### Compelling Indications

Hypertension may exist in association with other conditions in which there are compelling indications for use of a particular treatment based on clinical trial data demonstrating benefits of such therapy on the natural history of the associated condition (table 12). Compelling indications for specific therapy involve high-risk conditions that can be direct sequelae of hypertension (HF, IHD, chronic kidney disease, recurrent stroke) or commonly associated with hypertension (diabetes, etc.).

<table>
<thead>
<tr>
<th>Compelling Indication*</th>
<th>Recommended Drugs</th>
<th>Clinical Trial Basis†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretic</td>
<td>BB, ACEI, ARB, CCB, Aldo ANT</td>
<td>ACC/AHA Heart Failure Guideline, MERIT-HF, COPERNICUS, CIBIS, SOLVD, AIRE, TRACE, ValHEFT, RALES, CHARM</td>
</tr>
<tr>
<td>Heart failure</td>
<td>● ● ● ● ●</td>
<td>ACC/AHA Heart Failure Guideline, MERIT-HF, COPERNICUS, CIBIS, SOLVD, AIRE, TRACE, ValHEFT, RALES, CHARM</td>
</tr>
<tr>
<td>Heart failure</td>
<td>● ● ● ●</td>
<td>ACC/AHA Heart Failure Guideline, MERIT-HF, COPERNICUS, CIBIS, SOLVD, AIRE, TRACE, ValHEFT, RALES, CHARM</td>
</tr>
<tr>
<td>Postmyocardial infarction</td>
<td>● ● ●</td>
<td>ACC/AHA Post-MI Guideline, BHAT, SAVE, Capricorn, EPHESUS</td>
</tr>
<tr>
<td>High coronary disease risk</td>
<td>● ● ● ●</td>
<td>ALLHAT, HOPE, ANBP2, LIFE, CONVINCE, EUROPA, INVEST</td>
</tr>
<tr>
<td>Diabetes</td>
<td>● ● ● ● ●</td>
<td>NKF-ADA Guideline, UKPDS, ALLHAT</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>● ● ○</td>
<td>NKF Guideline, Captopril Trial, RENAAL, IDNT, REIN, AASK</td>
</tr>
<tr>
<td>Recurrent stroke prevention</td>
<td>● ● ○</td>
<td>PROGRESS</td>
</tr>
</tbody>
</table>

AASK, African American Study of Kidney Disease and Hypertension; ACC/AHA, American College of Cardiology/American Heart Association; ACEI, angiotensin converting enzyme inhibitor; Aldo ANT, aldosterone antagonist; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ANBP2, Second Australian National Blood Pressure Study; ARB, angiotensin receptor blocker; BB, beta blocker; BHAT, Blocker Heart Attack Trial; Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction; CCB, calcium channel blocker; CHARM, Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity; CIBIS, Cardiac Insufficiency Bisoprolol Study; CONVINCE, Controlled Onset Verapamil Investigation of Cardiovascular End Points; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival Study; EPHESUS, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; EUROPA, European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease; HOPE, Heart Outcomes Prevention Evaluation Study; IDNT, Irbesartan Diabetic Nephropathy Trial; INVEST, The International Verapamil-Trandolapril Study; LIFE, Losartan Intervention for Endpoint Reduction in Hypertension Study; MERIT-HF, Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; NKF-ADA, National Kidney Foundation-American Diabetes Association; PROGRESS, Perindopril Protection against Recurrent Stroke Study; RALES, Randomized Aldactone Evaluation Study; REIN, Ramipril Efficacy in Nephropathy Study; RENAAL, Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan Study; SAVE, Survival and Ventricular Enlargement Study; SOLVD, Studies of Left Ventricular Dysfunction; TRACE, Trandolapril Cardiac Evaluation Study; UKPDS, United Kingdom Prospective Diabetes Study; ValHEFT,Valsartan Heart Failure Trial

* Compelling indications for antihypertensive drugs are based on benefits from outcome studies or existing clinical guidelines; the compelling indication is managed in parallel with the BP.

† Conditions for which clinical trials demonstrate the benefit of specific classes of antihypertensive drugs used as part of an antihypertensive regimen to achieve BP goal to test outcomes.
The absence of a positive indication can signify a lack of information for a particular drug class. For example, in recurrent stroke, there is no study employing CCBs or ARBs. Different stages of the conditions may dictate different strategies. In HF management, thiazide-type diuretics are recommended for reducing the incidence of HF but not in lengthening survival in individuals who already have the condition. Furthermore, widespread use of combination therapy in clinical trials confounds interpretation of the effects of single drugs. In the Perindopril Protection against Recurrent Stroke Study (PROGRESS), recurrent stroke rate was reduced only when a thiazide-type diuretic was added to ACEI background therapy.

**Ischemic Heart Disease**

Hypertensive patients are at increased risk for MI or other major coronary events and may be at higher risk of death following an acute MI. Myocardial oxygen supply in hypertensive individuals may be limited by coronary artery disease (CAD), while myocardial oxygen demand is often greater because of the increased impedance to left ventricular ejection and the frequent presence of left ventricular hypertrophy (LVH). Lowering both SBP and DBP reduces ischemia and prevents CVD events in patients with CAD, in part by reducing myocardial oxygen demand. One caveat with respect to antihypertensive treatment in patients with CAD is the finding in some studies of an apparent increase in coronary risk at low levels of DBP. For example, in the SHEP study, lowering DBP to <55 or 60 mmHg was associated with an increase in cardiovascular events, including MI. No similar increase in coronary events (a J-shaped curve) has been observed with SBP. Patients with occlusive CAD and/or LVH are put at risk of coronary events if DBP is low. Overall, however, many more events are prevented than caused if BP is aggressively treated.

**Stable angina and silent ischemia.** Therapy is directed toward preventing MI and death and reducing symptoms of angina and the occurrence of ischemia. Unless contraindicated, pharmacologic therapy should be initiated with a BB. BBs will lower BP; reduce symptoms of angina; improve mortality; and reduce cardiac output, heart rate, and AV conduction. The reduced inotropy and heart rate decrease myocardial oxygen demand. Treatment should also include smoking cessation, management of diabetes, lipid lowering, antiplatelet agents, exercise training, and weight reduction in obese patients.

If angina and BP are not controlled by BB therapy alone, or if BBs are contraindicated, as in the presence of severe reactive airways disease, severe peripheral arterial disease, high-degree AV block, or the sick sinus syndrome, either long-acting dihydropyridine or nondihydropyridine type CCBs may be used. CCBs decrease total peripheral resistance, which leads to reduction in BP and in wall tension. CCBs also decrease coronary resistance and enhance post-stenotic coronary perfusion. Nondihydropyridine CCBs also can decrease heart rate; when in combination with a BB however, they may cause severe bradycardia or high degrees of heart block. Therefore, long-acting dihydropyridine CCBs are preferred for combination therapy with BBs. If angina or BP is still not controlled on this two-drug regimen, nitrates can be added, but these should be used with caution in patients taking phosphodiesterase-5 inhibitors such as sildenafil. Short-acting dihydropyridine CCBs should not be used because of their potential to increase mortality, particularly in the setting of acute MI.

**Heart Failure**

The HF syndrome occurs when the heart is incapable of maintaining sufficient flow to accommodate tissue perfusion and metabolic requirements. Forty to fifty percent of patients with symptoms of HF may have preserved systolic function. These patients are more likely to have hypertension, LVH, and isolated diastolic dysfunction, and are more likely to be women. A variety of neurohormonal systems, especially the renin-angiotensin-aldosterone and sympathetic nervous systems may be activated in response to the left ventricular dysfunction, but such activation may lead to abnormal ventricular
remodeling, further left ventricular enlargement, and reduced cardiac contractility. The inexorable progression to more severe stages of left ventricular dysfunction can be significantly reduced by effective therapy with ACEIs, BBs, and diuretics.

Hypertension precedes the development of HF in approximately 90 percent of patients and increases risk for HF by two- to threefold. Hypertension is especially important in HF affecting African American and elderly persons. CAD is the cause of HF in approximately two-thirds of HF patients in the United States. The true incidence of HF has been unchanged in men and has declined among women over the past 50 years. However, HF hospitalization rates have more than doubled in the past 20 years because of the improved therapy resulting in increased life expectancy. HF will probably become even more prevalent in the future as our population ages.

Optimal therapy for HF may require the use of specialized HF disease-management programs and utilization of a variety of health professionals to reinforce treatment recommendations. American College of Cardiology/American Heart Association guidelines are available to manage HF. In the stage A group (New York Heart Association [NYHA] class I), for those at high risk for HF but with no demonstrable clinical symptoms or left ventricular dysfunction, treatment should include fastidious risk-factor management to control BP, hypercholesterolemia, and hyperglycemia. ACEIs may be appropriate due to their beneficial effects on mortality in patients at high risk for CVD. The ALLHAT study also has suggested that thiazide-diuretic therapy is useful in preventing disease progression. In stage B HF (NYHA class I), defined by the presence of reduced left ventricular function (ejection fraction [EF] ≤40 percent) in otherwise asymptomatic individuals, ACEIs and BBs are recommended. Stage C HF patients (NYHA class II–III) manifest left ventricular dysfunction and overt symptoms; in these individuals, ACEIs and BBs are again indicated. Aldosterone antagonists also may be of value in this situation.

BP targets in HF have not been firmly established, but lowering SBP is almost uniformly beneficial. In most successful trials, systolic blood pressures were lowered to the range of 110–130 mmHg. One trial demonstrated benefits of beta blockade in patients with SBP >85 mmHg, suggesting that very low BPs (e.g., SBP <100 mmHg) may be desirable in some HF patients.

Digoxin continues to be used in HF despite inconsistent clinical results. In the DIG trial, it did not reduce mortality in NYHA class II–III patients taking ACEIs and diuretics, but did reduce HF symptoms and hospitalizations.
Diabetes and Hypertension

The combined unadjusted prevalence of total diabetes and impaired fasting glucose in those over age 20 is 14.4 percent and is the leading cause of blindness, ESRD, and nontraumatic amputations. Type 2 diabetes comprises >90 percent of diabetes in the United States and is associated with a 70–80 percent chance of premature death from CVD and stroke. The concordance of hypertension and diabetes is increased in the population; hypertension is disproportionately higher in diabetics, while persons with elevated BP are two and a half times more likely to develop diabetes within 5 years. The common absence of normal nocturnal “dipping” of BP in diabetics is linked to other CVD surrogates such as LVH and microalbuminurias.

The coexistence of hypertension in diabetes is particularly pernicious because of the strong linkage of the two conditions with all CVD, stroke, progression of renal disease, and diabetic retinopathy. The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that each 10 mmHg decrease in SBP was associated with average reductions in rates of diabetes-related mortality (15 percent), myocardial infarction (11 percent), and the microvascular complications of retinopathy or nephropathy (13 percent). Randomized controlled trials that have included large diabetic populations including UKPDS, Hypertension Optimal Treatment (HOT) Trial, SHEP, the Syst-EUR, HOPE Study, LIFE, and ALLHAT, have demonstrated that adequate BP control improves CVD outcomes, especially stroke, when aggressive BP targets are achieved.

