

Therapy for preeclampsia consists of hospitalization with bed rest, control of blood pressure, seizure prophylaxis when signs of impending eclampsia are present, and timely delivery. If preeclampsia develops before the fetus is mature, the physician must carefully consider both the maternal and fetal health and decide whether postponement of delivery is safe. Delivery is indicated, regardless of gestational age, when there are signs of fetal distress, uncontrollable hypertension in the mother, evidence of deteriorating renal or hepatic function, epigastric pain, or signs of impending eclampsia (eg, headache, visual disturbance, and hyperreflexia).

The decision to use antihypertensive drugs should be based on maternal safety, because there is no clear-cut fetal benefit of lowering blood pressure, and such treatment does not cure or reverse preeclampsia. Although there is disagreement regarding what level of blood pressure should be treated, most authorities would begin therapy when DBP is greater than or equal to 100 mm Hg.[79] If delivery is not anticipated in 24 hours, an oral agent is preferable, and methyldopa is the drug of choice.[81] Hydralazine, calcium antagonists, α-β-blockers, and β-blockers are reasonable additions or alternatives.

When delivery is imminent, a parenteral antihypertensive agent is preferable. Intravenous hydralazine is effective and has been used safely in pregnancy.[83] Limited data are available on the use of diazoxide, labetalol, and clonidine. Potent diuretics, such as furosemide, are generally not advisable.

Encouraging preliminary data involving 13 small trials suggest that low-dose aspirin may prevent preeclampsia by reversing the imbalance between prostacyclin and thromboxane that may be responsible for some of the manifestations of this disease.[84] While recommendations for the general pregnant population are not warranted, low-dose aspirin (approximately 60 mg) may be useful in high-risk patients, eg, patients whose previous pregnancies were complicated by preeclampsia of early onset, those who may be at risk for recurrent fetal death or severe fetal growth retardation due to placental insufficiency, and those with poor obstetric histories.

Estrogen Replacement Therapy and Blood Pressure. The presence of hypertension is not a contraindication to postmenopausal estrogen replacement therapy; in fact, such treatment may have a beneficial effect on blood pressure as well as on overall cardiovascular risk.[85] However, because a few women may experience a rise in blood pressure attributable to estrogen therapy, it is recommended that all women treated with hormonal replacement have their blood pressures monitored more frequently after such therapy is instituted. The effects of transdermal estrogen and of progestogen in addition to estrogen replacement on blood pressure in postmenopausal women have not been documented.

Hypertension in Older Patients

Hypertension is present in approximately 60% of non-Hispanic whites, 71% of non-Hispanic blacks, and 61% of Mexican-Americans aged 60 years or older (National Health and Nutrition Examination Survey III). Systolic hypertension is a well-established independent risk factor for CHD, stroke, and CVD. The prevalence of isolated systolic hypertension (defined as SBP of ≥140 mm Hg with a DBP <90 mm Hg) increases after age 60 years.

In older patients, the sudden onset of hypertension suggests the presence of secondary hypertension, particularly occlusive atherosclerotic renovascular disease. Pseudohypertension is sometimes encountered in elderly patients who have such rigid brachial arteries that they cannot be compressed by the sphygmomanometer cuff, giving falsely high readings. This should be suspected when TOD is absent in spite of high blood pressures and can be confirmed when the pulseless radial artery is palpable even though the sphygmomanometer cuff is inflated to pressures high enough to occlude the brachial artery (Osler's sign).[86]

The value of treating hypertension in older patients has now been established[57-59,87-90] (**Table 14**). The Systolic Hypertension in the Elderly Program compared treatment with a low-dose diuretic, chlorthalidone, and, if needed, atenolol or reserpine with treatment with placebo in patients with baseline average SBP of 160 mm Hg or greater and DBP less than 90 mm Hg. The results after an average of 4.5 years clearly favored active treatment, with 36% fewer fatal and nonfatal strokes and 27% fewer fatal and nonfatal myocardial infarctions in actively treated patients compared with placebo-treated patients. Benefit was evident across all age, race, sex, and blood pressure subgroups, and active treatment was well tolerated. Data from other clinical trials indicate that older patients who have DBP of 90 mm Hg or greater will also benefit from antihypertensive therapy (Table 14).

