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KEY CONCEPTS

- 1 The risk of cardiovascular (CV) morbidity and mortality is directly correlated with blood pressure (BP). Even patients with prehypertension have an increased risk of CV disease.
- 2 Outcome trials have shown that antihypertensive drug therapy substantially reduces the risks of CV events and death in patients with hypertension.
- 3 Essential hypertension is usually an asymptomatic condition. A diagnosis cannot be made based on one elevated BP measurement. Elevated values from the average of two or more measurements on two or more clinical encounters are needed to diagnose hypertension.
- 4 The overall goal of treating hypertension is to reduce hypertension-associated morbidity and mortality from CV events. The selection of specific drug therapy is based on evidence that demonstrates CV risk reduction.
- 5 A goal BP of less than 140/90 mm Hg is appropriate for general prevention of CV events or CV disease. However, achieving BP of less than 130/80 mm Hg goal is recommended in patients with diabetes, significant chronic kidney disease, known coronary artery disease (myocardial infarction, stable angina, unstable angina), noncoronary atherosclerotic vascular disease (ischemic stroke, transient ischemic attack, peripheral arterial disease, abdominal aortic aneurism), or a 10% or greater 10-year risk of fatal coronary heart disease or nonfatal myocardial infarction based on Framingham risk scoring. Patients with left ventricular dysfunction (systolic heart failure) have a BP goal of less than 120/80 mm Hg.
- 6 Lifestyle modifications should be prescribed in all patients with hypertension and prehypertension. However, they should never be used as a replacement for antihypertensive drug therapy in patients with hypertension, especially patients with additional CV risk factors.
- 7 Thiazide-type diuretics have traditionally been classified as first-line agents for treating most patients with hypertension. This recommendation is supported by clinical trials showing reduced CV morbidity and mortality with thiazide diuretic therapy. Comparative data from the landmark Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) confirm the first-line role of thiazide-type diuretics.
- 8 An angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blocker (ARB), or calcium channel blocker (CCB) may be used as first-line agents in patients without compelling indications. Clinical trials have demonstrated that these agents reduce the risk of CV events when used to treat hypertension.
- 9 β -Blockers do not reduce CV events to the extent that thiazide-type diuretics, ACE inhibitors, ARBs, or CCBs do when used as the primary antihypertensive agent in patients with hypertension but without a compelling indication for β -blocker therapy.
- 10 Compelling indications are comorbid conditions where specific drug therapies have been shown in outcome trials to provide unique long-term benefits (reducing the risk of CV events).
- 11 Patients with diabetes are at very high risk for CV events. All patients with diabetes and hypertension should be managed with either an ACE inhibitor or an ARB. These are typically in combination with one or more other antihypertensive agents because multiple agents frequently are needed to lower BP to less than 130/80 mm Hg.
- 12 Older patients with isolated systolic hypertension are often at risk for orthostatic hypotension when antihypertensive drug therapy is started, particularly with diuretics, ACE inhibitors, and ARBs. Although overall treatment should be the same, low initial doses should be used and dosage titrations should be gradual to minimize risk of orthostatic hypotension.
- 13 Alternative antihypertensive agents have not been proven to reduce the risk of CV events compared with first-line antihypertensive agents. They should be used primarily in combination with first-line agents to provide additional BP lowering.
- 14 Hypertensive urgency is ideally managed by adjusting maintenance therapy (adding a new antihypertensive and/or increasing the dose of a present medication). This provides a gradual reduction in BP, which is a safer treatment approach than very rapid reductions in BP.
- 15 Most patients require combination therapy to achieve goal BP values. Combination regimens should include a diuretic, preferably a thiazide-type. If a diuretic was not the first drug used, it should be the second drug add-on therapy for most patients.
- 16 Patients have resistant hypertension when they fail to attain goal BP values while adherent with an appropriate three drug-regimen. This three-drug regimen must include full doses and include a diuretic.

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Hypertension is a common disease that is simply defined as persistently elevated arterial blood pressure (BP). Although elevated BP was perceived to be “essential” for adequate perfusion of essential

organs during the early and middle 1900s, it is now identified as one of the most significant risk factors for cardiovascular (CV) disease. Increasing awareness and diagnosis of hypertension, and improving control of BP with appropriate treatment, are considered critical public health initiatives to reduce CV morbidity and mortality.

The Seventh Report of the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) is the most prominent evidence-based clinical guideline in the United States for the management of hypertension,¹ supplemented by the 2007 American Heart Association (AHA) Scientific Statement on the treatment of hypertension.² This chapter reviews relevant components of these guidelines and additional evidence from clinical trials, with a focus on the pharmacotherapy of hypertension. Data from the National Health and Nutrition Examination Survey from 1999 to 2000 indicate that of the population of Americans with hypertension, 68.9% are aware that they have hypertension, only 58.4% are on some form of antihypertensive treatment, and only 34% of all patients have controlled BP.³ Therefore, there are ample opportunities for clinicians to improve the care of patients with hypertension.

EPIDEMIOLOGY

Approximately 31% of the population (72 million Americans) have high BP ($\geq 140/90$ mm Hg).⁴ The percentage of men with high BP is higher than that of women before the age of 45 years, but between the ages of 45 and 54 years the percentage is slightly higher with women.⁴ After age 55 years, a much higher percentage of women have high BP than men.⁴ Prevalence rates are highest in non-Hispanic blacks (33.5%) followed by non-Hispanic whites (28.9%) and Mexican Americans (20.7%).³

BP values increase with age, and hypertension (persistently elevated BP values) is very common in the elderly. The lifetime risk of developing hypertension among those 55 years of age and older who are normotensive is 90%.¹ Most patients have prehypertension before they are diagnosed with hypertension, with most diagnoses occurring between the third and fifth decades of life. In the population age ≥ 60 years, the prevalence of hypertension in 2000 was estimated at 65.4%, which is significantly higher than the 57.9% prevalence estimated in 1988.³

ETIOLOGY

In most patients, hypertension results from an unknown pathophysiologic etiology (*essential or primary hypertension*). This form of hypertension cannot be cured, but it can be controlled. A small percentage of patients have a specific cause of their hypertension (*secondary hypertension*). There are many potential secondary causes that are either concurrent medical conditions or are endogenously induced. If the cause can be identified, hypertension in these patients has the potential to be cured.

ESSENTIAL HYPERTENSION

More than 90% of individuals with hypertension have essential hypertension.¹ Numerous mechanisms have been identified that may contribute to the pathogenesis of this form of hypertension, so identifying the exact underlying abnormality is not possible. Genetic factors may play an important role in the development of essential hypertension. There are monogenic and polygenic forms of BP dysregulation that may be responsible for essential hypertension.⁵ Many of these genetic traits feature genes that affect sodium balance, but genetic mutations altering urinary kallikrein excretion, nitric oxide release, and excretion of aldosterone, other adrenal

steroids, and angiotensinogen are also documented.⁵ In the future, identifying individuals with these genetic traits could lead to alternative approaches to preventing or treating hypertension; however, this is not currently recommended.

SECONDARY HYPERTENSION

Fewer than 10% of patients have secondary hypertension where either a comorbid disease or drug is responsible for elevating BP (Table 15-1).^{1,6} In most of these cases, renal dysfunction resulting from severe chronic kidney disease or renovascular disease is the most common secondary cause. Certain drugs, either directly or indirectly, can cause hypertension or exacerbate hypertension by increasing BP. Table 15-1 lists the most common agents. Some of these agents are herbal products. Although these are not technically drugs, they have been identified as secondary causes. When a secondary cause is identified, removing the offending agent (when feasible) or treating/correcting the underlying comorbid condition should be the first step in management.