Thiazide-type diuretics are beneficial in diabetics, either alone or as part of a combined regimen. In the prespecified diabetic subgroup of ALLHAT, therapy that began with chlorthalidone reduced the primary endpoint of fatal CHD and MI to the same degree as therapy based on lisinopril or amlodipine. Of potential concern is the tendency for thiazide-type diuretics to worsen hyperglycemia, but this effect tended to be small and did not produce more cardiovascular events compared to the other drug classes.

Therapy with an ACEI also is an important component of most regimens to control BP in diabetic patients. ACEIs may be used alone for BP lowering but are much more effective when combined with a thiazide-type diuretic or other antihypertensive drugs. The ADA has recommended ACEIs for diabetic patients older than 55 years of age at high risk for CVD, and BBs for those with known CAD. In the Micro-Hope subanalysis of the HOPE Study, which included both hypertensive and normotensive individuals, high-risk diabetic patients treated with
ACEI added on to conventional therapy showed a reduction in combined MI, stroke, and CVD death of about 25 percent and a reduction in stroke by about 33 percent compared to placebo plus conventional therapy. With respect to microvascular complications, the ADA has recommended both ACEIs and ARBs for use in type 2 diabetic patients with CKD because these agents delay the deterioration in GFR and the worsening of albuminuria.88,164,171,181

BBs, especially beta1-selective agents, are beneficial to diabetics as part of multidrug therapy, but their value as monotherapy is less clear. A BB is indicated in a diabetic with IHD but may be less effective in preventing stroke than an ARB as was found in the LIFE study.187 Although BBs can cause adverse effects on glucose homeostasis in diabetics, including worsening of insulin sensitivity and potential masking of the epinephrine-mediated symptoms of hypoglycemia, these problems are usually easily managed and are not absolute contraindications for BB use.

CCBs may be useful to diabetics, particularly as part of combination therapy to control BP. They were shown to reduce CVD events in diabetics compared to placebo in several clinical outcome trials.87,101,113,118 In the diabetic cohort of ALLHAT, amlodipine was as effective as chlorthalidone in all categories except HF, where it was significantly inferior.109 The Appropriate Blood Pressure Control in Diabetes (ABCD) Trial in diabetics was stopped prematurely when it was found that the dihydropyridine nitrendipine was inferior to lisinopril in reducing the incidence of ischemic cardiac events.188 However, in normotensive diabetics in the ABCD2 Trial, nitrendipine was equivalent to lisinopril in stroke prevention and in retardation of the development of albuminuria.189

**Chronic Kidney Disease**

**Age and kidney function.** Renal excretory function, as represented by GFR, deteriorates with age beginning in the third or fourth decade of life. By the sixth decade, GFR commonly declines by 1–2 mL/min per year. This age-related loss of renal function is proportional to BP level, and the rate of GFR deterioration can accelerate to 4–8 mL/min per year if SBP remains uncontrolled.165 Such rates of deterioration may lead to the development of ESRD and the need for dialysis or transplantation, especially in those with other coexistent renal diseases.

CKD is defined as either: (1) reduced excretory function with an eGFR <60 mL/min/1.73 m² (approximately corresponding to a creatinine of >1.5 mg/dL in men or >1.3 mg/dL in women); or (2) the presence of albuminuria (>300 mg/d or 200 mg/g creatinine). In a number of laboratories, serum creatinine is being replaced as an index of renal function by eGFR, the values of which are derived from newer algorithms that include adjustments for gender, race, and age. These algorithms are available on Web sites.66 The measurements appear to be of greater value than 24-hour urine collections for creatinine clearance.

Urinary albumin excretion has diagnostic and prognostic value equivalent to reduced eGFR. To avoid inaccuracies associated with 24-hour urine collections, spot urine samples may be used and the albumin/creatinine ratio (ACR) determined. Microalbuminuria is present when the spot urine ACR is between 30–200 mg albumin/g creatinine. ACR values >200 mg albumin/g creatinine signify the presence of CKD.

**CVD risk in CKD.** CVD is the most common cause of death in individuals with CKD, and CKD is an independent risk factor for CVD. Individuals with eGFR <60 mL/min have an approximate 16 percent increase in CVD mortality, and individuals with eGFR <30 mL/min have a 30 percent increase.190 CVD risk also exhibits a continuous relationship with albuminuria; the presence of microalbuminuria confers a 50 percent increase in risk and the presence of macroalbuminuria, a 350 percent increase.191

**Therapy.** NHANES III data indicated that about 3 percent of adults (5.6 million people) in the United States had elevated serum creatinine values, and 70 percent of these people had hypertension.192 While 75 percent of individuals received treatment, only 11 percent with hypertension and elevated serum creatinine had BPs <130/85 mmHg,
In the prevention of CKD, the value of vigorous antihypertensive therapy is most pronounced in those individuals with the greatest degrees of albuminuria. In the Modification of Diet and Renal Disease (MDRD) Study, individuals with proteinuria had slower rates of progression to ESRD if their SBP values were <130 mmHg. A meta-analysis of individuals with CKD and albuminuria found that positive predictors of outcome were lower SBP levels (110–129 mmHg), lower albumin excretion ratio (AER) (<1.0 g/day), and the presence of ACEI therapy. However, in the African American Study of Kidney Disease and Hypertension (AASK) study of African Americans with hypertensive CKD, those achieving a mean BP of 128/78 mmHg experienced renal deterioration at the same rate as those achieving a mean of 141/85 mmHg. Many studies demonstrate that antihypertensive regimens that include an ACEI or ARB are more effective in slowing progression of CKD than other antihypertensive regimens.

The joint recommendations of the American Society of Nephrology and the National Kidney Foundation provide useful guidelines for management of hypertensive patients with CKD. They recommend a goal BP for all CKD patients of <130/80 mmHg and the need for more than one antihypertensive drug to achieve this goal. The guidelines indicate that most patients with CKD should receive an ACEI or an ARB in combination with a diuretic, and many will require a loop diuretic rather than a thiazide. In addition, if there is a conflict between the goals of slowing progression of CKD and CVD risk reduction, individual decision making is recommended based on risk stratification.

Patients With Cerebrovascular Disease

The risk of clinical complications of cerebrovascular disease including ischemic stroke, hemorrhagic stroke, and dementia increases as a function of BP levels. Given the population distribution of BP, most ischemic strokes occur in individuals with prehypertension or stage 1 hypertension. The incidence of ischemic or hemorrhagic stroke is reduced substantially by treatment of hypertension. No specific agent has been proven to be clearly superior to all others for stroke protection. In the LIFE study, there were fewer strokes in the losartan-treated group than in the group treated with atenolol. In the ALLHAT study, the stroke incidence was 15 percent greater with ACEI than with thiazide-type diuretic or dihydropyridine CCB, but the BP reduction in the lisinopril group was also less than with chlorthalidone or amlodipine.

With respect to the prevention of recurrent stroke, PROGRESS demonstrated that addition of the diuretic, indapamide, to the ACEI, perindopril, caused a 43 percent reduction in stroke occurrence. The reduced incidence of stroke appeared related to the BP reduction obtained by the combination therapy even though many patients on entry into the study were not hypertensive. No significant reduction was present in those on perindopril alone whose BP was only 5/3 mmHg lower than in the control group.

The management of BP during an acute stroke remains controversial. BP is often elevated in the immediate poststroke period and is thought by some to be a compensatory physiologic response to improve cerebral perfusion to ischemic brain tissue. As a result, it has been common practice after acute cerebral infarction to reduce or withhold BP treatment until the clinical condition has stabilized. There still are no large clinical studies upon which to base definitive recommendations. Nevertheless, the American Stroke Association has provided the following guidelines: in patients with recent ischemic stroke whose SBP is >220 mmHg or DBP 120–140 mmHg, cautious reduction of BP by about 10–15 percent is suggested, while carefully monitoring the patient for neurologic deterioration related to the lower pressure. If the DBP is >140 mmHg, carefully monitored infusion of sodium nitroprusside should be used to reduce the BP by 10–15 percent. BP control affects the use of thrombolytic agents in ischemic stroke. SBP >185 mmHg or diastolic pressures >110 mmHg are contraindications to the use of tissue plasminogen activator (tPA) within the first 3 hours of an ischemic stroke. Once a thrombolytic agent has been initiated, BP should be monitored closely, especially in the first 24
hours after initiation of treatment. SBP ≥180 mmHg or DBP ≥105 mmHg usually necessitates therapy with intravenous agents to prevent intracerebral bleeding.199

Other Special Situations

Minorities

The prevalence, impact, and control of hypertension differ across racial and ethnic subgroups of the U.S. population. In African Americans, hypertension is more common, more severe, develops at an earlier age, and leads to more clinical sequelae than in age-matched non-Hispanic Whites.200 Mexican Americans and Native Americans have lower control rates than non-Hispanic Whites and African Americans.201,202 The pathogenesis of hypertension in different racial subgroups may differ with respect to the contributions of such factors as salt, potassium, stress, cardiovascular reactivity, body weight, nephron number, sodium handling, or hormonal systems, but in all subgroups, the etiology is multifactorial.200,203 African Americans have a greater prevalence of other cardiovascular risk factors, especially obesity.200,203 Much of the variance in hypertension-related sequelae across racial or ethnic groups may be attributable to differences in socioeconomic conditions; access to healthcare services; or attitudes, beliefs, and deficits in accurate health-related information.200,203 For example, when medications and provider services were provided free of charge, as in the Hypertension Detection and Follow-up Program, African American men treated with the intensive “Stepped-Care Approach” actually benefited more than Whites.204

Weight reduction and sodium reduction are recommended for all prehypertensive and hypertensive patients but may be particularly effective in minorities. The salt content of some minorities’ traditional diets may be very high.205 The low-sodium DASH eating plan was associated with greater reductions in BP in African Americans than in other demographic subgroups.94 In clinical trials, lowering BP prevents sequelae of hypertension in all racial or ethnic groups.200,203 Nonetheless, monotherapy with BBs, ACEIs, or ARBs lowers BP to a somewhat lesser degree in African Americans than Whites.109,206–208 In the ALLHAT trial with more than 15,000 Blacks, ACEI was less effective in lowering blood pressure than either the thiazide-type diuretic or the CCB. This was associated with a 40 percent greater risk of stroke, 32 percent greater risk of HF, and 19 percent greater risk of CVD in those randomized to the ACEI versus the diuretic.109 The interracial differences in BP lowering observed with these drugs are abolished when they are combined with a diuretic.109,203,208 Racial differences in the incidence of antihypertensive drug side effects may occur; African Americans and Asians have a three- to fourfold higher risk of angioedema109,209,210 and have more cough attributed to ACEIs than Caucasians.211

Several other benefits of treatment have been demonstrated in minority populations. A 28 percent reduction in mortality was observed in African Americans who received BB therapy after acute MI compared to those not receiving a BB.212 A greater degree of preservation of renal function occurred in African Americans with hypertensive nephrosclerosis treated with a regimen containing an ACEI compared to a BB or a calcium antagonist.196 No large outcome studies have been carried out with ARBs in African American and other minority patients. Unfortunately, sufficient numbers of Mexican Americans, other Hispanic Americans, Native Americans, or Asian/Pacific Islanders have not been included in most of the major clinical trials to allow reaching strong conclusions about their responses to individual antihypertensive therapies.