Therefore, the initial goal of therapy is to reduce the SBP to less than 160 mm Hg for those with SBP greater than 180 mm Hg and to lower blood pressure by 20 mm Hg for those with SBP between 160 and 179 mm Hg. If this is well tolerated, it may be appropriate to reduce the blood pressure even further. At SBP levels of 140 to 160 mm Hg in patients with isolated systolic hypertension, life-style modifications may be adjunctive or definitive therapy. In general, goals of therapy for DBP in older persons are similar to those for the general population.

Antihypertensive drug therapy should be carried out more cautiously in older patients. Older patients may be more sensitive to volume depletion and sympathetic inhibition than are younger individuals, because older individuals may have impaired cardiovascular reflexes that make them more suscep-

Table 14. Effects of Therapy in Older Hypertensive Patients*

	[illegible]	EWPHE†	[illegible]	STOP-Hypertension†	MRC†	SHEP†	HDFP†‡
No. of patients	582	840	884	1627	4396	4736	2374
Age range, y	60-69	≥60	60-79	70-84	65-74	60-≥80	60-69
Mean BP at entry, mm Hg	165/101	182/101	197/100	195/102	185/91	170/77	170/101
Relative risk of event (treated vs control)							
Stroke	0.67	0.64	0.58‡	0.53‡	0.75‡	0.67‡	0.58‡
CAD	0.82	0.80	1.03	0.87§	0.81	0.73§	0.85‡
CHF	...	0.78	0.69	0.49‡	...	0.45‡	...
All CVD	0.69	0.71‡	0.76‡	0.60‡	0.83‡	0.68‡	0.84‡

*EWPHE indicates European Working Party on High Blood Pressure in the Elderly; STOP-Hypertension, Swedish Trial in Old Patients With Hypertension; MRC, Medical Research Council; SHEP, Systolic Hypertension in the Elderly Program; HDFP, Hypertension Detection and Follow-up Program; BP, blood pressure; CAD, coronary artery disease; CHF, congestive heart failure; and CVD, cardiovascular disease.

†Includes data calculated by the HDFP Coordinating Center.

‡Statistically significant.

§Myocardial infarction only; sudden deaths decreased from 13 to four.

tible to hypotension. For this reason, blood pressure should always be measured in the standing as well as seated (or supine) positions, and antihypertensive treatment should be initiated with smaller doses than usual. Increases in dosage also should be smaller and spaced at longer intervals than might be appropriate for younger patients. Drugs that have a propensity to cause orthostatic hypotension (eg, guanethidine monosulfate, guanadrel sulfate, α_1-receptor blockers, and labetalol) should be used with caution. All classes of antihypertensive drugs have been shown to be effective in lowering blood pressure in older patients. However, only diuretics and β-blockers have been used in controlled trials that have shown a reduction in cardiovascular morbidity and mortality.

Patients With Hypertension and Coexisting Cardiovascular Diseases

Patients With Cerebrovascular Disease. The presence of clinically evident cerebrovascular disease is an indication for antihypertensive treatment. Immediately after the occurrence of an ischemic cerebral infarction, it may be appropriate to withhold treatment (unless the blood pressure is very high) until the situation has been stabilized. Even when treatment has been temporarily withheld, the eventual goal is to reduce blood pressure gradually with avoidance of orthostatic hypotension.

Severe hypertension that appears in the course of an acute stroke poses a difficult therapeutic problem. Some data suggest that DBP in excess of 120 mm Hg warrants cautious treatment, particularly when the hypertension is accompanied by such a complication as congestive heart failure.[91,92]

Patients With Coronary Artery Disease. Hypertension in patients with coronary artery disease should be treated. The incidence of angina pectoris or myocardial infarction does not increase when elevated blood pressures are carefully reduced, and many patients experience a decrease in symptoms with pressure reduction. In the Multiple Risk Factor Intervention Trial, men with abnormal results of stress tests benefited substantially from risk factor reductions.[93,94] Among men in the Multiple Risk Factor Intervention Trial with abnormal results of stress tests who were hypertensive at baseline, risk of CHD was significantly higher for those who received usual care than for participants who received special intervention.[95] As with patients who have cerebrovascular disease, blood pressure should be reduced gradually to avoid hypotensive episodes. β-Blockers or calcium antagonists (especially those that reduce heart rate) may be specifically useful in patients with angina pectoris. For those who have had a myocardial infarction, β-blockers without intrinsic sympathomimetic activity are the drugs of choice because they have been shown to reduce the risk of a subsequent event and sudden death.[96]