PATHOPHYSIOLOGY^{5,7}

Multiple factors that control BP are potential contributing components in the development of essential hypertension. These include malfunctions in either humoral (i.e., the renin-angiotensin-aldosterone system [RAAS]) or vasodepressor mechanisms, abnormal

TABLE 15-1 Secondary Causes of Hypertension

Diseases	Drugs Associated with Hypertension in Humans ^a
Chronic kidney disease	Prescription drugs
Cushing's syndrome	• Adrenal steroids (e.g., prednisone, fludrocortisone, triamcinolone)
Coarctation of the aorta	• Amphetamines/anorexiant (e.g., phendimetrazine, phentermine, sibutramine)
Obstructive sleep apnea	• Antivascular endothelin growth factor agents (bevacizumab, sorafenib, sunitinib), estrogens (usually oral contraceptives)
Parathyroid disease	• Calcineurin inhibitors (cyclosporine and tacrolimus)
Pheochromocytoma	• Decongestants (phenylpropanolamine and analogs)
Primary aldosteronism	• Erythropoiesis stimulating agents (erythropoietin and darbepoietin)
Renovascular disease	• Nonsteroidal antiinflammatory drugs, cyclooxygenase-2 inhibitors
Thyroid disease	• Others: venlafaxine, bromocriptine, bupropion, buspirone, carbamazepine, clozapine, desulfurane, ketamine, metoclopramide
	Situations: β -blocker or centrally acting α -agonists (when abruptly discontinued); β -blocker without α -blocker first when treating pheochromocytoma
	Street drugs and other natural products
	Cocaine and cocaine withdrawal
	Ephedra alkaloids (e.g., Ma-huang), "herbal ecstasy," other phenylpropanolamine analogs ^a
	Nicotine withdrawal, anabolic steroids, narcotic withdrawal, methylphenidate, phencyclidine, ketamine, ergotamine and other ergot-containing herbal products, St. John's wort
	Food substances
	Sodium
	Ethanol
	Licorice
	Tyramine-containing foods if taking a monoamine oxidase inhibitor

^aAgents of most clinical importance.

Data from Kaplan NM, Kaplan's Clinical Hypertension. 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2002:1-550.

neuronal mechanisms, defects in peripheral autoregulation, and disturbances in sodium, calcium, and natriuretic hormones. Many of these factors are cumulatively affected by the multifaceted RAAS, which ultimately regulates arterial BP. It is probable that none of these factors is solely responsible for essential hypertension; however, most antihypertensives specifically target these mechanisms and components of the RAAS.

ARTERIAL BLOOD PRESSURE

Arterial BP is the pressure in the arterial wall measured in millimeters of mercury (mm Hg). The two typical arterial BP values are *systolic BP* (SBP) and *diastolic BP* (DBP). SBP is achieved during cardiac contraction and represents the peak value. DBP is achieved after contraction when the cardiac chambers are filling, and represents the nadir value. The difference between SBP and DBP is called the pulse pressure and is a measure of arterial wall tension. Mean arterial pressure is the average pressure throughout the cardiac cycle of contraction. It is sometimes used clinically to represent overall arterial BP, especially in hypertensive emergency. During a cardiac cycle, two-thirds of the time is spent in diastole and one-third in systole. Consequently, the mean arterial pressure can be estimated by using the following equation:

$$\text{mean arterial pressure} = (\text{SBP} \times 1/3) + (\text{DBP} \times 2/3)$$

Arterial BP is hemodynamically generated by the interplay between blood flow and the resistance to blood flow. It is mathematically defined as the product of cardiac output and total peripheral resistance according to the following equation:

$$\text{BP} = \text{cardiac output} \times \text{total peripheral resistance}$$

Cardiac output is the major determinant of SBP, whereas total peripheral resistance largely determines DBP. In turn, cardiac output is a function of stroke volume, heart rate, and venous capacitance. Table 15–2 lists physiologic causes of increased cardiac output and total peripheral resistance and correlates them to potential mechanisms of pathogenesis.

Under normal physiologic conditions, arterial BP fluctuates throughout the day. It typically follows a circadian rhythm, where it

TABLE 15-3 Classification of Blood Pressure in Adults (Age ≥18 Years)^a

Classification	Systolic Blood Pressure (mm Hg)	and	Diastolic Blood Pressure (mm Hg)
Normal	<120	and	<80
Prehypertension ^b	120–139	or	80–89
Stage 1 hypertension	140–159	or	90–99
Stage 2 hypertension	≥160	or	≥100

^aClassification determined based on the average of two or more properly measured seated blood pressure measurements from two or more clinical encounters. If systolic and diastolic blood pressure values yield different classifications, the highest category is used for the purpose of determining a classification.

^bFor patients with diabetes mellitus, significant chronic kidney disease, known coronary artery disease (myocardial infarction, stable angina, unstable angina), noncoronary atherosclerotic vascular disease (ischemic stroke, transient ischemic attack, peripheral arterial disease, abdominal aortic aneurism), or a Framingham risk score of 10% or greater, values ≥130/80 mm Hg are considered above goal; patients with left ventricular dysfunction have a blood pressure goal of less than 120/80 mm Hg.

decreases to its lowest daily values during sleep. This is followed by a sharp rise starting a few hours prior to awakening with the highest values occurring midmorning. BP is also increased acutely during physical activity or emotional stress.

Classification

The JNC7 classification of BP in adults (age ≥18 years) is based on the average of two or more properly measured BP readings from two or more clinical encounters (Table 15–3).¹ It includes four categories: normal, prehypertension, stage 1 hypertension, and stage 2 hypertension. Prehypertension is not considered a disease category, but identifies patients whose BP is likely to increase into the classification of hypertension in the future.

Hypertensive crises are clinical situations where BP values are very elevated, typically greater than 180/120 mm Hg.⁷ They are categorized as either a *hypertensive emergency* or *hypertensive urgency*. Hypertensive emergencies are extreme elevations in BP that are accompanied by acute or progressing target-organ damage. Hypertensive urgencies are high elevations in BP without acute or progressing target-organ injury. Recommendations for managing hypertensive crises are described later in this chapter.

1 Cardiovascular Risk and Blood Pressure

Epidemiologic data clearly indicate a strong correlation between BP and CV morbidity and mortality.⁸ Risk of stroke, myocardial infarction, angina, heart failure, kidney failure, or early death from a CV cause are directly correlated with BP. Starting at a BP of 115/75 mm Hg, risk of CV disease doubles with every 20/10 mm Hg increase.¹ Even patients with prehypertension have an increased risk of CV disease.

2 Treating patients with hypertension with antihypertensive drug therapy provides significant benefits. Large-scale, placebo-controlled, outcome trials show that the increased risks of CV events and death associated with elevated BP are reduced substantially by antihypertensive drug therapy.^{9–12}

SBP is a stronger predictor of CV disease than DBP in adults ≥50 years of age and is the most important clinical BP parameter for most patients.¹ Patients with DBP values less than 90 mm Hg and SBP values ≥140 mm Hg have *isolated systolic hypertension*. Isolated systolic hypertension is believed to result from pathophysiologic changes in the arterial vasculature consistent with aging. These changes decrease the compliance of the arterial wall and portend an increased risk of CV morbidity and mortality. Pulse pressure is the difference between the SBP and the DBP. It is believed to reflect extent of atherosclerotic disease in the elderly and is a measure of increased arterial stiffness. Higher pulse pressure values are correlated with an increased risk of CV mortality, especially in those with isolated systolic hypertension.

TABLE 15-2 Potential Mechanisms of Pathogenesis

Blood pressure is the mathematical product of cardiac output and peripheral resistance. Elevated blood pressure can result from increased cardiac output and/or increased total peripheral resistance.	
Increased cardiac output	<p>Increased cardiac preload:</p> <ul style="list-style-type: none"> Increased fluid volume from excess sodium intake or renal sodium retention (from reduced number of nephrons or decreased glomerular filtration) <p>Venous constriction:</p> <ul style="list-style-type: none"> Excess stimulation of the RAAS Sympathetic nervous system overactivity
Increased peripheral resistance	<p>Functional vascular constriction:</p> <ul style="list-style-type: none"> Excess stimulation of the RAAS Sympathetic nervous system overactivity Genetic alterations of cell membranes Endothelial-derived factors <p>Structural vascular hypertrophy:</p> <ul style="list-style-type: none"> Excess stimulation of the RAAS Sympathetic nervous system overactivity Genetic alterations of cell membranes Endothelial-derived factors Hyperinsulinemia resulting from obesity or the metabolic syndrome

RAAS, renin–angiotensin–aldosterone system.

HUMORAL MECHANISMS

Several humoral abnormalities may be involved in the development of essential hypertension. These abnormalities may involve the RAAS, natriuretic hormones, and hyperinsulinemia.

The Renin–Angiotensin–Aldosterone System

The RAAS is a complex endogenous system that is involved with most regulatory components of arterial BP. Activation and regulation are primarily governed by the kidney (Fig. 15–1). The RAAS regulates sodium, potassium, and fluid balance. Consequently, this system significantly influences vascular tone and sympathetic nervous system activity and is the most influential contributor to the homeostatic regulation of BP.

Renin is an enzyme that is stored in the juxtaglomerular cells, which are located in the afferent arterioles of the kidney. The release of renin is modulated by several factors: intrarenal factors (e.g., renal perfusion pressure, catecholamines, angiotensin II), and extrarenal factors (e.g., sodium, chloride, and potassium).