Irrespective of whether race or ethnicity should be a significant consideration in the choice of individual antihypertensive drugs, in minority groups the use of combination or multiple antihypertensive drug therapy that usually includes a thiazide-type diuretic will lower BP and reduce the burden of hypertension-related CVD and renal disease.

Metabolic Syndrome

Definition and associations. The term “metabolic syndrome” describes a constellation of cardiovascular risk factors related to hypertension,
abdominal obesity, dyslipidemia, and insulin resistance. The definition adopted by the National Cholesterol Education Program (Adult Treatment Panel [ATP] III) guidelines in 2001\textsuperscript{21} is the presence of three or more of the five risk factors (table 13). The World Health Organization has a somewhat different definition of the metabolic syndrome, but for consistency, JNC 7 has adopted the ATP III definition.

Several other associated features have been reported, including hyperinsulinemia, insulin resistance, and higher density of LDL-cholesterol particles.\textsuperscript{213} The metabolic syndrome has also been associated with high levels of inflammatory risk markers,\textsuperscript{214} reduced fibrinolysis (including elevated plasminogen activator inhibitor-1),\textsuperscript{215} heightened magnitude of oxidative stress,\textsuperscript{216,217} microalbuminuria,\textsuperscript{218} abnormalities in autonomic regulation,\textsuperscript{219} and activation of the renin-angiotensin-aldosterone axis.\textsuperscript{220}

Prevalence

When the ATP III criteria were applied to the data from the NHANES III survey (1988–1994), the prevalence of the metabolic syndrome in adults in the United States was estimated at 23.7 percent or about 47 million individuals.\textsuperscript{221} BMI, kg/m\textsuperscript{2} is related to the metabolic syndrome in both men and women (table 14).\textsuperscript{222} In addition, because abdominal obesity is also correlated with the metabolic syndrome, ATP III uses it rather than BMI. This becomes important in overweight individuals with a BMI of 25–29.9 kg/m\textsuperscript{2} and large waist circumference (>40 inches in men, >35 inches in women) who may have metabolic syndrome despite not being obese.

The metabolic syndrome will likely increase further in the next several years, primarily because of the rapid increase in obesity. The health problems related to the metabolic syndrome will likely escalate dramatically.

### Table 13. Clinical criteria defining the metabolic syndrome in Adult Treatment Panel III

- Waist circumference:
  - >102 cm (>40 inches) for men
  - >88 cm (>35 inches) for women
- Blood pressure:
  - ≥130 mmHg systolic and/or
  - ≥85 mmHg diastolic
- Fasting glucose:
  - ≥110 mg/dL or 6.1 mmol/L
- Triglycerides:
  - ≥150 mg/dL or 1.69 mmol/L
- HDL-cholesterol:
  - <40 mg/dL (1.04 mmol/L) in men
  - <50 mg/dL (1.29 mmol/L) in women

HDL, high-density lipoprotein


### Table 14. Estimated prevalence of the metabolic syndrome using the Adult Treatment Panel III definition among normal weight, overweight, and obese men and women in the National Health and Nutrition Examination Survey III

<table>
<thead>
<tr>
<th>Category</th>
<th>BMI, kg/m\textsuperscript{2}</th>
<th>Metabolic Syndrome Prevalence, Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Men</td>
</tr>
<tr>
<td>Normal weight</td>
<td>&lt;25.0</td>
<td>4.6%</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0–29.9</td>
<td>22.4%</td>
</tr>
<tr>
<td>Obese</td>
<td>&gt;30</td>
<td>59.6%</td>
</tr>
</tbody>
</table>

BMI, body mass index

**Age Trends**

The prevalence of the metabolic syndrome is highly age dependent. A prevalence of 7 percent among adults 20–29 years of age rises to 40 percent or more among Americans over age 60.

**Clinical Impact**

The metabolic syndrome is associated in men with a fourfold increase in risk for fatal CHD, and a twofold greater risk of CVD and all-cause mortality, even after adjustment for age, LDL-cholesterol, smoking, and family history of CHD. The metabolic syndrome is associated with increased CHD risk in women. Patients with the metabolic syndrome have a five- to ninefold increased risk of developing diabetes.

**Clinical Management of the Metabolic Syndrome**

The cornerstone for clinical management in adults is appropriate lifestyle changes.

**Overweight and obesity.** Treatment of overweight and obesity is summarized in the next section, using key principles in the Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults.

**Physical activity.** The metabolic syndrome can improve with increased physical activity (See Prevention and Lifestyle Modification for Overweight and Obesity.)

**Prehypertension and hypertension.** The vast majority of individuals with the metabolic syndrome will fall into the categories of prehypertension or stage 1 hypertension. Lifestyle modification is the cornerstone of management in all patients with prehypertension or with the metabolic syndrome, but if BP exceeds 140/90 mmHg, pharmacological therapy is indicated as described in the hypertension treatment algorithm (figure 16).

**Lipids.** Elevated triglycerides and reduced HDL are typical lipid abnormalities in metabolic syndrome. Elevated LDL is not a prime feature of metabolic syndrome but is important in clinical management.

**Impaired glucose tolerance and diabetes.** Modest lifestyle change including healthful nutrition and increased physical activity can reduce the development of diabetes by nearly 60 percent in high-risk individuals. Management guidelines published by the ADA are appropriate for individuals with impaired fasting glucose and diabetes.

**Lipids**

All patients with lipid abnormalities for LDL, HDL, or triglycerides should be treated according to the ATP III recommendations.

**Overweight and Obesity**

**Prevalence and epidemiology.** Using the NHANES databases for the periods 1988–1994 vs. 1999–2000, the age-adjusted prevalence of obesity (BMI ≥30 kg/m²) among U.S. adults increased from 22.9 percent to 30.5 percent, while the prevalence of overweight (BMI ≥25 kg/m²) increased from 55.9 percent to 64.5 percent. Obese subjects, especially men, with no other risk factors, have increased relative risk for CVD.

Obesity occurs more often among Hispanics, Native Americans, and African Americans than Caucasians in the United States. These demographic differences extend to children, where obesity and related health problems are increasing at nearly double the rate in ethnic minorities compared to Caucasians. The rapid increase in the population of ethnic minorities in the United States is another factor that will lead to a rise in the prevalence of obesity and its complications unless effective, culturally diverse, population-based health promotion strategies are encouraged.
Prevention and lifestyle modifications for overweight and obesity. The major goal of management of both the metabolic syndrome and overweight and obesity is to reduce the age-related rate of weight gain. This challenging task will require a complex combination of healthy behaviors, including decrease in sedentary activities, increase in physical activity, and reduction in calorie intake (table 16). Simple yet practical suggestions include reducing time spent watching television or being online, and increasing time spent walking or in activities that raise the heart rate. The emphasis for weight management should be on avoidance of excess total energy intake and a regular pattern of physical activity. Reducing food portion sizes and limiting fat intake can assist in reducing overall calorie intake. High-sodium diets may be especially deleterious in obese subjects.\(^2\)

Specific nutrient intakes for individuals should be based on lipoprotein levels, BP, and the presence of coexisting heart disease, diabetes, and other risk factors. For example, adoption of the well-studied low sodium DASH eating plan\(^9\) provides heart healthy foods that can be used to promote weight loss, reduce BP in both hypertensive and prehypertensive individuals, and reduce LDL. The benefits of modest lifestyle changes on cardiovascular risk factors are well documented. In the Framingham Heart Study, weight loss of 5 lbs or greater was associated with reductions in cardiovascular risk of about 40 percent.\(^2\) A 10 percent reduction in body weight can reduce disease risk factors.\(^2\)

Physical activity is a key feature of treatment. Increased physical activity, when combined with a reduction in calories, is essential to weight loss success. Based on the available evidence, the recommendation is to engage in regular physical activity at least 30 minutes per day, most days of the week (see table 9). In addition, physical activity is critical to the maintenance of weight loss and is important for overall reduction in cardiovascular risk; 60–90 minutes per week of walking can reduce CHD mortality by about 50 percent.\(^2\) The CVD benefits of slow walking appear to be comparable to those of walking more quickly, suggesting that the most important predictor of benefit was walking time, not speed. Exercise programs appear beneficial at any age and are associated with overall reductions in CVD outcomes by about 50 percent.\(^2\) Although aerobic fitness may negate much of the cardiovascular risk associated with obesity,\(^2\) studies report that individuals who are obese have much lower levels of physical activity and poorer aerobic fitness than leaner individuals.\(^2\)

### Table 9. Relative 10-year risk for diabetes, hypertension, heart disease, and stroke over the next decade among men initially free of disease stratified by baseline body mass index

<table>
<thead>
<tr>
<th>BMI</th>
<th>Diabetes</th>
<th>Hypertension</th>
<th>Heart Disease</th>
<th>CVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.5–21.9</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>22.0–24.9</td>
<td>1.8</td>
<td>1.5</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>25.0–29.9</td>
<td>5.6</td>
<td>2.4</td>
<td>1.7</td>
<td>1.3</td>
</tr>
<tr>
<td>30.0–34.9</td>
<td>18.2</td>
<td>3.8</td>
<td>2.2</td>
<td>2.1</td>
</tr>
<tr>
<td>&gt;35.0</td>
<td>41.2</td>
<td>4.2</td>
<td>2.4</td>
<td>2.5</td>
</tr>
</tbody>
</table>

BMI, body mass index; CVA, cerebrovascular accident


### Table 16. Lifestyle changes beneficial in reducing weight*

- Decrease time in sedentary behaviors such as watching television, playing video games, or spending time online.
- Increase physical activity such as walking, biking, aerobic dancing, tennis, soccer, basketball, etc.
- Decrease portion sizes for meals and snacks.
- Reduce portion sizes or frequency of consumption of calorie-containing beverages.

Left Ventricular Hypertrophy

The common feature of all forms of LVH is increased left ventricular mass, although there are many different presentations and subtypes, each with a different prognosis and therapy. LVH subclasses can be characterized generally by the relative wall thickness, the presence or absence of reduced contractility, and the end-diastolic chamber size. LVH can occur in endurance athletes with normal or supranormal systolic function, large end-diastolic volumes, and elongation of myofibrils (eccentric hypertrophy). LVH due to hypertension is usually characterized by “concentric” hypertrophy with circumferential hypertrophy of myofibrils, normal or increased contractility, increased relative wall thickness, normal or low end-diastolic volumes, and at times, impaired relaxation (“diastolic dysfunction”). In population-based samples, 30–50 percent of individuals with stages 1 and 2 hypertension have impaired left ventricular relaxation, and in more severe forms of hypertension, about two-thirds have abnormal left ventricular relaxation. In untreated or poorly treated individuals, LVH becomes a major risk factor for dilated cardiomyopathy and HF.