Patients With Cardiac Failure. Control of elevated arterial pressure can improve myocardial function, prevent cardiac failure, and reduce mortality. Angiotensin-converting enzyme inhibitors, when used alone or in combination with digitalis or diuretics in patients with congestive failure, are effective in reducing mortality due to progressive congestive heart failure.[97] The use of ACE inhibitors may decrease mortality even more than other vasodilator therapy does.[98]

Patients With Left Ventricular Hypertrophy. Left ventricular hypertrophy permits cardiac adaptation to the increased afterload imposed by elevated blood pressure. However, left ventricular hypertrophy represents a major independent risk factor for cardiac death, myocardial infarction, and other morbid events,[99] and control of elevated blood pressure should prevent this condition.

Echocardiography is the most sensitive and specific way to diagnose left ventricular hypertrophy, but its use is limited by cost.[100] The electrocardiogram remains of value not only for detecting left ventricular hypertrophy but also for identifying evidence of myocardial ischemia or cardiac dysrhythmias.

All major drug classes, with the exception of direct-acting vasodilators, may reduce left ventricular mass and wall thickness,[101] as may weight loss[102] and decrease of dietary salt intake.[103] It is not known whether reversal of hypertension-induced cardiac hypertrophy improves the independent risk of cardiovascular morbidity and mortality associated with left ventricular hypertrophy. However, the presence of left ventricular hypertrophy is an indication for effective blood pressure control.

Patients With Peripheral Vascular Diseases. Hypertension is a major risk factor for the development of carotid atherosclerosis, arteriosclerosis obliterans, intermittent claudication, and aneurysms, including dissecting aneurysms; however, it is not known whether antihypertensive therapy will alter the course of the diseases. Arterial hypertrophy and atherosclerosis may further increase SBP and the pulse pressure. Effective control of pressure and other atherogenic factors may help retard or even reverse the stiffening of arteries.

Patients With Hypertension and Other Coexisting Diseases

Patients With Renal Disease. The hypertension of chronic renal failure is largely volume dependent, due to retention of sodium and water. Thus, relatively large doses of diuretics are often needed as part of the treatment regimen. A loop diuretic (furosemide, bumetanide, ethacrynic acid) or metolazone or indapamide is usually necessary to accomplish substantial diuresis when the serum creatinine level has reached 221 μmol/L (2.5 mg/dL) or more. Potassium supplements and potassium-sparing diuretics are relatively contraindicated in the presence of even mild renal insufficiency.

All of the commonly used classes of antihypertensive drugs are usually effective in lowering blood pressure in patients with renal disease. In those whose hypertension has become resistant to multiple drug therapy that includes large doses of loop diuretics, minoxidil may be needed. In animal experiments as well as short-term clinical trials of small subsets of selected patients with diabetic nephropathy, ACE inhibitors have been shown to reduce proteinuria and slow progression of renal disease.[104] However, acute renal failure can be precipitated by ACE inhibitors in hypertensive patients with bilateral renal artery stenosis, renal artery stenosis to a solitary kidney, and preexisting renal disease. Hyperkalemia is a definite risk in azotemic patients receiving ACE inhibitors, especially those who have diabetic renal disease or those using nonsteroidal anti-inflammatory drugs. Therefore, serum creatinine and potassium levels should be monitored carefully before and after initiation of treatment with ACE inhibitors in patients who have renal insufficiency.

Controlling high blood pressure clearly preserves renal function. Aggressive control of hypertension also prevents or slows the progression of renal failure. It is unclear whether any antihypertensive agent is preferred in this regard. It has been suggested that blood pressure should be reduced to 130/85 mm Hg or less to provide adequate protection of renal function in hypertensive patients.[105]

Dietary protein and phosphate restriction are appropriate nondrug therapies that may preserve renal function and should be implemented early in the course of renal insufficiency. In the advanced stages of renal insufficiency, hypertension often becomes relatively resistant to multiple-drug therapy, and adequate control requires either long-term dialysis or renal transplantation.