Juxtaglomerular cells function as a baroreceptor-sensing device. Decreased renal artery pressure and kidney blood flow are sensed by these cells and stimulate secretion of renin. The juxtaglomerular apparatus also includes a group of specialized distal tubule cells referred to collectively as the *macula densa*. A decrease in sodium

and chloride delivered to the distal tubule stimulates renin release. Catecholamines increase renin release probably by directly stimulating sympathetic nerves on the afferent arterioles that in turn activate the juxtaglomerular cells. Decreased serum potassium and/or intracellular calcium are detected by the juxtaglomerular cells resulting in renin secretion.

Renin catalyzes the conversion of angiotensinogen to angiotensin I in the blood. Angiotensin I is then converted to angiotensin II by angiotensin-converting enzyme (ACE). After binding to specific receptors (classified as either AT₁ or AT₂ subtypes), angiotensin II exerts biologic effects in several tissues. The AT₁ receptor is located in brain, kidney, myocardium, peripheral vasculature, and the adrenal glands. These receptors mediate most responses that are critical to CV and kidney function. The AT₂ receptor is located in adrenal medullary tissue, uterus, and brain. Stimulation of the AT₂ receptor does not influence BP regulation.

Circulating angiotensin II can elevate BP through pressor and volume effects. Pressor effects include direct vasoconstriction, stimulation of catecholamine release from the adrenal medulla, and centrally mediated increases in sympathetic nervous system activity. Angiotensin II also stimulates aldosterone synthesis from the adrenal cortex. This leads to sodium and water reabsorption that increases plasma volume, total peripheral resistance, and ultimately BP. Aldosterone also has a deleterious role in the pathophysiology of other CV diseases (heart failure, myocardial infarction [MI] and kidney dis-

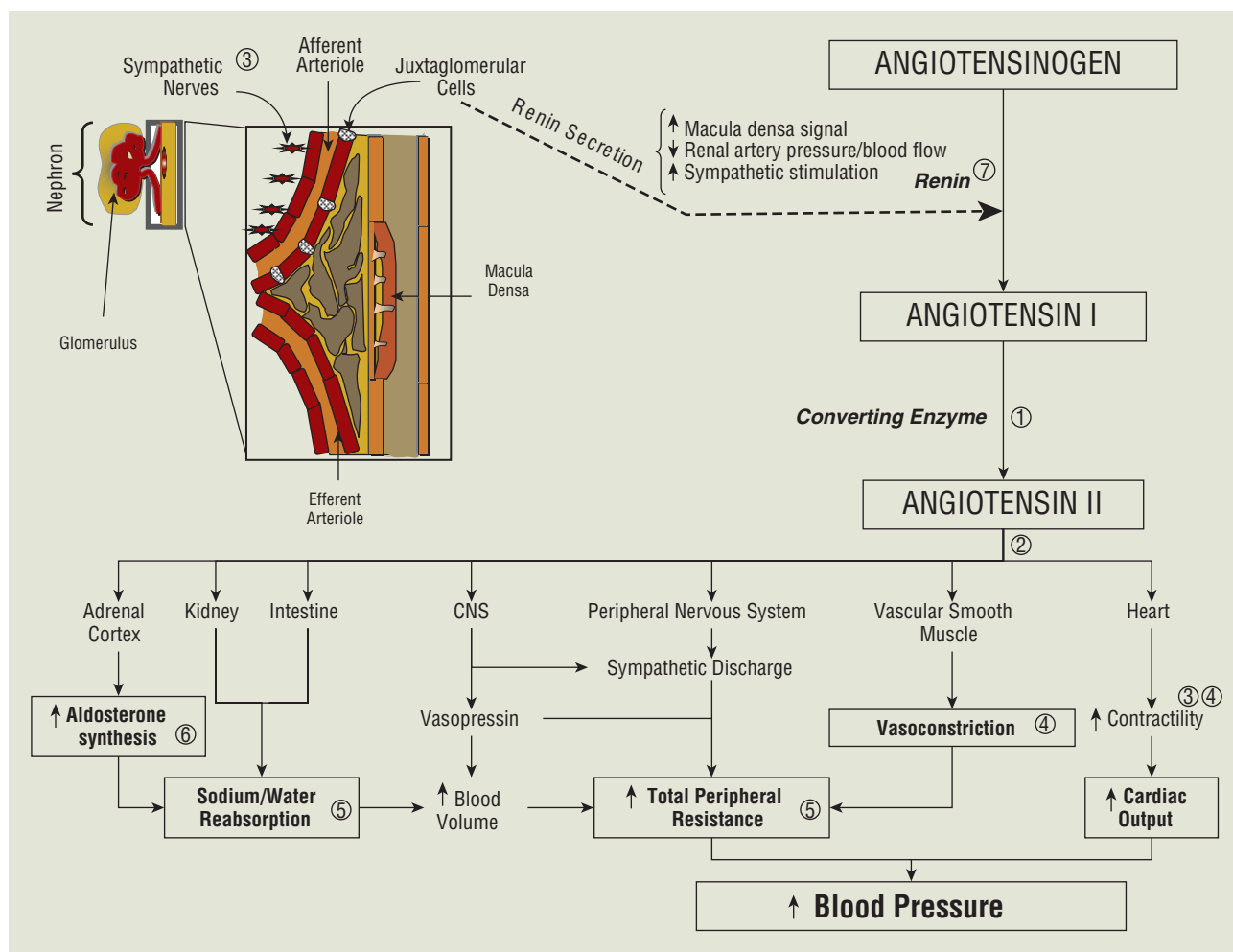


FIGURE 15-1. Diagram representing the renin–angiotensin–aldosterone system. The interrelationship between the kidney, angiotensin II, and regulation of blood pressure are depicted. There are three major regulators of renin secretion from the juxtaglomerular cells in this system. The primary sites of action for major antihypertensive agents are included. (①, angiotensin-converting enzyme inhibitors; ②, angiotensin II receptor blockers; ③, β -blockers; ④, calcium channel blockers; ⑤, diuretics; ⑥, aldosterone antagonists; ⑦, direct renin inhibitor; CNS, central nervous system.)

ease) by promoting tissue remodeling leading to myocardial fibrosis and vascular dysfunction. Clearly, any disturbance in the body that leads to activation of the RAAS could explain chronic hypertension.

The heart and brain contain a local RAAS. In the heart, angiotensin II is also generated by a second enzyme, angiotensin I convertase (human chymase). This enzyme is not blocked by ACE inhibition. Activation of the myocardial RAAS increases cardiac contractility and stimulates cardiac hypertrophy. In the brain, angiotensin II modulates the production and release of hypothalamic and pituitary hormones, and enhances sympathetic outflow from the medulla oblongata.

Peripheral tissues can locally generate biologically active angiotensin peptides, which may explain the increased vascular resistance seen in hypertension. Some evidence suggests that angiotensin produced by local tissue may interact with other humoral regulators and endothelium-derived growth factors to stimulate vascular smooth muscle growth and metabolism. These angiotensin peptides may, in fact, instigate increased vascular resistance in low plasma renin forms of hypertension. Components of the tissue RAAS may also be responsible for the long-term hypertrophic abnormalities seen with hypertension (left ventricular hypertrophy, vascular smooth muscle hypertrophy, and glomerular hypertrophy).

Natriuretic Hormone

Natriuretic hormone inhibits sodium and potassium-adenosine triphosphatase and thus interferes with sodium transport across cell membranes. Inherited defects in the kidney's ability to eliminate sodium can cause an increased blood volume. A compensatory increase in the concentration of circulating natriuretic hormone theoretically could increase urinary excretion of sodium and water. However, this same hormone is also thought to block the active transport of sodium out of arteriolar smooth muscle cells. The increased intracellular sodium concentration ultimately would increase vascular tone and BP.

Insulin Resistance and Hyperinsulinemia

The development of hypertension and associated metabolic abnormalities is referred to as the metabolic syndrome.¹³ Hypothetically, increased insulin concentrations may lead to hypertension because of increased renal sodium retention and enhanced sympathetic nervous system activity. Moreover, insulin has growth hormone-like actions that can induce hypertrophy of vascular smooth muscle cells. Insulin also may elevate BP by increasing intracellular calcium, which leads to increased vascular resistance. The exact mechanism by which insulin resistance and hyperinsulinemia occur in hypertension is unknown. However, this association is strong because many of the criteria used to define this population (elevated BP, abdominal obesity, dyslipidemia, and elevated fasting glucose) are often present in patients with hypertension.¹³

NEURONAL REGULATION

Central and autonomic nervous systems are intricately involved in the regulation of arterial BP. A number of receptors that either enhance or inhibit norepinephrine release are located on the presynaptic surface of sympathetic terminals. The α and β presynaptic receptors play a role in negative and positive feedback to the norepinephrine-containing vesicles located near the neuronal ending. Stimulation of presynaptic α -receptors (α_2) exerts a negative inhibition on norepinephrine release. Stimulation of presynaptic β -receptors facilitates norepinephrine release.