Detection and risk. Echocardiography is much more sensitive than electrocardiography (ECG) for detection of LVH although ECG-LVH is a highly specific indicator for the condition. Individuals with LVH, are more than twice as likely to suffer premature cardiovascular events or death. Current ECG algorithms defining LVH produce a high false-positive rate in African Americans and overestimate the prevalence of LVH in this population. The attributable risk of LVH for all-cause mortality is greater than that of single or multivessel coronary artery disease or low EF.

Therapy. Several studies suggest that LVH regression is associated with a lower overall CVD risk. Weight loss, salt restriction, and BP lowering with most antihypertensive agents produce LVH regression. Selection of individual drugs appears to be less important, but certain trends have emerged. Fifty studies of LVH regression conducted before 1996 were subjected to meta-analysis. In these studies, predictors of left ventricular mass reduction during treatment were higher pretreatment left ventricular mass, greater fall in SBP or DBP, and longer duration of treatment. The most consistent reduction in left ventricular mass was achieved with ACEIs, the least reduction occurred with BBs, and intermediate benefits occurred for diuretics and calcium antagonists. However, in both the Treatment of Mild Hypertension study and the VA Cooperative Monotherapy trial, diuretic therapy achieved the greatest benefit in left ventricular mass reduction. The LIFE study found that LVH, defined by ECG, was reduced significantly more by a losartan-based regimen despite equivalent BP lowering.

Peripheral Arterial Disease

Major risk factors for peripheral arterial disease (PAD) are hypertension, diabetes, and smoking. Symptomatic PAD is associated with a greatly increased risk of death from CVD, in part because diffuse atherosclerosis, CAD, and renovascular disease frequently coexist in these patients. Therefore, more intensive screening for these related cardiovascular disorders is appropriate in persons with PAD. Renovascular hypertension should be strongly considered in this population if BP is uncontrolled and if ACEI or ARB treatment is being considered.

Antihypertensive drug treatment is ineffective in relieving the symptoms of PAD, and vasodilator agents such as ACEIs, CCBs, alpha-adrenergic blockers, and direct vasodilators do not improve walking distance or symptoms of claudication. This lack of efficacy may be due to: (1) inability of maximally dilated diseased vessels to dilate further during exercise; (2) redistribution of flow caused by the creation of a “steal” phenomenon where blood flow increases in nondiseased vascular beds at the expense of diseased beds; or (3) alteration of pressure-flow relationships distal to the occluded areas by BP reduction. BBs may cause peripheral vasoconstriction and have the potential to increase the frequency of intermittent claudication in individuals with PAD. However, recent studies have shown that BBs have little effect on walking distance or calf blood flow in patients with intermittent claudication.
BBs can be used in PAD patients, especially if needed for treatment of CAD or HF.

No selective outcome benefit has been demonstrated for any individual class of antihypertensive medication in patients with PAD. Therefore, antihypertensive drug choices should be made on the basis of the presence or absence of compelling indications. If Raynaud’s phenomenon is present, CCBs can be used. LDL lowering will reduce the risk for CVD events in people with PAD.

**Therapy.** Treating hypertension in PAD patients reduces the risk of MI, stroke, heart failure, and death. A structured walking program has been shown to increase the pain-free and maximum walking distance in patients with intermittent claudication. Smoking cessation may be the single most important factor whether PAD progresses. Patients should be encouraged and assisted to stop smoking. Lipid abnormalities should be controlled using lifestyle modification or drugs as appropriate. Coexisting glucose intolerance or insulin resistance calls for increased exercise and weight reduction, and aggressive management of diabetes is indicated. Table 17 outlines medical therapies of PAD.

**Figure 17.** Frequency distribution of untreated hypertensive individuals by age and hypertension subtype

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Frequency of Hypertension Subtypes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>17%</td>
</tr>
<tr>
<td>40–49</td>
<td>16%</td>
</tr>
<tr>
<td>50–59</td>
<td>16%</td>
</tr>
<tr>
<td>60–69</td>
<td>20%</td>
</tr>
<tr>
<td>70–79</td>
<td>20%</td>
</tr>
<tr>
<td>80+</td>
<td>11%</td>
</tr>
</tbody>
</table>

Frequency distribution of untreated hypertensive individuals by age and hypertension subtype. Numbers at the tops of bars represent the overall percentage distribution of untreated hypertension in that age group. ISH (SBP >140 mmHg and DBP <90 mmHg); SDH (SBP ≥140 mmHg and DBP ≥90 mmHg); IDH (SBP <140 mmHg and DBP ≥90 mmHg).


---

Table 17. Medical therapies of peripheral arterial disease

- Stop smoking.
- Achieve ideal body weight.
- Engage in structured exercise program.
- Achieve goal blood pressure.
- Control lipids (goal: low-density lipoprotein <100 mg/dL).
- Prevent or control diabetes.
- Administer antiplatelet therapy (aspirin, clopidogrel, or both).
- Consider use of Cilostazol for symptoms of claudication if exercise alone is ineffective.

**Hypertension in Older People**

The number of Americans 65 years of age or older has increased from 24.2 million to 32.6 million from 1980 to 2000 and is expected to continue to rise. SBP increases almost linearly with age in industrialized societies (figure 12) as does the overall prevalence of hypertension and the proportion of hypertensives with isolated SBP elevation (ISH) (figure 17). In contrast, DBP increases in parallel with SBP until about age 55, after which it declines as a manifestation of age-related increases in central arterial stiffness. By age 60, about two-thirds of those with hypertension have ISH; by age 75, almost all hypertensive
individuals have systolic hypertension and about three-fourths have ISH.

Individuals over age 60 represent the most rapidly growing segment of the U.S. population, and even in those who remain normotensive between 55 and 65 years of age, there remains a lifetime risk of developing hypertension that exceeds 90 percent. At the same time, there is a three- to fourfold increase in CVD risk in older compared to younger individuals. These facts prompted the NHBPEP to issue a clinical advisory statement in May 2000 stating that SBP should be the primary target for the diagnosis and management of older people with hypertension. Currently, BP control rates (systolic <140 mmHg and diastolic <90 mmHg) are only about 20 percent in older hypertensive individuals, largely due to poor control of SBP.

**Treatment benefits.** In the SHEP study involving hypertensive individuals over age 60 with pretreatment SBP >160 and DBP <90 mmHg, individuals treated with chlorthalidone (with or without BB) had reductions in the primary endpoint of stroke (36 percent), as well as HF events (54 percent), MI (27 percent), and overall CVD (32 percent) as compared with the placebo group. Using a similar design and sample size, the Syst-EUR study compared a regimen based on nitrendipine to placebo and found a significant reduction in stroke (41 percent) as well as overall CVD events (31 percent). A meta-analysis of eight placebo-controlled trials in 15,693 elderly patients followed for 4 years found that active antihypertensive treatment reduced coronary events (23 percent), strokes (30 percent), cardiovascular deaths (18 percent), and total deaths (13 percent), with the benefit particularly great in those older than 70 years. Benefits of therapy have been demonstrated even in individuals over 80 years of age. Analyses of treatment trials in the elderly by the Hypertension Trialists group have suggested that the choice of initial agent is less important than the degree of BP reduction achieved.

Accurate and representative BP measurement can pose special problems in some older individuals (see Accurate Blood Pressure Measurement in the Office). BP is more variable in older patients, often due to stiff large arteries and age-related decreases in baroreflex buffering. Exaggerated BP drops may occur in the elderly during postural change (see next section), after meals, and after exercise. Pseudohypertension, where cuff BP overestimates the actual intra-arterial pressure due to relative inability of the BP cuff to compress a thickened, stiff, or calcified brachial artery is an uncommon condition in older persons. But this condition should be strongly considered if usual treatment does not reduce BP, especially in those patients who complain of symptoms consistent with postural hypotension. A relatively small percentage of elderly patients have a reversible form of hypertension, most commonly due to renovascular disease, which is seen most often in smokers.

SBP provides more appropriate classification and risk stratification than DBP in the elderly. In the Framingham Heart Study, SBP alone correctly classified the BP stage in 94 percent of adults over the age of 60, while DBP alone correctly classified 66 percent. Pulse pressure (PP) (SBP–DBP) is only marginally stronger than SBP for risk stratification in individuals over age 60, but under age 60, PP is not useful as a CVD risk predictor. PP generally decreases as a result of SBP lowering, but no prospective clinical trial has used PP as the primary clinical endpoint. Thus, on balance, SBP is superior to PP and DBP as a way to stratify patients and as a target for treatment in older persons.

Although no randomized prospective clinical trial has conclusively proven the benefits of treatment in individuals with stage 1 systolic hypertension (140–159 mmHg), hypertension therapy should not be withheld in these patients, and therapy should not be withheld on the basis of age. There is no definitive evidence of an increase in risk of aggressive treatment (a J-curve) unless DBP is lowered to <55 or 60 mmHg by treatment.

**Treatment.** Weight loss and reduced sodium intake are particularly beneficial in older people. In the Trial of Nonpharmacologic Interventions in the Elderly (TONE), reducing sodium to 80 mmol (2 grams) per day reduced BP over 30 months, and about 40 percent of those on the low-salt diet...
were able to discontinue their antihypertensive medications. When weight loss was combined with salt reduction, an additional BP decrease was seen. Older persons should also be encouraged to avoid excessive alcohol intake and to remain as physically active as is feasible.

Use of specific drug classes in older people is largely similar to that recommended in the general algorithm and for individual compelling indications. Combination therapy with two or more drugs is generally needed to achieve optimal BP control. In routine practice, if the systolic goal is achieved, the diastolic goal will almost always be reached as well.

A significant number of elderly individuals have widely variable BP with exaggerated high and low extremes. Such individuals deserve consideration for a slow titration approach as do individuals with a history of medication side effects and those with orthostatic hypotension (OH). Unfortunately, the misperception that many elderly have “brittle hypertension” has contributed to widespread inadequacy of drug titration and to poor BP control.

**Orthostatic Hypotension**

BP measurements are typically recorded in the sitting position. This practice, while convenient for the practitioner, limits the ability to diagnose OH. Normally, standing is accompanied by a small increase in DBP and a small decrease in SBP when compared to supine values. OH is present when there is a supine-to-standing BP decrease >20 mmHg systolic or >10 mmHg diastolic. There is more OH in diabetic individuals. OH occurred in about 7 percent of men over 70 years of age in the Honolulu Heart Study, was highly age-dependent, and carried with it a 64 percent increase in age-adjusted mortality compared with a control population. There is a strong correlation between the severity of OH and premature death as well as increased incidents of falls and fractures. The causes of OH include severe volume depletion, baroreflex dysfunction, autonomic insufficiency, and certain venodilator antihypertensive drugs, especially alpha blockers and alpha-beta blockers. Diuretics and nitrates may further aggravate OH.