Patients With Diabetes Mellitus. Patients with hypertension and diabetes mellitus are especially vulnerable to cardiovascular complications; therefore, the control of hypertension and dyslipidemia as well as cessation of cigarette smoking are particularly important. For these patients, the blood pressure goal should be 130/85 mm Hg or less. Life-style modifications are beneficial for control of hyperglycemia, dyslipidemia, and hypertension, which often coexist in obese patients with insulin resistance.[106,107]

No antihypertensive agent is specifically contraindicated for use in the diabetic population, but caution is needed with most drugs. Diuretic-induced hypokalemia may worsen glucose tolerance; β-blockers may worsen glucose tolerance and mask the symptoms of and prolong recovery from hypoglycemia; α_1-receptor blockers may aggravate postural hypotension; and ACE inhibitors may induce hyperkalemia.

The potentially beneficial effect of ACE inhibitors on proteinuria and renal function in patients with diabetic renal disease is discussed in the previous section.

The syndrome of insulin resistance closely parallels type II diabetes mellitus. Hypertension, dyslipidemia, hyperinsulinemia, glucose intolerance, and, frequently, upper-body obesity comprise this syndrome. Insulin resistance can be improved by weight loss and exercise. Short-term studies in small numbers of patients have shown that α_1-receptor blockers and ACE inhibitors decrease insulin resistance.

Patients With Dyslipidemia. The common coexistence of hypercholesterolemia and hypertension mandates effective management of both conditions.[30] Since life-style modifications are the first approach to treatment of both conditions, great emphasis must be placed on control of excessive weight, reduction of cholesterol and saturated fat intake, and increased physical activity in pa-

tients with elevated lipid levels and hypertension.

If life-style modifications are not successful in controlling blood pressure, drug therapy must be added. Thiazide and loop diuretics can induce at least short-term, small increases in levels of total plasma cholesterol, triglycerides, and low-density lipoprotein cholesterol. Several studies have suggested that this dyslipidemic effect may decrease or disappear with long-term therapy. Dietary modifications may reduce or eliminate these effects.

β-Blockers may increase levels of plasma triglycerides and reduce those of high-density lipoprotein cholesterol. Despite this effect, β-blockers without intrinsic sympathomimetic activity are the only agents that have been shown to decrease, in those with previous myocardial infarction, the rate of sudden death, overall mortality, and recurrent myocardial infarction.[108] β-Blockers with intrinsic sympathomimetic activity and labetalol have little or no adverse effect on lipids, but these agents have not been demonstrated to have a cardioprotective effect after a myocardial infarction.

The α_1-receptor blockers and the central adrenergic agonists may decrease serum cholesterol concentration slightly, especially in the low-density lipoprotein subfraction. Therefore, these agents may offer an advantage in the treatment of hypertensive patients with dyslipidemia. Angiotensin-converting enzyme inhibitors and calcium antagonists have no adverse effects on levels of serum lipids and lipoprotein.

Patients With Chronic Airway Disease or Bronchial Asthma. In hypertensive patients with chronic obstructive pulmonary disease—including chronic bronchitis, emphysema, and/or asthma—β-adrenergic blocking drugs can worsen bronchoconstriction and are therefore relatively contraindicated. Calcium antagonists do not cause bronchial constriction but in rare cases can cause or aggravate hypoxemia by dilating the pulmonary arterial circulation, thereby worsening the mismatch between regional ventilation and regional perfusion. Angiotensin-converting enzyme inhibitors can cause cough, which may be more significant when it complicates chronic obstructive pulmonary disease. With recognition of these limitations, all antihypertensive agents, except β-blockers and alpha β-blockers, can be used in hypertensive patients who have chronic obstructive pulmonary disease.

Methylxanthines (theophylline) and corticosteroids, often used in managing chronic obstructive pulmonary disease, can worsen hypertension; in addition, methylxanthines cause tachycardia and are arrhythmogenic. β-Adrenergic agonists used to treat chronic obstructive pulmonary disease are not as likely as methylxanthines to worsen hypertension, but they do cause tachycardia and can be arrhythmogenic.

Over-the-counter asthma preparations may contain ephedrine as a bronchodilator, and over-the-counter common cold preparations frequently contain phenylpropanolamine or pseudoephedrine as a vasoconstrictor, all of which can increase blood pressure and heart rate.

Patients With Gout. Hyperuricemia is a frequent finding, even in untreated patients with hypertension, and may reflect a decrease in renal blood flow. In addition, all of the commonly used diuretics, including the potassium-sparing class, can increase serum uric acid levels and induce acute gout. Body mass and serum uric acid level are closely correlated; weight loss can produce a fall in serum uric acid level in overweight hypertensive patients even with diuretic treatment. For patients with poorly controlled gout, diuretics should be avoided (or used intermittently). Diuretic-induced hyperuricemia does not require treatment in the absence of gout or urate stones.