Sympathetic neuronal fibers located on the surface of effector cells innervate the α - and β -receptors. Stimulation of postsynaptic α -receptors (α_1) on arterioles and venules results in vasoconstriction. There are two types of postsynaptic β -receptors, β_1 and β_2 .

Both are present in all tissue innervated by the sympathetic nervous system. However, in some tissues β_1 -receptors predominate and in other tissues β_2 -receptors predominate. Stimulation of β_1 -receptors in the heart results in an increase in heart rate and contractility, whereas stimulation of β_2 -receptors in the arterioles and venules causes vasodilation.

The baroreceptor reflex system is the major negative-feedback mechanism that controls sympathetic activity. Baroreceptors are nerve endings lying in the walls of large arteries, especially in the carotid arteries and aortic arch. Changes in arterial pressure rapidly activate baroreceptors that then transmit impulses to the brainstem through the ninth cranial nerve and vagus nerves. In this reflex system, a decrease in arterial BP stimulates baroreceptors, causing reflex vasoconstriction and increased heart rate and force of cardiac contraction. These baroreceptor reflex mechanisms may be blunted (less responsive to changes in BP) in the elderly and those with diabetes.

Stimulation of certain areas within the central nervous system (nucleus tractus solitarius, vagal nuclei, vasomotor center, and the area postrema) can either increase or decrease BP. For example, α_2 -adrenergic stimulation within the central nervous system decreases BP through an inhibitory effect on the vasomotor center. However, angiotensin II increases sympathetic outflow from the vasomotor center, which increases BP.

The purpose of these neuronal mechanisms is to regulate BP and maintain homeostasis. Pathologic disturbances in any of the four major components (autonomic nerve fibers, adrenergic receptors, baroreceptors, or central nervous system) could conceivably lead to chronically elevated BP. These systems are physiologically interrelated. A defect in one component may alter normal function in another, and such cumulative abnormalities may then explain the development of essential hypertension.

PERIPHERAL AUTOREGULATORY COMPONENTS

Abnormalities in renal or tissue autoregulatory systems could cause hypertension. It is possible that a renal defect in sodium excretion may first develop, which can then cause resetting of tissue autoregulatory processes resulting in a higher arterial BP. The kidney usually maintains normal BP through a volume-pressure adaptive mechanism. When BP drops, the kidneys respond by increasing retention of sodium and water. These changes lead to plasma volume expansion that increases BP. Conversely, when BP rises above normal, renal sodium and water excretion are increased to reduce plasma volume and cardiac output. This ultimately will maintain homeostatic BP conditions.

Local autoregulatory processes maintain adequate tissue oxygenation. When tissue oxygen demand is normal to low, the local arteriolar bed remains relatively vasoconstricted. However, increases in metabolic demand trigger arteriolar vasodilation that lowers peripheral vascular resistance and increases blood flow and oxygen delivery through autoregulation.

Intrinsic defects in these renal adaptive mechanisms could lead to plasma volume expansion and increased blood flow to peripheral tissues, even when BP is normal. Local tissue autoregulatory processes that vasoconstrict would then be activated to offset the increased blood flow. This effect would result in increased peripheral vascular resistance, and if sustained, would also result in thickening of the arteriolar walls. This pathophysiologic component is plausible because increased total peripheral resistance is a common underlying finding in patients with essential hypertension.

VASCULAR ENDOTHELIAL MECHANISMS

Vascular endothelium and smooth muscle play important roles in regulating blood vessel tone and BP. These regulating functions are

mediated through vasoactive substances that are synthesized by endothelial cells. It has been postulated that a deficiency in the local synthesis of vasodilating substances (prostacyclin and bradykinin) or excess vasoconstricting substances (angiotensin II and endothelin I) contribute to essential hypertension, atherosclerosis, and other CV diseases.

Nitric oxide is produced in the endothelium, relaxes the vascular epithelium, and is a very potent vasodilator. The nitric oxide system is an important regulator of arterial BP. Patients with hypertension may have an intrinsic deficiency in nitric oxide, resulting in inadequate vasodilation.

ELECTROLYTES AND OTHER CHEMICALS

Epidemiologic and clinical data have associated excess sodium intake with hypertension. Population-based studies indicate that high salt diets are associated with a high prevalence of stroke and hypertension. Conversely, low salt diets are associated with a low prevalence of hypertension. Clinical studies consistently show that dietary sodium restriction lowers BP in many (but not all) patients with elevated BP. The exact mechanisms by which excess sodium leads to hypertension are unknown. However, they may be linked to increased circulating natriuretic hormones, which would inhibit intracellular sodium transport causing increased vascular reactivity and increased BP.

Altered calcium homeostasis also may play an important role in the pathogenesis of hypertension. A lack of dietary calcium hypothetically can disturb the balance between intracellular and extracellular calcium, resulting in an increased intracellular calcium concentration. This imbalance can alter vascular smooth muscle function by increasing peripheral vascular resistance. Some studies show that dietary calcium supplementation results in a modest BP reduction in patients with hypertension.

The role of potassium fluctuations is also inadequately understood. Potassium depletion may increase peripheral vascular resistance, but the clinical significance of small serum potassium concentration changes is unclear. Furthermore, data demonstrating reduced CV risk with dietary potassium supplementation is very limited.

CLINICAL PRESENTATION

CLINICAL PRESENTATION OF HYPERTENSION

General

- The patient may appear very healthy, or may have the presence of additional CV risk factors:
 - Age (≥ 55 years for men and 65 years for women)
 - Diabetes mellitus
 - Dyslipidemia (elevated low-density lipoprotein-cholesterol, total cholesterol, and/or triglycerides; low high-density lipoprotein-cholesterol)
 - Microalbuminuria
 - Family history of premature CV disease
 - Obesity (body mass index ≥ 30 kg/m²)
 - Physical inactivity
 - Tobacco use

Symptoms

- Most patients are asymptomatic.

Signs

- Previous BP values in the prehypertension or hypertension category.

Laboratory Tests

- Blood urea nitrogen/serum creatinine, fasting lipid panel, fasting blood glucose, serum electrolytes, spot urine albumin-to-creatinine ratio. The patient may have normal values and still have hypertension. However, some may have abnormal values consistent with either additional CV risk factors or hypertension-related damage.

Other Diagnostic Tests

- 12-lead electrocardiogram (to detect left ventricular hypertrophy), estimated glomerular filtration rate (using Modification of Diet in Renal Disease equation).
- 10-year risk of fatal coronary heart disease or non-fatal myocardial infarction, based on Framingham scoring.

Target-Organ Damage

- The patient may have a previous medical history or diagnostic findings that indicate the presence of hypertension-related target-organ damage:
 - Brain (stroke, transient ischemic attack)
 - Eyes (retinopathy)
 - Heart (left ventricular hypertrophy, angina or prior MI, prior coronary revascularization, heart failure)
 - Kidney (chronic kidney disease)
 - Peripheral vasculature (peripheral arterial disease)

3 DIAGNOSTIC CONSIDERATIONS

Hypertension is termed the “silent killer” because most patients do not have symptoms. The primary physical finding is elevated BP. The diagnosis of hypertension cannot be made based on one elevated BP measurement. The average of two or more measurements taken during two or more clinical encounters should be used to diagnose hypertension.¹ Thereafter, this BP average can be used to establish a diagnosis, and then classify the stage of hypertension present using Table 15–3.

Measuring Blood Pressure

Indirect measurement of BP using a sphygmomanometer is a common routine medical screening tool that should be conducted at every healthcare encounter.¹

Sphygmomanometry—American Heart Association Procedure¹⁴ The appropriate procedure to measure BP has been described by the AHA.¹⁴ It is imperative that the measurement equipment (inflation cuff, stethoscope, manometer) meet certain national standards to ensure maximum quality and precision with the auscultatory measurement of BP.

The AHA stepwise technique is recommended:

- Patients should refrain from nicotine or caffeine ingestion for 30 minutes and be seated with the lower back supported in a chair and with their bare arm supported and resting near heart level. Feet should be flat on the floor (with legs not crossed). Measuring BP in the supine or standing position may be required under special circumstances (suspected orthostatic hypotension, volume depletion, or dehydration). The measurement environment should be relatively quiet and provide privacy.
- Measurement should begin only after a 5-minute period of rest.
- A properly sized cuff (pediatric, small, regular, large, or extra large) should be used. If the cuff is too small, the measured BP can be overestimated. The inflatable rubber bladder inside the cuff should encircle at least 80% of the arm of the upper arm in length and 40% in width.