In treating older hypertensive patients, clinicians should be alert to potential OH symptoms such as postural unsteadiness, dizziness, or even fainting. Lying and standing BPs should be obtained periodically in all hypertensive individuals over age 50. OH is a common barrier to intensive BP control that should be clearly documented; if present, drug therapy should be adjusted accordingly and appropriate warnings given to patients.

**Resistant Hypertension**

Resistant hypertension is defined as the failure to achieve goal BP in patients who are adhering to full doses of an appropriate three-drug regimen that includes a diuretic. Several causes of resistant hypertension may be present.

Improper BP measurement can lead to overestimation of intra-arterial pressure (see Accurate Blood Pressure Measurement in the Office). Falsely high readings may also be observed in those whose brachial arteries are heavily calcified or arteriosclerotic and cannot be fully compressed. Clinic or “white-coat” hypertension may also lead to transient high readings that are not experienced throughout the day. This can be documented by home BP or ambulatory BP readings (see prior sections).

Inadequate diuretic therapy is common in resistant hypertension. Volume overload, once recognized, can be managed by use of appropriate diuretics. While a thiazide-type diuretic is recommended for the majority of hypertensive patients, a loop diuretic is often required for patients who have a decreased GFR or HF.

Failure to receive adequate medications can be the result of reluctance on the part of the patient or practitioner to use effective medication doses. Causes and approaches to nonadherence are discussed in subsequent sections.

Drug interactions that induce resistance may be difficult to detect unless the patient is asked open-ended questions regarding what they take when experiencing pain and what food supplements, health-food preparations, over-the-counter and Internet-purchased medications, and supplements
they use. Nonsteroidal anti-inflammatory drugs and pressor agents in cold remedies, nasal vasodilators, and some nontraditional remedies may counter the antihypertensive effects of prescribed medications. If resistant hypertension persists after remediable causes are identified and corrected, then a concerted search for a cause of secondary hypertension should be conducted (table 7). If resistance still persists, consultation with a hypertension specialist is the next logical step.

Specific causes of resistant hypertension are listed in table 18. They usually can be identified by appropriate evaluation, and once identified, can almost always be treated effectively. The prevalence of truly resistant hypertension is small.

### Table 18. Causes of resistant hypertension

**Improper Blood Pressure Measurement**
- Volume overload
  - Excess sodium intake
  - Volume retention from kidney disease
  - Inadequate diuretic therapy

**Drug-induced or other causes**
- Nonadherence
- Inadequate doses
- Inappropriate combinations
- Nonsteroidal anti-inflammatory drugs; cyclooxygenase 2 inhibitors
- Cocaine, amphetamines, other illicit drugs
- Sympathomimetics (decongestants, anorectics)
- Oral contraceptive hormones
- Adrenal steroid hormones
- Cyclosporine and tacrolimus
- Erythropoietin
- Licorice (including some chewing tobacco)
- Selected over-the-counter dietary supplements and medicines (e.g., ephedra, ma huang, bitter orange)

**Associated conditions**
- Obesity
- Excess alcohol intake

Identifiable causes of hypertension (see table 7).

**Cognitive Function and Dementia**

Dementia and cognitive impairment occur more commonly in people with hypertension. Reduced progression of cognitive impairment may occur with effective antihypertensive therapy.\(^{269,270}\) Narrowing and sclerosis of small penetrating arteries in the subcortical regions of the brain are common findings on autopsy in chronic hypertension.\(^{271–274}\) These changes are believed to contribute to hypoperfusion, loss of autoregulation, compromise of the blood-brain barrier, and ultimately to subcortical white matter demyelination, microinfarction, and cognitive decline. Magnetic resonance imaging (MRI) studies in persons with chronic hypertension have revealed greater numbers of subcortical white matter lesions and microinfarcts, astrogliosis, ventricular enlargement, and extracellular fluid accumulation than in age-matched controls.\(^{275–285}\)

Mild cognitive impairment (MCI) is a diagnostic category that represents a transitional state between normal aging and mild dementia in which patients exhibit signs of poor recent memory but can still perform daily tasks such as managing finances, driving, shopping, and preparing meals.\(^{286}\) Hypertension and hypercholesterolemia are risk factors for MCI and for other signs of cognitive decline, such as impaired attention, reaction time, verbal fluency, or executive function.\(^{275,276,278,287–289}\)

Effective antihypertensive therapy strongly reduces the risk of developing significant white matter changes on MRI.\(^{290}\) However, existing white matter changes, once established, do not appear to be reversible.\(^{291,292}\) The optimal SBP/DBP to prevent cognitive decline in older individuals is thought by some to be in the SBP 135–150 mmHg and DBP 70–79 mmHg range.\(^{287,288}\) In the SystEUR trial, CCB therapy was superior to placebo in slowing the decline in cognitive function,\(^{293}\) but no comparative data are available regarding whether certain classes of antihypertensive drugs are superior to others in preventing cognitive decline.
Hypertension in Women

Nonpregnant Women

Sexual dimorphism of BP and hypertension prevalence in women. There is a sexual dimorphism in BP, such that women have lower SBP levels than men during early adulthood, while the opposite is true after the sixth decade of life. DBP tends to be just marginally lower in women than men regardless of age. Similarly, in early adulthood, hypertension is less common among women than men. However, after the fifth decade of life, the incidence of hypertension increases more rapidly in women than men, and the prevalence of hypertension in women is equal to or exceeds that in men during the sixth decade of life. The highest prevalence rates of hypertension are observed in elderly black women, with hypertension occurring in >75 percent of women older than 75 years of age.

Awareness, treatment, and control of high BP in women. Women are more likely than men to know that they have hypertension, to have it treated, and to have it controlled. In NHANES III, approximately 75 percent of hypertensive Black and White women were aware of their high BP in contrast to 65 percent of hypertensive men in these ethnic groups. Overall, 61 percent of hypertensive women, but only 44 percent of men, were being treated with antihypertensive medications. The higher treatment rates in women have been attributed to increased numbers of physician contact.

Menopause and blood pressure. The effect of menopause on BP is controversial. Longitudinal studies have not documented a rise in BP with menopause, while cross-sectional studies have found significantly higher SBP and DBP in postmenopausal versus premenopausal women. In NHANES III, the rate of rise in SBP tended to be steeper in postmenopausal compared to premenopausal women until the sixth decade, when the rate of increase tended to slow. Staessen et al. reported that, even after adjustment for age and BMI, postmenopausal women are more than twice as likely to have hypertension as premenopausal women. In a prospective study of conventional and ambulatory BP levels, postmenopausal women had higher SBP (4–5 mmHg) than pre- and perimenopausal controls. The increase in SBP per decade was 5 mmHg greater in the peri- and postmenopausal women than in the premenopausal group. Thus, there is evidence that at least part of the rise in BP (particularly SBP) seen later in life in women is due to menopause. A menopause-related increase in BP has been attributed to a variety of factors, including estrogen withdrawal, overproduction of pituitary hormones, weight gain, or a combination of these and other yet undefined neurohumoral influences.

Postmenopausal hormone therapy and BP. Results of studies evaluating the effects of hormone replacement therapy (HRT) on BP have been inconsistent. The Women’s Health Initiative (WHI), the largest longitudinal study to address this question, found an average 1 mmHg increase in SBP over 5.6 years of followup among 8,506 postmenopausal women randomized to conjugated equine estrogen and medroxyprogesterone acetate as compared to a placebo group. There was no difference in DBP between the hormone treatment groups. Further, in the WHI cross-sectional analysis of almost 100,000 women 50–79 years of age, current hormone use was associated with a >25 percent likelihood of having hypertension compared to past use or no prior use.

Smaller observational and interventional studies have found different results. In the Baltimore Longitudinal Study on Aging (BLSA), women receiving HRT had a significantly smaller increase in SBP over time than nonusers, but DBP was not affected. The Postmenopausal Estrogen/Progestin Intervention trial showed no effect of HRT on SBP or DBP. In small studies that used 24-hour ABPM to evaluate the effects of HRT on BP, while overall results were inconsistent, several of the studies suggest that HRT improves or restores the normal nighttime reduction (“dipping”) in BP that may be diminished in postmenopausal women. Such an effect would tend to reduce total BP load and thereby reduce target organ damage.

Overall, HRT-related change in BP is likely to be modest and should not preclude hormone use in normotensive or hypertensive women. All hyper-
tensive women treated with HRT should have their BP monitored closely at first and then at 6-month intervals.

**Oral contraceptives and BP.** Many women taking oral contraceptives experience a small but detectable increase in BP; a small percentage experience the onset of frank hypertension. This is true even with modern preparations that contain only 30 µg estrogen. The Nurses’ Health Study found that current users of oral contraceptives had a significantly increased (relative risk [RR]=1.8; 95 percent confidence interval [CI]=1.5–2.3) risk of hypertension compared with those who had never used oral contraceptives.\(^{302}\) Absolute risk was small: only 41.5 cases of hypertension per 10,000 person/years could be attributed to oral contraceptive use. Controlled prospective studies have demonstrated a return of BP to pretreatment levels within 3 months of discontinuing oral contraceptives, indicating that their BP effect is readily reversible.

Oral contraceptives occasionally may precipitate accelerated or malignant hypertension. Family history of hypertension, including preexisting pregnancy-induced hypertension, occult renal disease, obesity, middle age (>35 years), and duration of oral contraceptive use increase susceptibility to hypertension. Contraceptive-induced hypertension appears to be related to the progestogenic, not the estrogenic, potency of the preparation.

Regular monitoring of BP throughout contraceptive therapy is recommended, and it has been suggested that contraceptive prescriptions be limited to 6 months to ensure at least semiannual reevaluations. Withdrawal of the offending contraceptive agent is generally desirable in cases of contraceptive-induced hypertension, but such therapy may have to be continued in some women (e.g., if other contraceptive methods are not suitable) and combined with antihypertensive therapy.

**Outcomes of antihypertensive trials in women.** Relative benefits of antihypertensive therapy do not appear to differ between the sexes.\(^{303}\) Absolute risk reduction for stroke was also similar in men and women, but for coronary events, it was greater in men. Similarly, a placebo-controlled trial of CCB treatment showed treatment benefits for both sexes.\(^{113,304}\) More recent outcome trials comparing ACEIs, ARBs, or CCBs to diuretics and BBs in older, high-risk patients have generally shown similar benefits for women and men.\(^{101,102,109}\) The current evidence indicates that the sex of the patient should not play a role in decisions about whether to treat high BP.