Patients Undergoing Surgery

Surgical candidates who are adequately controlling their blood pressure with medication should be maintained on their regimen until the time of surgery, and therapy should be reinstated as soon as possible after surgery. If oral intake must be interrupted, parenteral therapy with diuretics, adrenergic inhibitors, vasodilators, ACE inhibitors, calcium antagonists, or transdermal clonidine may be used to prevent the rebound hypertension that may follow sudden discontinuation of some of the adrenergic-inhibiting agents.

Adequate potassium supplementation should be provided to correct hypokalemia well in advance of surgery. A brief course of intravenous potassium just before surgery may not be sufficient to correct long-standing hypokalemia. In all cases, anesthesiologists must be aware of the patient's medication status. Patients with hypertension whose blood pressure has been controlled with medication usually tolerate anesthesia better than do those whose pressures are poorly controlled.[109]

Miscellaneous Causes of Increased Blood Pressure

Cocaine. Cocaine, like the amphetamines, increases release of norepinephrine and prevents neuronal reuptake of norepinephrine. As a result, it induces acute hypertension, tachycardia, tremor, and seizures[110] and produces coronary artery vasoconstriction. Cocaine use is also associated with ischemic and hemorrhagic cerebrovascular strokes in young adults.[111-113] The onset of symptoms, especially severe headache, often occurs within 1 hour of use of the drug. The treatment of choice is α-adrenergic inhibition (eg, phentolamine). A β-blocker should be used for complicating cardiac dysrhythmias induced by the catecholamine excess.

Lithotripsy. Extracorporeal shock-wave lithotripsy can cause localized vascular injury that may be associated with transient decreases in renal blood flow and glomerular filtration rate in the treated kidney,

transient proteinuria, and slight elevation of DBP. Acute hypertension after extracorporeal shock-wave lithotripsy has been reported but is exceedingly uncommon. The procedure can also cause subcapsular and perirenal hematomas and fluid collection, with the incidence of bleeding higher in patients with hypertension. There is little or no evidence, however, that these complications of extracorporeal shock-wave lithotripsy lead to permanent renal damage or hypertension, but there is some concern that they may lead to capsular and perirenal scarring. There are no data to suggest specifically that existing hypertension is made worse by the procedure.[114]

Cyclosporine. Cyclosporine causes vasoconstriction mediated in part by stimulation of the sympathetic nervous system and imbalance in the production of eicosanoids, such as prostacyclin and thromboxane.[115] Vasoconstriction of the afferent arteriole leads to reduction in renal blood flow and glomerular filtration rate, resulting in increased resorption of sodium, water, and urea.[116] Cyclosporine also has direct nephrotoxic effects manifested histologically by nephrosclerosis and interstitial fibrosis. Acute nephrotoxic effects usually reverse promptly with intravenous fluids and temporary discontinuation or reduction in the dose of cyclosporine.

The vasoconstrictive and salt-retaining properties of cyclosporine lead to hypertension in 50% to 70% of transplant recipients receiving the drug and in 20% of patients receiving the drug for other reasons. Diuretics are an effective therapy, but they exaggerate prerenal azotemia and may precipitate gout. Calcium antagonists and labetalol are effective, as are central α-agonists, such as clonidine. Diltiazem, nicardipine, and verapamil should be used with caution, as they increase cyclosporine blood levels, but they may be given if the interaction is appreciated.

Erythropoietin. Recombinant human erythropoietin increases blood pressure in one third of patients with end-stage renal disease. In most cases this necessitates initiation or increase of antihypertensive therapy. The mechanism of hypertension related to recombinant human erythropoietin remains uncertain. It is not related to the dose of recombinant human erythropoietin, the final hematocrit level achieved, or the rate of increase of hematocrit. It is associated with an increase in systemic vascular resistance due largely to an increase in blood viscosity and reversal of hypoxic vasodilatation. Acute elevation in blood pressure during therapy with recombinant human erythropoietin occasionally results in hypertensive encephalopathy and seizures. Frequent blood pressure monitoring during the first 4 months of treatment is mandatory. If conventional antihypertensive therapy does not control hypertension, the dose of recombinant human erythropoietin should be reduced or therapy should be temporarily discontinued.[117]

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