- The palpatory method should be used to estimate the SBP:
 - Place the cuff on the upper arm 2 to 3 cm above the antecubital fossa and attach it to the manometer (either a mercury or aneroid)
 - Close the inflation valve with the thumb and index finger, and inflate the cuff to 70 mm Hg
 - Simultaneously palpate the radial pulse with the index and middle fingers of the opposite hand
 - Inflate in increments of 10 mm Hg by pumping the inflation bulb (as it is resting in the palm of your hand) with the pinky, ring, and middle fingers (the last three) until the radial pulse disappears
 - Note the pressure at which radial pulse disappears; this is the estimated SBP
 - Release pressure from the cuff by turning the valve counter-clockwise
- The bell (not the diaphragm) of the stethoscope should be placed on the skin of the antecubital fossa, directly over where the brachial artery is palpated. The stethoscope earpieces should be inserted appropriately. The valve should be closed with the cuff then inflated rapidly to about 30 mm Hg above the estimated SBP from the palpatory method. The valve should be only slightly opened to release pressure at a very slow rate of 2 to 3 mm Hg per second.
- The clinician should listen for Korotkoff sounds with the stethoscope. The first phase of Korotkoff sounds are the initial presence of clear tapping sounds. Note the pressure at the first recognition of these sounds. This is the SBP. As pressure continues to deflate, note the pressure when all sounds disappear (also known as the fifth Korotkoff phase). This is the DBP.
- Measurements should be taken to the nearest 2 mm Hg.
- A second measurement should be obtained after a minimum of 1 minute, and the average should be documented. If these values differ by more than 5 mm Hg, additional measurements should be collected and averaged.
- Neither the patient nor the observer should talk during measurement.
- At the first visit, BP should be measured in both arms. When consistent interarm differences exist, the higher number should be used for diagnostic and treatment purposes.

It is recommended that the stethoscope bell, rather than the diaphragm, be used for measurement, although some studies suggest little difference between two.¹⁴ Low-frequency Korotkoff sounds, however, may not be heard clearly and accurately with the diaphragm. This is especially problematic in patients with faint or “distant” sounds.

Inaccuracies with indirect measurements result from inherent biologic variability of BP, inaccuracies related to suboptimal technique, and the white coat effect.¹⁴ Variations in BP occur with environmental temperature, the time of day and year, meals, physical activity, posture, alcohol, nicotine, and emotions. In the clinic setting, standard BP measurement procedures (e.g., appropriate rest period, poor technique, minimal number of measurements) are often not followed, which results in poor estimation of true BP. Approximately 15% to 20% of patients have *white coat hypertension*, where BP values rise in a clinical setting but return to normal in nonclinical environments using home or ambulatory BP measurements.¹⁴ Interestingly, the rise in BP dissipates gradually over several hours after leaving the clinical setting. It may or may not be precipitated by other stresses in the patient’s daily life.

CLINICAL CONTROVERSY

Aggressive treatment of white coat hypertension is controversial. However, patients with white coat hypertension may have increased CV risk compared with those without such BP changes.¹⁵

Several additional factors can result in erroneous BP measurements. *Pseudohypertension* is a falsely elevated BP measurement. It may be seen in the elderly, those with long-standing diabetes, or in those with chronic kidney disease caused by rigid, calcified brachial arteries.¹⁴ In these patients, the true arterial BP when measured directly with intraarterial measurement (the most accurate measurement of BP) is much lower than that measured using the indirect cuff method. The Osler maneuver can be used to test for pseudohypertension. In this maneuver, the BP cuff is inflated above peak SBP. If the radial artery remains palpable, the patient has a positive Osler sign (rigid artery), which may indicate pseudohypertension.

Elderly patients with a wide pulse pressure may have an auscultatory gap which can lead to underestimated SBP or overestimated DBP measurements.¹⁴ In this situation, as the cuff pressure falls from the true SBP value, the Korotkoff sound may disappear (indicating a false DBP measurement), reappear (a false SBP measurement), and then disappear again at the true DBP value. This is often identified by using the palpatory method to estimate SBP and then inflating the cuff an additional 30 mm Hg above this estimate because the “gap” is usually less than 30 mm Hg. When an auscultatory gap is present, Korotkoff sounds are usually heard when pressure in the cuff first starts to decrease after inflation. This may be eliminated by raising the arm overhead for 30 seconds before bringing it to the proper position and inflating the cuff. This maneuver decreases the intravascular volume and improves inflow thereby allowing Korotkoff sounds to be heard.¹⁴

Patients with irregular ventricular heart rates (e.g., atrial fibrillation, atrial flutter) may have misleading BP values when measured indirectly. In this situation, SBP and DBP values may vary from one heartbeat to the next.

Ambulatory and Self Blood Pressure Monitoring

Ambulatory BP monitoring using an automated device can document BP at frequent time intervals (e.g., every 15 to 30 minutes) throughout a 24-hour period.¹⁴ Ambulatory BP values are usually lower than clinic-measured values. The upper limit for normal ambulatory BP is 140/90 mm Hg during the day, 125/75 mm Hg at night, and 135/85 mm Hg during 24 hours. Home BP measurements are collected by patients, preferably in the morning, using home monitoring devices. Either of these may be warranted in patients with suspected white coat hypertension (without hypertension-related target-organ damage) to differentiate white coat from essential hypertension.¹ Moreover, ambulatory BP monitoring may be helpful in patients with apparent drug resistance, hypotensive symptoms while on antihypertensive therapy, episodic hypertension (e.g., white coat hypertension), autonomic dysfunction, and to identify “nondippers” whose BP does not decrease by >10% during sleep and which may portend increased risk of BP-related complications.^{1,14}

Some data suggest that 24-hour and home BP measurements correlate better with CV risk than do conventional office-based BP measurements.^{14,16} However, one controlled study found that ambulatory BP and self BP monitoring are complementary to conventional clinic-based measurements.¹⁷ Limitations of these measurements that may prohibit routine use of such technology include lack of validated devices, complexity of use, costs, and lack of prospective outcomes data describing normal ranges for these measurements. Although self-monitoring of BP at home is less complicated and less costly than ambulatory monitoring, patients may omit or fabricate readings. Thus, devices that have a memory or printouts are recommended.¹⁴

CLINICAL EVALUATION

Frequently, the only sign of essential hypertension is elevated BP. The rest of the physical examination may be completely normal. However, a complete medical evaluation (a comprehensive medical history, physical examination, and laboratory and/or diagnostic tests) is recommended after diagnosis to (a) identify secondary causes, (b) identify other CV risk factors or comorbid conditions that may define prognosis and/or guide therapy, and (c) assess for the presence or absence of hypertension-associated target-organ damage.¹ All patients with hypertension should have the following measured prior to initiating therapy: 12-lead electrocardiogram; spot urine albumin-to-creatinine ratio; blood glucose and hematocrit; serum potassium, creatinine (with estimated glomerular filtration rate [GFR]), and calcium; and a fasting lipid panel.^{1,18} For patients without a history of coronary artery disease, noncoronary atherosclerotic vascular disease (also referred to as coronary artery disease risk equivalents), left ventricular dysfunction, or diabetes, it is also important to estimate a 10-year risk of fatal coronary heart disease or nonfatal myocardial infarction using Framingham Risk scoring (http://www.nhlbi.nih.gov/guidelines/cholesterol/risk_tbl.htm).²

Secondary Causes

Table 15–1 lists the most common secondary causes of hypertension. A complete medical evaluation may provide clues for identifying secondary hypertension.

Patients with secondary hypertension may complain of symptoms suggestive of the underlying disorder, but some are asymptomatic. Patients with pheochromocytoma may have a history of paroxysmal headaches, sweating, tachycardia, and palpitations. Over half of these patients suffer from episodes of orthostatic hypotension. In primary aldosteronism, symptoms related to hypokalemia usually include muscle cramps and muscle weakness. Patients with Cushing's syndrome may complain of weight gain, polyuria, edema, menstrual irregularities, recurrent acne, or muscular weakness and have several classic physical features (e.g., moon face, buffalo hump, hirsutism, abdominal striae). Patients with coarctation of the aorta may have diminished or even absent femoral pulses, and patients with renal artery stenosis may have an abdominal systolic–diastolic bruit.

Routine laboratory tests may also help identify secondary hypertension. Baseline hypokalemia may suggest mineralocorticoid-induced hypertension. Protein, blood cells, and casts in the urine may indicate renovascular disease. Some laboratory tests are used specifically to diagnose secondary hypertension. These include plasma norepinephrine and urinary metanephrine for pheochromocytoma, plasma and urinary aldosterone concentrations for primary aldosteronism, and plasma renin activity, captopril stimulation test, and renal artery angiography for renovascular disease.