**Choice of antihypertensive drugs for women.** While women generally respond to antihypertensive drugs similarly to men, some special considerations may dictate treatment choices for women. ACEIs and ARBs are contraindicated for women who are or intend to become pregnant because of the risk of fetal developmental abnormalities. Diuretics are particularly useful in elderly individuals because of a decreased risk of hip fracture. Some antihypertensive drugs have gender-specific adverse effect profiles. For example, in the TOMHS, women reported twice as many adverse effects as men.\(^{305}\) Women are more likely to develop diuretic-induced hyponatremia, and men are more likely to develop gout. Hypokalemia is more common in women taking a diuretic. ACEI-induced cough is twice as common in women as in men, and women are more likely to complain of CCB-related peripheral edema and minoxidil-induced hirsutism.

**Pregnant Women**

Hypertensive disorders in pregnancy are a major cause of maternal, fetal, and neonatal morbidity and mortality. Hypertension in pregnancy is classified into one of five categories (table 19), and it is critical to differentiate preeclampsia, a pregnancy-specific syndrome of exaggerated vasoconstriction and reduced organ perfusion, from pre-existing chronic hypertension.\(^{7,306}\)

**Prepregnancy assessment.** Women should be evaluated prior to conception to define their BP status, and if hypertensive, to assess its severity, possible secondary causes, and presence of target organ damage, and to plan treatment strategies. Many hypertensive women who plan to become pregnant should be screened for pheochromocytoma due to the high morbidity and mortality of this condition if not diagnosed antepartum.
In hypertensive women planning to become pregnant, it may be prudent prior to conception to change to antihypertensive medications known to be safe during pregnancy, such as methyldopa or BBs. ACEIs and ARBs should be discontinued prior to attempts at conception or as soon as pregnancy is confirmed. Those with progressive renal diseases should be encouraged to complete their childbearing while their renal function is relatively well preserved. Mild renal disease (serum creatinine <1.4 mg/dL) has a minimal effect on fetal survival, and the underlying renal disease does not generally worsen during pregnancy. However, moderate or severe renal insufficiency in pregnancy may accelerate both hypertension and the underlying disease and markedly reduce fetal survival.

Treatment of chronic hypertension during pregnancy. Women with stage 1 hypertension are at low risk for cardiovascular complications during pregnancy and are candidates for lifestyle modification therapy only, as there is no evidence that pharmacologic treatment improves neonatal outcomes. Further, BP usually falls during the first half of pregnancy; therefore, hypertension may be easier to control with reduced or no medications. With lifestyle modification, aerobic exercise should be restricted based on theoretical concerns that inadequate placental blood flow may increase the risk of preeclampsia, and weight reduction should not be attempted, even in obese pregnant women. Although the data on pregnant women are sparse, many experts recommend restriction of sodium intake to the same 2.4 g sodium intake recommended for those with

**Table 19. Classification of hypertension in pregnancy**

<table>
<thead>
<tr>
<th>Chronic hypertension</th>
<th>BP &gt;140 mmHg systolic or 90 mmHg diastolic prior to pregnancy or before 20 weeks gestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preeclampsia</td>
<td>BP &gt;140 mmHg systolic or 90 mmHg diastolic with proteinuria (&gt;300 mg/24 hrs) after 20 weeks gestation</td>
</tr>
<tr>
<td></td>
<td>Can progress to eclampsia (seizures)</td>
</tr>
<tr>
<td></td>
<td>More common in nulliparous women, multiple gestation, women with hypertension for &gt;4 years, family history of preeclampsia, hypertension in previous pregnancy, renal disease</td>
</tr>
<tr>
<td>Chronic hypertension with superimposed preeclampsia</td>
<td>New onset proteinuria after 20 weeks in a woman with hypertension</td>
</tr>
<tr>
<td></td>
<td>In a woman with hypertension and proteinuria prior to 20 weeks gestation</td>
</tr>
<tr>
<td></td>
<td>Sudden two- to threefold increase in proteinuria</td>
</tr>
<tr>
<td></td>
<td>Sudden increase in BP</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Elevated AST or ALT</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>Hypertension without proteinuria occurring after 20 weeks gestation</td>
</tr>
<tr>
<td></td>
<td>Temporary diagnosis</td>
</tr>
<tr>
<td></td>
<td>May represent preproteinuric phase of preeclampsia or recurrence of chronic hypertension abated in midpregnancy</td>
</tr>
<tr>
<td></td>
<td>May evolve to preeclampsia</td>
</tr>
<tr>
<td></td>
<td>If severe, may result in higher rates of premature delivery and growth retardation than mild preeclampsia</td>
</tr>
<tr>
<td>Transient hypertension</td>
<td>Retrospective diagnosis</td>
</tr>
<tr>
<td></td>
<td>BP normal by 12 weeks postpartum</td>
</tr>
<tr>
<td></td>
<td>May recur in subsequent pregnancies</td>
</tr>
<tr>
<td></td>
<td>Predictive of future primary hypertension</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; AST, aspartate aminotransaminase; BP, blood pressure
primary hypertension. Use of alcohol and tobacco must be strongly discouraged.

Use of antihypertensive drugs in pregnant women with chronic hypertension varies greatly among centers. Some clinicians prefer to stop antihypertensive medications while maintaining close observation, including use of home BP monitoring. This approach reflects concern about the safety of antihypertensive drug treatment during pregnancy. A meta-analysis of 45 randomized controlled studies of treatment with several classes of antihypertensive drugs in stages 1 and 2 hypertension during pregnancy showed a direct linear relationship between treatment-induced fall in mean arterial pressure and the proportion of small-for-gestational-age infants. This relationship was independent of type of hypertension, type of antihypertensive agent, and duration of therapy.

However, for pregnant women with target organ damage or a prior requirement for multiple antihypertensive agents for BP control, antihypertensive medication should be continued as needed to control BP. In all cases, treatment should be re-instituted once BP reaches 150–160 mmHg systolic or 100–110 mmHg diastolic, in order to prevent increases in BP to very high levels during pregnancy. Aggressive treatment of severe chronic hypertension in the first trimester is critical, since fetal loss rates of 50 percent and significant maternal mortality have been reported in these patients. Most of the poor outcomes are related to superimposed preeclampsia (table 19). Further, women with chronic hypertension are also at higher risk for adverse neonatal outcomes if proteinuria is present early in pregnancy. Fetal loss and acceleration of maternal renal disease increase at serum creatinine levels >1.4 mg/dL at conception.

**Antihypertensive drug selection.** The primary goal of treating chronic hypertension in pregnancy is to reduce maternal risk, but the choice of antihypertensive agent(s) is largely driven by the safety of the fetus. Methyldopa is preferred by many as first-line therapy, based on reports of stable uteroplacental blood flow and fetal hemodynamics and the absence of long-term (7.5-year followup) adverse effects on development of children exposed to methyldopa in utero. Other treatment options are summarized in table 20.

**Preeclampsia.** Preeclampsia is more common in women with chronic hypertension, with an incidence of approximately 25 percent. Risk factors for superimposed preeclampsia include renal insufficiency, a history of hypertension for 4 years or longer, and hypertension in a previous pregnancy. Prevention of preeclampsia relies on: (1) identification of high-risk women; (2) close clinical and laboratory monitoring aimed at its early recognition; and

<table>
<thead>
<tr>
<th>AGENT</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyldopa</td>
<td>Preferred based on long-term followup studies supporting safety</td>
</tr>
<tr>
<td>BBs</td>
<td>Reports of intrauterine growth retardation (atenolol) Generally safe</td>
</tr>
<tr>
<td>Labetalol</td>
<td>Increasingly preferred to methyldopa due to reduced side effects</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Limited data</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>Limited data</td>
</tr>
<tr>
<td></td>
<td>No increase in major teratogenicity with exposure</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Not first-line agents</td>
</tr>
<tr>
<td></td>
<td>Probably safe</td>
</tr>
<tr>
<td>ACEIs, angiotensin II receptor antagonists</td>
<td>Contraindicated</td>
</tr>
<tr>
<td></td>
<td>Reported fetal toxicity and death</td>
</tr>
</tbody>
</table>

**Table 20. Treatment of chronic hypertension in pregnancy**

ACEIs, angiotensin converting enzyme inhibitors; BBs, beta-blockers
(3) institution of intensive monitoring or delivery when indicated. Treatment of preeclampsia includes hospitalization for bed rest, control of BP, seizure prophylaxis in the presence of signs of impending eclampsia, and timely delivery. Importantly, many women with preeclampsia have previously been normotensive, so acute BP elevations even to modest levels (i.e., 150/100 mmHg) may cause significant symptomatology and require treatment. Treatment does not alter the underlying pathophysiology of the disease, but it may slow its progression and provide time for fetal maturation. Preeclampsia rarely remits spontaneously and in most cases worsens with time.

While delivery may be appropriate therapy for the mother, it may compromise a fetus of <32 weeks gestation. Regardless of gestational age, delivery should be strongly considered when there are signs of fetal distress or intrauterine growth retardation or signs of maternal problems, including severe hypertension, hemolysis, elevated liver enzymes, low platelet count, deteriorating renal function, visual disturbance, and headache or epigastric pain. Vaginal delivery is preferable to cesarean delivery to avoid the added stress of surgery.

**Antihypertensive drug therapy.** Antihypertensive therapy should be prescribed only for maternal safety; it does not improve perinatal outcomes and may adversely affect uteroplacental blood flow. Selection of antihypertensive agents and route of administration depends on anticipated timing of delivery. If delivery is likely more than 48 hours away, oral methyldopa is preferred due to its safety record. Oral labetalol is an alternative, and other BBs and calcium antagonists are also acceptable based on limited data (table 20). If delivery is imminent, parenteral agents are practical and effective (table 21). Antihypertensives are administered before induction of labor for persistent DBPs of 105–110 mmHg or higher, aiming for levels of 95–105 mmHg.

### Treating hypertension during lactation.
Hypertensive mothers can usually breast-feed safely. However, all antihypertensive drugs that have been studied are excreted into human breast milk. Therefore, in mothers with stage 1 hypertension who wish to breast-feed for a few months, it might be prudent to withhold antihypertensive medication, with close monitoring of BP, and reinstitute antihypertensive therapy following discontinuation of nursing. No short-term adverse effects have been reported from exposure to methyldopa or hydralazine. Propanolol and labetalol are preferred if a BB is indicated. ACEIs and ARBs should be avoided, based on reports of adverse fetal and neonatal renal effects. Diuretics may reduce milk volume and thereby suppress lactation. Breast-fed infants of mothers taking antihypertensive agents should be closely monitored for potential adverse effects.

**Recurrence of hypertension.** Hypertension recurs in a large proportion (20–50 percent) of subsequent deliveries.

### Table 21. Treatment of acute severe hypertension in preeclampsia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hydralazine</strong></td>
<td>■ 5 mg iv bolus, then 10 mg every 20–30 minutes to a maximum of 25 mg, repeat in several hours as necessary</td>
</tr>
<tr>
<td><strong>Labetalol</strong></td>
<td>■ 20 mg iv bolus, then 40 mg 10 minutes later, 80 mg every 10 minutes for two additional doses to a maximum of 220 mg</td>
</tr>
<tr>
<td><strong>Nifedipine</strong></td>
<td>■ 10 mg po, repeat every 20 minutes to a maximum of 30 mg&lt;br&gt;■ Caution when using nifedipine with magnesium sulfate, can see precipitous blood pressure drop&lt;br&gt;■ Short-acting nifedipine is not approved by the Food and Drug Administration for managing hypertension</td>
</tr>
<tr>
<td><strong>Sodium nitroprusside</strong></td>
<td>■ 0.25 ug/kg/min to a maximum of 5 ug/kg/min&lt;br&gt;■ Fetal cyanide poisoning may occur if used for more than 4 hours</td>
</tr>
</tbody>
</table>

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
pregnancies. Risk factors for recurrence include early onset of hypertension in the first pregnancy, a history of chronic hypertension, persistent hypertension beyond 5 weeks postpartum, and elevated BP early in pregnancy. Women with preeclampsia have a greater tendency to develop hypertension than those with normotensive pregnancies.

**Hypertension in Children and Adolescents**

In children and adolescents, hypertension is defined as elevated BP that persists on repeated measurement at the 95th percentile or greater for age, height, and gender (table 22). As with adults, the fifth Korotkoff sound is used to define DBP.311

Clinicians should be alert to the possibility of identifiable causes of hypertension in younger children. Secondary forms of hypertension are more common in children and in individuals with severe hypertension (>20 mmHg above the 95th percentile). Chronic hypertension is becoming increasingly common in adolescence and is generally associated with obesity, sedentary lifestyle, and a positive family history of hypertension and other CVDs. As in adults, children and adolescents with established hypertension develop target organ damage including LVH. Appropriate assessment for LVH, including echocardiography, should be considered in children who have significant and persistent hypertension.

Lifestyle interventions should be recommended for all children with hypertension, with pharmacologic therapy instituted for higher levels of BP or if insufficient response to lifestyle modifications occurs. Teenage children with BP below but near the 95th percentile should adopt healthy lifestyles similar to adults with prehypertension. Although the recommendations for choice of drugs are generally similar in children and adults, dosages of antihypertensive medication for children should be smaller and adjusted very carefully. ACEIs and ARBs should not be used if the patient is pregnant. These agents should be used with extreme caution in sexually active teenage girls and only when careful counseling and effective pregnancy precautions are established.

The presence of uncomplicated hypertension is not a reason to restrict children from participating in physical activities, particularly because exercise may lower BP. Use of anabolic steroid hormones for the purpose of bodybuilding should be strongly discouraged. Efforts should be made to identify other modifiable risk factors in children (e.g., obesity, lack of physical activity, smoking), and vigorous interventions should be made when these factors are present. Detailed recommendations regarding hypertension in children and adolescents can be found in the 1996 NHBPEP Working Group Report on Hypertension Control in Children and Adolescents.311

### Table 22. The 95th percentile of blood pressure by selected ages, by the 50th and 75th height percentiles, and by gender in children and adolescents

<table>
<thead>
<tr>
<th>Age</th>
<th>Girls' SBP/DBP</th>
<th>Boys' SBP/DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50th Percentile for Height</td>
<td>75th Percentile for Height</td>
</tr>
<tr>
<td>1</td>
<td>104/58</td>
<td>105/59</td>
</tr>
<tr>
<td>6</td>
<td>111/73</td>
<td>112/73</td>
</tr>
<tr>
<td>12</td>
<td>123/80</td>
<td>124/81</td>
</tr>
<tr>
<td>17</td>
<td>129/84</td>
<td>130/85</td>
</tr>
</tbody>
</table>

DBP, diastolic blood pressure; SBP, systolic blood pressure

Hypertensive Crises: Emergencies and Urgencies

Hypertensive emergencies are characterized by severe elevations in BP (>180/120 mmHg) complicated by evidence of impending or progressive target organ dysfunction. They require immediate BP reduction (not necessarily to normal) to prevent or limit target organ damage. Examples include hypertensive encephalopathy, intracerebral hemorrhage, acute MI, acute left ventricular failure with pulmonary edema, unstable angina pectoris, dissecting aortic aneurysm, or eclampsia. Hypertensive urgencies are those situations associated with severe elevations in BP without progressive target organ dysfunction. Examples include upper levels of stage II hypertension associated with severe headache, shortness of breath, epistaxis, or severe anxiety. The majority of these patients present as noncompliant or inadequately treated hypertensive individuals, often with little or no evidence of target organ damage.

Early triage to establish the appropriate therapeutic strategies for these patients is critical to limiting morbidity and mortality. Patients presenting with severe hypertension may represent as much as 25 percent of all patient visits to busy urban emergency rooms (ERs). Patients with hypertensive emergencies should be admitted to an intensive care unit for continuous monitoring of BP and parenteral administration of an appropriate agent (table 23). The initial goal of therapy in hypertensive emergencies is to reduce mean arterial BP by no more than 25 percent (within minutes to 1 hour), then if stable, to 160/100–110 mmHg within the next 2–6 hours. Excessive falls in pressure that may precipitate renal, cerebral, or coronary ischemia should be avoided. For this reason, short-acting nifedipine is no longer considered acceptable in the initial treatment of hypertensive emergencies or urgencies. If this level of BP is well tolerated and the patient is clinically stable, further gradual reductions toward a normal BP can be implemented in the next 24–48 hours. There are exceptions to the above recommendation—patients with an ischemic stroke in which there is no clear evidence from clinical trials to support the use of immediate antihypertensive treatment, patients with aortic dissection who should have their SBP lowered to <100 mmHg if tolerated, and patients in whom BP is lowered to enable the use of thrombolytic agents (see Stroke).

Some patients with hypertensive urgencies may benefit from treatment with an oral, short-acting agent such as captopril, labetalol, or clonidine followed by several hours of observation. However, there is no evidence to suggest that failure to aggressively lower BP in the ER is associated with any increased short-term risk to the patient who presents with severe hypertension. Such a patient may also benefit from adjustment in their antihypertensive therapy, particularly the use of combination drugs, or reinstitution of medications if noncompliance is a problem. Most importantly, patients should not leave the ER without a confirmed followup visit within several days.

Unfortunately, the term “urgency” has led to overly aggressive management of many patients with severe, uncomplicated hypertension. Aggressive dosing with intravenous drugs or even oral agents, to rapidly lower BP is not without risk. Oral loading doses of antihypertensive agents can lead to cumulative effects causing hypotension, sometimes following discharge from the ER. Patients who continue to be noncompliant will often return to the ER within weeks.

Erectile Dysfunction and Hypertension

Erectile dysfunction (ED), defined as the inability to have and maintain an erection adequate for intercourse, becomes increasingly common in men over age 50 and is even more common if they are hypertensive. In a survey of over 3,000 health professionals, the frequency of ED was 4 percent in men under age 50, 26 percent in those 50–59, and 40 percent in those 60–69. The frequency was significantly higher if they were hypertensive, diabetic, obese, smokers, or were taking antidepressants or BBs.

Whereas hypertension per se may be associated with ED, the use of various antihypertensive medications may increase the incidence, in part because BP lowering itself may cause reduction of perfusion of genital organs. Available data
regarding individual effects of antihypertensive drug therapy are confounded by age, vascular disease, and hormonal status. In the TOHMS study involving antihypertensive drugs from five different classes (excluding ARBs) participants randomized to chlorothalidone reported a significantly higher incidence of erection problems, at 24 months of the study, than participants randomized to placebo. Incidence rates through 48 months were more similar among treatment groups than at 24 months, with nonsignificant differences between chlorothalidone and placebo groups. In the VA Cooperative Trial, no difference on incidence of sexual dysfunction was noted.

Table 23. Parenteral drugs for treatment of hypertensive emergencies*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Onset of Action</th>
<th>Duration of Action</th>
<th>Adverse Effects†</th>
<th>Special Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium nitroprusside</td>
<td>0.25–10 µg/kg/min as IV infusion†</td>
<td>Immediate</td>
<td>1–2 min</td>
<td>Nausea, vomiting, muscle twitching, sweating, thiocyanate and cyanide intoxication</td>
<td>Most hypertensive emergencies; caution with high intracranial pressure or azotemia</td>
</tr>
<tr>
<td>Nicardipine hydrochloride</td>
<td>5–15 mg/h IV</td>
<td>5–10 min</td>
<td>15–30 min, may exceed 4 hrs</td>
<td>Tachycardia, headache, flushing, local phlebitis</td>
<td>Most hypertensive emergencies except acute heart failure; caution with coronary ischemia</td>
</tr>
<tr>
<td>Fenoldopam mesylate</td>
<td>0.1–0.3 µg/kg per min IV infusion‡</td>
<td>&lt;5 min</td>
<td>30 min</td>
<td>Tachycardia, headache, nausea, flushing</td>
<td>Most hypertensive emergencies; caution with glaucoma</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>5–100 µg/min as IV infusion†</td>
<td>2–5 min</td>
<td>5–10 min</td>
<td>Headache, vomiting, methemoglobinemia, tolerance with prolonged use</td>
<td>Coronary ischemia</td>
</tr>
<tr>
<td>Enalapril</td>
<td>1.25–5 mg every 6 hrs IV</td>
<td>15–30 min</td>
<td>6–12 hrs</td>
<td>Precipitous fall in pressure in high-renin states; variable response</td>
<td>Acute left ventricular failure; avoid in acute myocardial infarction</td>
</tr>
<tr>
<td>Hydralazine hydrochloride</td>
<td>10–20 mg IV</td>
<td>10–20 min IV</td>
<td>1–4 hrs IV</td>
<td>Tachycardia, flushing, headache, vomiting, aggravation of angina</td>
<td>Eclampsia</td>
</tr>
<tr>
<td>Adrenergic Inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labetalol hydrochloride</td>
<td>20–80 mg IV bolus every 10 min</td>
<td>5–10 min</td>
<td>3–6 hrs</td>
<td>Vomiting, scalp tingling, bronchoconstriction, dizziness, nausea, heart block, orthostatic hypotension</td>
<td>Most hypertensive emergencies except acute heart failure</td>
</tr>
<tr>
<td>Esmolol hydrochloride</td>
<td>250–500 µg/kg/min IV bolus, then 50–100 µg/kg/min by infusion; may repeat bolus after 5 min or increase infusion to 300 µg/min</td>
<td>1–2 min</td>
<td>10–30 min</td>
<td>Hypotension, nausea, asthma, first degree heart block, heart failure</td>
<td>Aortic dissection, perioperative</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>5–15 mg IV bolus</td>
<td>1–2 min</td>
<td>10–30 min</td>
<td>Tachycardia, flushing, headache</td>
<td>Catecholamine excess</td>
</tr>
</tbody>
</table>

h or hr, hour; IM, intramuscular; IV, intravenous; min, minute(s)

† These doses may vary from those in the Physicians’ Desk Reference (51st ed.)