Certain medications and herbal products can result in drug-induced hypertension (see Table 15–1). For some patients, the addition of these agents can be the cause of hypertension or can exacerbate underlying hypertension. Identifying a temporal relationship between starting the suspected agent and developing elevated BP is most suggestive of drug-induced BP elevation.

NATURAL COURSE OF DISEASE

Essential hypertension is usually preceded by elevated BP values that are in the prehypertension category. BP values may fluctuate between elevated and normal levels for an extended period of time. These changes may begin as early as the second decade of life. During this stage, many patients have a hyperdynamic circulation with increased cardiac output and normal or even low peripheral vascular resistance. As the disease progresses, peripheral vascular resistance increases, and BP elevation is sustained to the point where essential hypertension is diagnosed.

Target-Organ Damage

Target-organ damage (see Clinical Presentation of Hypertension above) can develop as a complication of hypertension. The primary organs involved are the eye, brain, heart, kidneys, and peripheral blood vessels. Clinical CV events (e.g., MI, stroke, kidney failure) are clinical end points of target-organ damage and are the primary causes of CV morbidity and mortality in patients with hypertension. The probability of CV events and CV morbidity and mortality in patients with hypertension is directly correlated with the severity of BP elevation and additional CV risk factors.

Hypertension accelerates atherosclerosis and stimulates left ventricular and vascular hypertrophy. These pathologic changes are thought to be secondary to both a chronic pressure overload and a variety of nonhemodynamic stimuli. Some of the nonhemodynamic disturbances that have been implicated in these effects include the adrenergic system, RAAS, increased synthesis and secretion of endothelin I, and a decreased production of prostacyclin and nitric oxide. Accelerated atherogenesis in hypertension is accompanied by proliferation of smooth muscle cells, lipid infiltration into the vascular endothelium, and an enhancement of vascular calcium accumulation.

Cerebrovascular disease is a consequence of hypertension. A neurologic assessment can detect either gross neurologic deficits or a slight hemiparesis with some incoordination and hyperreflexia that are indicative of cerebrovascular disease. Stroke can result from lacunar infarcts caused by thrombotic occlusion of small vessels or intracerebral hemorrhage resulting from ruptured microaneurysms. Transient ischemic attacks secondary to atherosclerotic disease in the carotid arteries are possible long-term complications of hypertension.

Retinopathies can occur in hypertension and may manifest as a variety of different findings. A fundoscopic examination can detect hypertensive retinopathy and can be categorized according to the Keith-Wagener-Barker retinopathy classification. Retinopathy manifests as arteriolar narrowing, focal arteriolar constrictions, arteriovenous crossing changes (nicking), retinal hemorrhages and exudates, and disk edema. Accelerated arteriosclerosis, a long-term consequence of essential hypertension, can cause nonspecific changes such as increased light reflex, increased tortuosity of vessels, and arteriovenous nicking. Focal arteriolar narrowing, retinal infarcts, and flame-shaped hemorrhages usually are suggestive of accelerated or malignant phase of hypertension. Papilledema is swelling of the optic disk and is caused by a breakdown in autoregulation of capillary blood flow in the presence of high pressure. It is usually only present in hypertensive emergencies.

Heart disease is the best identified form of target-organ damage. A thorough cardiac and pulmonary examination can identify cardiopulmonary abnormalities. Clinical manifestations include left ventricular hypertrophy, coronary heart disease (angina, prior MI, and prior coronary revascularization), and heart failure. These complications may lead to cardiac arrhythmias, angina, MI, and sudden death. Coronary disease (also called coronary heart disease or coronary artery disease) and associated CV events are the most common causes of death in patients with hypertension.

The kidney damage caused by hypertension is characterized pathologically by hyaline arteriosclerosis, hyperplastic arteriosclerosis, arteriolar hypertrophy, fibrinoid necrosis, and atheroma of the major renal arteries. Glomerular hyperfiltration and intraglomerular hypertension are early stages of hypertensive nephropathy. Microalbuminuria is followed by a gradual decline in renal function. The primary renal complication in hypertension is nephrosclerosis, which is secondary to arteriosclerosis. Atheromatous disease of a major renal artery may give rise to renal artery stenosis. Although overt kidney failure is an uncommon complication of essential hypertension, it is an important cause of end-stage kidney disease, especially in African Americans, Hispanics, and Native Americans. It is not completely understood why these ethnic groups are more at risk for kidney decline than other ethnic groups.

The peripheral vasculature is a target organ. Physical examination of the vascular system can detect evidence of atherosclerosis, which may present as arterial bruits (aortic, abdominal, or peripheral), distended veins, diminished or absent peripheral arterial pulses, or lower-extremity edema. Peripheral arterial disease is a clinical condition that can result from atherosclerosis, which is accelerated in hypertension. Other CV risk factors (e.g., smoking) can increase the likelihood of peripheral arterial disease as well as all other forms of target-organ damage.

TREATMENT

Hypertension

■ DESIRED OUTCOMES

④ Overall Goal of Therapy

The overall goal of treating hypertension is to reduce hypertension-associated morbidity and mortality.¹ This morbidity and mortality is related to target-organ damage (e.g., CV events, heart failure, and kidney disease). Reducing risk remains the primary purpose of hypertension therapy and the specific choice of drug therapy is significantly influenced by evidence demonstrating such risk reduction.

⑤ Surrogate Goal of Therapy

Treating patients with hypertension to achieve a desired target BP value is simply a surrogate goal of therapy. Reducing BP to goal does not guarantee that target-organ damage will not occur. However, attaining goal BP values is associated with lower risk of CV disease and target-organ damage.^{1,19} Targeting a goal BP value is a tool that clinicians can easily use to evaluate response to therapy and is the primary method used to determine the need for titration and regimen modification.

Most patients have a goal BP of less than 140/90 mm Hg for the general prevention of CV events or CV disease (e.g., coronary artery disease).^{1,2} However, this goal is lowered to less than 130/80 mm Hg for patients with diabetes, significant chronic kidney disease, known coronary artery disease (myocardial infarction, stable angina, unstable angina), noncoronary atherosclerotic vascular disease (ischemic stroke, transient ischemic attack, peripheral arterial disease, abdominal aortic aneurism), or a 10% or greater 10-year risk of fatal coronary heart disease or nonfatal myocardial infarction based on Framingham risk scoring (http://www.nhlbi.nih.gov/guidelines/cholesterol/risk_tbl.htm).² Moreover, patients with left ventricular dysfunction (heart failure) have a BP goal of less than 120/80 mm Hg.²

GOAL BLOOD PRESSURE VALUES RECOMMENDED BY THE AMERICAN HEART ASSOCIATION IN 2007²

- | | |
|---|---------------|
| • Most patients for general prevention | <140/90 mm Hg |
| • Patients with diabetes (referred to as coronary artery disease risk equivalent), significant chronic kidney disease, known coronary artery disease (myocardial infarction, stable angina, unstable angina), noncoronary atherosclerotic vascular disease (ischemic stroke, transient ischemic attack, peripheral arterial disease, abdominal aortic aneurism [referred to as coronary artery disease risk equivalents]), or a Framingham risk score of 10% or greater | <130/80 mm Hg |
| • Patients with left ventricular dysfunction (heart failure) | <120/80 mm Hg |

Significant chronic kidney disease is considered to be moderate-to-severe chronic kidney disease, defined as estimated GFR <60 mL/min/1.73 m² (correlating to a serum creatinine >1.3 mg/dL in women and >1.5 in men) or albuminuria (>300 mg/day or >200 mg/g creatinine).

Framingham risk score is calculated using the risk calculator available at http://www.nhlbi.nih.gov/guidelines/cholesterol/risk_tbl.htm

Some clinicians advocate attaining BP goal values that are lower than what is recommended as a modality to further reduce CV risk following the myth that “lower is better.” Contrary to this, a *J-curve hypothesis*, where lowering BP too much might increase the risk of CV events, has been described.²⁰ However, these data are based off of observational studies and cannot establish a cause-and-effect relationship because of confounding variables.

Lower goal BP values have been evaluated prospectively in the Hypertension Optimal Treatment (HOT) trial.¹⁹ In this study, more than 18,700 patients were randomized to target DBP values of 90 mm Hg or less, 85 mm Hg or less, or 80 mm Hg or less. Although the actual DBP values achieved were 85.2, 83.2, and 81.1 mm Hg, respectively, the risk of major CV events was the lowest with a BP of 139/83 mm Hg, and the lowest risk of stroke was with a BP of 142/80 mm Hg. Risk of events in subjects with either diabetes or ischemic heart disease were lowest at DBP values of less than 80 mm Hg. No J-curve relationship was seen.

CLINICAL CONTROVERSY

There is increasing evidence suggesting that ambulatory BP measurements may be more accurate and better predict target-organ damage than manual BP measurements using a sphygmomanometer in a clinic setting (considered the gold standard).¹⁴ Studies document that large numbers of individuals may be misdiagnosed or misclassified based on clinic BP measurements as a result of a variety of factors such as poor technique, daily variability of BP, and white coat hypertension. Validated ambulatory BP monitoring may obviate some of these factors, but their role in the routine management of hypertension is unclear.

■ AVOIDING CLINICAL INERTIA

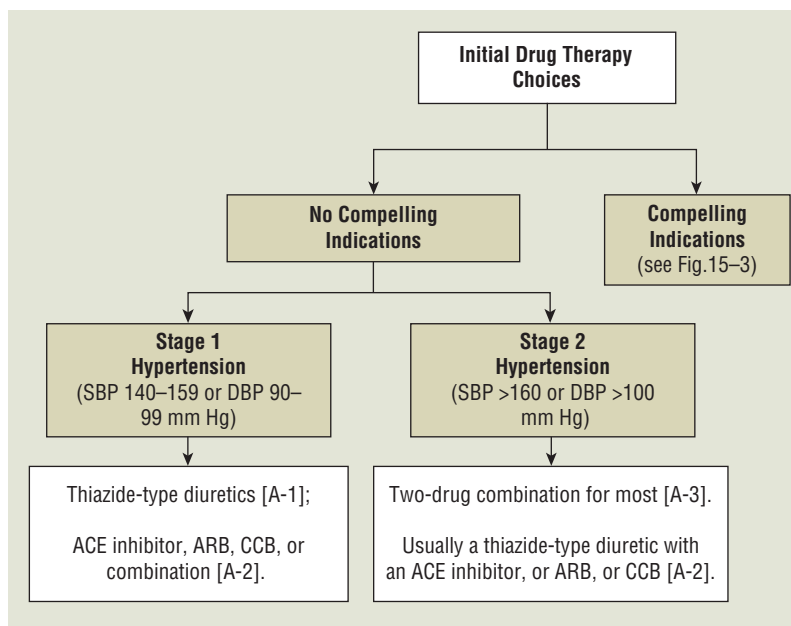
Although hypertension is one of the most common medical conditions, BP control rates are poor. Many patients, especially older patients, with hypertension are at goal DBP values but continue to have elevated SBP values. It has been estimated that of the hypertensive population that is treated, yet not controlled, 76.9% have SBP ≥140 mm Hg with DBP values less than 90 mm Hg.²¹ For most patients with hypertension, attaining the SBP goal almost always assures achievement of the DBP goal. When coupled with the fact that SBP is a better predictor of CV risk than DBP, SBP must be used as the primary clinical marker of disease control in hypertension.

Clinical inertia in hypertension has been defined as an office visit at which no therapeutic move was made to lower BP in a patient with uncontrolled hypertension.²² Clinical inertia is not the entire reason why most patients with hypertension do not have at-goal BP values. However, it is certainly a major reason that can be simply remedied through more aggressive treatment with drug therapy. This can involve initiating, titrating, or changing drug therapy.

■ GENERAL APPROACH TO TREATMENT

After a definitive diagnosis of hypertension is made, most patients should be placed on both lifestyle modifications and drug therapy concurrently. Lifestyle modification alone is considered appropriate therapy for patients with prehypertension. However, lifestyle modi-

FIGURE 15-2. Algorithm for treatment of hypertension. Drug therapy recommendations are graded with strength of recommendation and quality of evidence in brackets. Strength of recommendations: A, B, C = good, moderate, and poor evidence to support recommendation, respectively. Quality of evidence: 1 = Evidence from more than 1 properly randomized, controlled trial. 2 = Evidence from at least one well-designed clinical trial with randomization; from cohort or case-controlled analytic studies; or dramatic results from uncontrolled experiments or subgroup analyses. 3 = Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert communities. (ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure.) (Adapted from references 1 and 2.)



fications alone are not considered adequate for patients with hypertension and additional CV risk factors, especially patients with BP goals of less than 130/80 mm Hg (e.g., diabetes, coronary artery disease, chronic kidney disease) or less than 120/80 mm Hg (i.e., left ventricular dysfunction), who have not attained this goal BP.

The choice of initial drug therapy depends on the degree of BP elevation and presence of compelling indications (see Patients with Compelling Indications section). Most patients with stage 1 hypertension should be initially treated with a thiazide-type diuretic, ACE inhibitor, ARB, or CCB. For patients with more severe BP elevation (stage 2 hypertension), combination drug therapy, with one of the agents being preferably a thiazide type-diuretic, is recommended. Figure 15-2 outlines this general approach. There are six compelling indications where specific antihypertensive drug classes have evidence showing unique benefits in patients with the compelling indication (Fig. 15-3).

■ 6 NONPHARMACOLOGIC THERAPY

All patients with prehypertension and hypertension should be prescribed lifestyle modifications. Table 15-4 lists modifications that lower BP. These approaches are recommended by the JNC7 and the AHA.^{1,23} They can provide small to moderate reductions in SBP. Aside from lowering BP in patients with known hypertension, lifestyle modification can decrease the progression to hypertension in patients with prehypertension BP values.²³ In a portion of patients with hypertension that have relatively good BP control while on single antihypertensive drug therapy, sodium reduction and weight loss may allow withdrawal of drug therapy.²⁴

A sensible dietary program is one that is designed to reduce weight gradually, for overweight and obese patients, and one that restricts sodium intake with only moderate alcohol consumption. Successful implementation of dietary lifestyle modifications by clinicians requires aggressive promotion through reasonable patient education, encouragement, and continued reinforcement. Patients may better understand the rationale for dietary intervention in hypertension if they are provided the following observations and facts²³:

1. Hypertension is two to three times more likely in overweight than in lean persons.
2. More than 60% of patients with hypertension are overweight.

3. As little as 10 pounds of weight loss can decrease BP significantly in overweight patients.
4. Abdominal obesity is associated with the metabolic syndrome, which is a precursor to diabetes, dyslipidemia, and, ultimately, CV disease.¹³
5. Diets rich in fruits and vegetables and low in saturated fat lower BP in patients with hypertension.
6. Most people experience some degree of SBP reduction with sodium restriction.

The Dietary Approaches to Stop Hypertension (DASH) eating plan is a diet that is rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat. It is advocated by the JNC7 as a reasonable and feasible diet that is proven to lower BP. Intake of sodium should be minimized as much as possible, ideally to 1.5 g/day, although an interim goal of less than 2.3 g/day may be reasonable considering the difficulty in achieving these low intakes. Patients should be aware of the multiple sources of dietary sodium (e.g., processed foods, soups, table salt) so that they may follow these recommendations. Potassium intake should be encouraged through fruits and vegetables with high content (ideally 4.7 g/day) in those with normal kidney function. Excessive alcohol use can either cause or worsen hypertension. Patients with hypertension who drink alcoholic beverages should restrict their daily intake (see Table 15-4). Patients should be counseled that 1 drink is equivalent to 1.5 oz of 80-proof distilled spirits (e.g., whiskey), a 5 oz glass of wine (12%), or 12 oz of beer.²³

Carefully designed programs of physical activity can lower BP. Regular physical activity for at least 30 minutes most days of the week is recommended for all adults, with at least 60 minutes recommended for adults attempting to lose weight or maintain weight loss.²⁵ Studies show that aerobic exercise can reduce BP, even in the absence of weight loss. Patients should consult their physicians before starting an exercise program, especially those with CV and/or target-organ disease.

Cigarette smoking is a major, independent, modifiable risk factor for CV disease. Patients with hypertension who smoke should be thoroughly counseled regarding the additional health risks that result from smoking. Moreover, the potential benefits that cessation can provide should be explained to encourage cessation. Several smoking-cessation programs, pharmacotherapy options, and aids are available to assist patients.