‡ Hypotension may occur with all agents

§ Require special delivery system

55Special Situations in Hypertension Management
between a CCB, ACEI, hydrochlorothiazide, or BB compared to placebo. In other studies centrally acting alpha agonists have been associated with ED, while ACEIs, ARBs, and CCBs have not been observed to increase its incidence.

A lower risk of ED was reported among men who were physically active, not obese, and nonsmokers. Therefore, lifestyle modifications should be encouraged to forestall ED. If ED appears after institution of antihypertensive drug therapy, the offending agent should be discontinued and treatment restarted with another agent. Sildenafil or other phosphodiesterase-5 inhibitors may be prescribed without a significant likelihood of adverse reactions in those with concomitant antihypertensive therapy so long as nitrates are avoided.

There are no definitive data on a relation between sexual dysfunction and hypertension in women. Regardless of gender, clinicians should be willing to discuss sexual dysfunction problems and offer counseling to improve the patient’s quality of life.

**Urinary Outflow Obstruction**

Symptoms of urinary outflow obstruction or a known history of obstruction should be elicited as part of the hypertension work-up. When a normal bladder is distended beyond approximately 300 mL, sympathetic nervous system stimulation may cause a substantial increase in BP. Patients with high spinal cord injuries in particular may exhibit large acute BP increases similar to individuals with autonomic dysfunction. BP control can be improved by keeping the bladder volume below 300 mL and by the use of sympatholytic drugs. Nonsurgical treatment of patients with urinary outflow obstruction includes the use of alpha-1 blockers such as terazosin, doxazosin, or prazosin, which indirectly dilate prostatic and urinary sphincter smooth muscle and also lower BP.

**Patients Undergoing Surgery**

Uncontrolled hypertension is associated with wider fluctuations of BP during induction of anesthesia and intubation, and may increase the risk for perioperative ischemic events. BP levels of >180/110 mmHg should be controlled prior to surgery. For elective surgery, effective BP control can be achieved over several days to weeks of outpatient treatment. In urgent situations, rapidly acting parenteral agents, such as sodium nitroprusside, nicardipine, and labetalol, can be utilized to attain effective control very rapidly. Surgical candidates with controlled hypertension should maintain their medications until the time of surgery, and therapy should be reinstated as soon as possible postoperatively. Adequate potassium supplementation should be provided, if needed, to correct hypokalemia well in advance of surgery. Older patients may particularly benefit from treatment with beta-1 selective BBs before and during the perioperative period.

Sudden intraoperative hypertension is managed by many of the same parenteral antihypertensive agents that are utilized in the management of hypertensive emergencies. Intravenous infusions of sodium nitroprusside, nicardipine, and labetalol can be effective. Nitroglycerin is often an agent of choice in patients with coronary ischemia, while the very short-acting BB, esmolol, may be of benefit in managing intraoperative tachycardia.

Hypertension is very common in the early postoperative period and is related to increased sympathetic tone and vascular resistance. Contributing factors include pain and increased intravascular volume, which may require parenteral dosing with a loop diuretic such as furosemide. If resumption of oral treatment must be interrupted postoperatively, periodic dosing with intravenous enalaprilat or transdermal clonidine hydrochloride may be useful.

**Dental Issues in Hypertensive Individuals**

A concern in dental care is the use of epinephrine in local anesthetic solutions. Many dental providers do not use catecholamine-containing local anesthetic formulations for any patient with elevated BP, as they are concerned with an adverse cardiovascular response. A systematic review of this topic concluded that, although adverse events may occur in uncontrolled hypertensive patients during dental procedures, the use of epinephrine had a minimal effect. BP should be
monitored closely in the dental office if general anesthesia is administered to hypertensive individuals because of potential wide fluctuations in BP and the risk of hypotension in those receiving antihypertensive drugs. CCBs and other vasodilators may cause hypertrophy of the gums.

**Obstructive Sleep Apnea**

Obstructive sleep apnea (OSA) occurs in 2–4 percent of the adult population, and >50 percent of individuals with OSA have hypertension.263,326–333 Obesity is so common in OSA that the index of suspicion for OSA should be high in any hypertensive patient whose BMI is above 27 kg/m².331 These individuals should be questioned thoroughly for symptoms of OSA, including snoring, witnessed apnea, irregular breathing during sleep, restless sleeping, and chronic morning fatigue. Frequently it is the sleep partner who provides the most reliable history, especially regarding snoring, because the affected individual may deny or be unaware of the problem. If the diagnosis is suspected clinically, confirmation by a formal sleep study is indicated. The impact of sleep apnea on CVD is probably related in large part to its association with elevated BP. However, OSA may act through a number of mechanisms to elicit myocardial and vascular damage, including an increase in catecholamine release,333,334 activation of inflammatory mechanisms,335 insulin resistance,336,337 and endothelial dysfunction.338 Other cardiovascular conditions associated with OSA include arrhythmias, HF, MI, and stroke.331,332,339–344

Previous debate about whether OSA is an etiologic factor in hypertension has focused largely around the strong association of OSA with obesity. While obesity is known to contribute in large part to OSA,345–348 patients with OSA may also be at increased risk for weight gain,349 and treatment of OSA may reduce visceral fat.350 It now appears that the potential causal association between OSA and hypertension involves both the obesity-hypertension link and an independent role of OSA in chronic BP elevation. Episodes of apnea with repeated oxygen desaturation in OSA have been shown to stimulate strong sympathetic nervous system discharges that directly elevate BP.333,334 Poorer quality of sleep and shorter sleep periods may play a reinforcing role in the fatigue and daytime somnolence. Sleep deprivation alone may raise BP351 and impair glucose tolerance.352 There is also a direct relationship between the severity of sleep apnea and the level of BP. Finally, sustained and effective treatment of OSA with continuous positive airway pressure (CPAP) has been reported to lower nighttime and daytime BP in hypertensive individuals with OSA.353–355

In addition to weight loss, improvements in the quality of sleep in OSA patients can occur as a result of a variety of positioning measures during sleep, particularly sleeping on one’s side. Treatment with CPAP can be useful in overall BP lowering and may also improve cardiac ischemia356,357 and HF symptoms.331,332 The role of oral prostheses and surgical approaches remains to be fully defined.354 No specific class of antihypertensive drugs has yet been demonstrated to be superior for BP lowering in OSA patients.354

**Hypertension and the Eye**

Hypertension can affect the retina, choroid, and optic nerve of the eye, particularly with stage 2 hypertension. These changes can be appreciated with inspection of the retinal vessels by direct ophthalmoscopy, photography, or angiography. Hypertensive retinopathy is most commonly manifested by generalized or focal narrowing of retinal arterioles. In acute or advanced hypertension, the retinal vasculature may be injured sufficiently to cause occlusion or leakage. These changes may be manifested as nerve fiber layer infarcts (“soft” exudates or cotton-wool patches), extravascular edema (“hard” exudates), intraretinal hemorrhages, and retinal arterial macroaneurysms. Hypertensive choroidopathy is most frequently seen in young patients with acute hypertension, including cases of eclampsia or pheochromocytoma. Findings include Elschnig spots (nonperfused areas of the choriocapillaris) and Siegrist streaks (linear hyperpigmentation over choroidal arteries). Hypertensive optic neuropathy occurring with severe hypertension may present with flame hemorrhages, optic disc edema, venous congestion, and macular exudates.358–360
Renal Transplantation

Hypertension is a relatively common occurrence in patients receiving organ transplants; in those receiving kidney allografts, the prevalence of hypertension probably exceeds 65 percent.\textsuperscript{361} Nocturnal hypertension, a reversal of diurnal BP rhythm, may be present in these individuals, who may need ABPM to evaluate overall BP control.

Hypertension is less common in other forms of transplantation. The mechanisms of hypertension in transplant patients are multifactorial, but vasoconstriction and long-term vascular structural changes caused by chronic immunosuppressive drugs, which are calcineurin inhibitors (cyclosporin and tacrolimus) and corticosteroids, are among the most important.\textsuperscript{362} Impaired renal function is another exacerbating factor; despite successful renal transplantation, most patients have enough impairment in renal function to cause relative salt and water retention. Transplant renal artery stenosis may also be a factor.

Observational studies suggest that hypertension correlates with deterioration in graft function. Large-scale, controlled, clinical trials on the effects of BP control on decline in GFR or on CVD incidence are lacking in this population. The high risk of graft occlusion and cardiovascular events has suggested that BP should be lowered to 130/80 mmHg or less. Because of the absence of compelling data, no particular class of antihypertensives can be considered superior to any other. The difficulty of lowering BP in this group makes combination drugs necessary in almost all patients. As with other renal diseases, serum creatinine and potassium should be monitored 1–2 weeks following initiation or escalation in therapy with ACEIs or ARBs. A >1 mg/dL increase in serum creatinine should raise the question of renal artery stenosis.

Patients With Renovascular Disease

Hemodynamically significant renal artery stenosis may be associated with all stages of hypertension, but it is more commonly recognized in patients with stage 2 or resistant hypertension, since these are the individuals in whom special evaluation for the problem is carried out. If present bilaterally, renal artery stenosis can lead to reduced kidney function (ischemic nephropathy).\textsuperscript{363}

Clinical clues to renovascular disease include (1) onset of hypertension before age 30 (especially without a family history) or recent onset of significant hypertension after age 55; (2) an abdominal bruit, particularly if it continues into diastole and is lateralized; (3) accelerated or resistant hypertension; (4) recurrent (flash) pulmonary edema; (5) renal failure of uncertain etiology, especially with a normal urinary sediment; (6) coexisting diffuse atherosclerotic vascular disease, especially in heavy smokers; or (7) acute renal failure precipitated by antihypertensive therapy, particularly ACEIs or ARBs.\textsuperscript{78,79,81}

In patients with indications of renovascular disease, captopril-enhanced radionuclide renal scan, duplex Doppler flow studies, and magnetic resonance angiography may be used as noninvasive screening tests. Three-dimensional images can be obtained by spiral computed tomography, a technique that necessitates the use of intravenous contrast.\textsuperscript{81} Definitive diagnosis of renovascular disease requires renal angiography, which carries some risk, particularly of radiocounterast-induced acute renal failure or atheroembolism.\textsuperscript{364}

In patients, usually women, with fibromuscular dysplasia, results of percutaneous transluminal renal angioplasty (PTRA) have been excellent and comparable to surgical revascularization.\textsuperscript{365} Patients with normal renal function and atherosclerotic renal artery stenosis that is focal, unilateral, and nonostial also may be managed by angioplasty.\textsuperscript{365} Renal artery stenting has become an important adjunct to PTRA, being used to counteract elastic recoil and to abolish the residual stenosis often observed after PTRA.\textsuperscript{366}

Even though many patients with high-grade renal artery stenosis remain stable for prolonged periods if BP is well controlled,\textsuperscript{367} surgical revascularization or PTRA with renal artery stenting may be needed to preserve renal function.\textsuperscript{81}