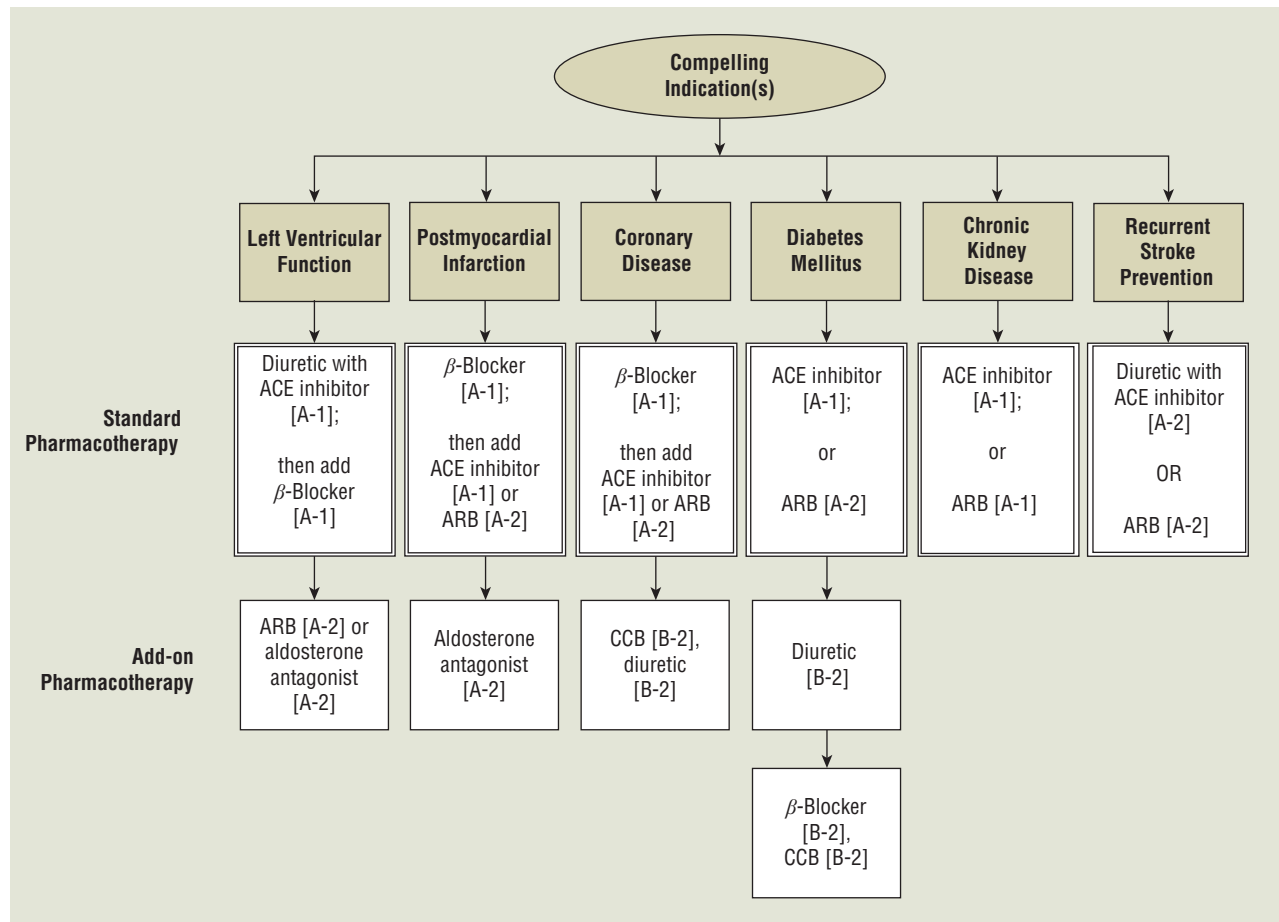


FIGURE 15-3. Compelling indications for individual drug classes. Compelling indications for specific drugs are evidence-based recommendations from outcome studies or existing clinical guidelines. The order of drug therapies serves as a general guidance that should be balanced with clinical judgment and patient response; however, standard pharmacotherapy should be considered first-line recommendations, preferably in the order depicted. Add-on pharmacotherapy recommendations then are intended to be used to further reduce risk of cardiovascular events and to lower blood pressure to goal values. Blood pressure control should be managed concurrently with the compelling indication. Drug therapy recommendations are graded with strength of recommendation and quality of evidence in brackets. Strength of recommendations: A, B, C = good, moderate, and poor evidence to support recommendation, respectively. Quality of evidence: 1 = Evidence from more than one properly randomized, controlled trial. 2 = Evidence from at least one well-designed clinical trial with randomization; from cohort or case-controlled analytic studies or multiple time series; or dramatic results from uncontrolled experiments or subgroup analyses. 3 = Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert communities. (ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.) (Adapted from references 1, 2, 58, and 74.)

■ PHARMACOTHERAPY

A diuretic (primarily a thiazide-type), ACE inhibitor, angiotensin II receptor blocker (ARB), or calcium channel blocker (CCB) are considered primary antihypertensive agents that are acceptable first-line options (Table 15–5). These agents should be used to treat the majority of patients with hypertension because evidence from out-

comes data have demonstrated CV risk reduction benefits with these classes. Several have subclasses where significant differences in mechanism of action, clinical use, side effects, or evidence from outcomes studies exist. β -Blockers are effective antihypertensive agents that previously were considered primary agents. They are now preferred either to treat a specific compelling indication, or in combination with one of the aforementioned primary antihypertensive agents for

TABLE 15-4 Lifestyle Modifications to Prevent and Manage Hypertension

Modification	Recommendation	Approximate Systolic Blood Pressure Reduction (mm Hg) ^a
Weight loss	Maintain normal body weight (body mass index 18.5–24.9 kg/m ²)	5–20 per 10-kg weight loss
DASH-type dietary patterns	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat	8–14
Reduced salt intake	Reduce daily dietary sodium intake as much as possible, ideally to \approx 65 mmol/day (1.5 g/day sodium, or 3.8 g/day sodium chloride)	2–8
Physical activity	Regular aerobic physical activity (at least 30 min/day, most days of the week)	4–9
Moderation of alcohol intake	Limit consumption to \leq 2 drinks/day in men and \leq 1 drink/day in women and lighter-weight persons	2–4

DASH, Dietary Approaches to Stop Hypertension.

^aEffects of implementing these modifications are time and dose dependent and could be greater for some patients.

Data from Chobanian et al.,¹ and Kostis et al.²⁴

TABLE 15-5 Primary Antihypertensive Agents

Class	Subclass	Drug (Brand Name)	Usual Dose Range (mg/day)	Daily Frequency	Comments
Diuretics	Thiazides	Chlorthalidone (Hygroton)	12.5–25	1	Dose in the morning to avoid nocturnal diuresis; thiazides are more effective antihypertensives than loop diuretics in most patients; use usual doses to minimize adverse metabolic effects; ideally maintain potassium concentration between 4.0–5.0 mEq/L to minimize metabolic effects; hydrochlorothiazide and chlorthalidone are generally preferred, with 25 mg/day generally considered the maximum effective dose; chlorthalidone is nearly twice as potent as hydrochlorothiazide; have additional benefits in osteoporosis; may require additional monitoring in patients with a history of gout or hyperglycemia
		Hydrochlorothiazide (Microzide)	12.5–25	1	
		Indapamide (Lozol)	1.25–2.5	1	
		Metolazone (Zaroxolyn)	2.5–5	1	
	Loops	Bumetanide (Bumex)	0.5–4	2	Dose in the morning and afternoon to avoid nocturnal diuresis; higher doses may be needed for patients with severely decreased glomerular filtration rate or left ventricular dysfunction
		Furosemide (Lasix)	20–80	2	
		Torsemide (Demadex)	5–10	1	
	Potassium sparing	Amiloride (Midamor)	5–10	1 or 2	Dose in the morning or afternoon to avoid nocturnal diuresis; weak diuretics that are generally used in combination with thiazide-type diuretics to minimize hypokalemia; avoid in patients with severe chronic kidney disease (estimated glomerular filtration rate <30 mL/min/1.73 m ²); may cause hyperkalemia, especially in combination with an ACE inhibitor, ARB, direct renin inhibitor or potassium supplements
		Amiloride/hydrochlorothiazide (Moduretic)	5–10/50–100	1	
		Triamterene (Dyrenium)	50–100	1 or 2	
		Triamterene/hydrochlorothiazide (Dyazide)	37.5–75/25–50	1	
	Aldosterone antagonists	Eplerenone (Inspra)	50–100	1 or 2	Dose in the morning or afternoon to avoid nocturnal diuresis; eplerenone contraindicated in patients with an estimated creatinine clearance <50 mL/min, elevated serum creatinine (>1.8 mg/dL in women, >2 mg/dL in men), and type 2 diabetes with microalbuminuria; avoid spironolactone in patients with chronic kidney disease (estimated glomerular filtration rate <30 mL/min/1.73 m ²); may cause hyperkalemia, especially in combination with an ACE inhibitor, ARB, direct renin inhibitor or potassium supplements
		Spironolactone (Aldactone)	25–50	1 or 2	
		Spironolactone/hydrochlorothiazide (Aldactazide)	25–50/25–50	1	
ACE inhibitors		Benazepril (Lotensin)	10–40	1 or 2	Starting dose may be reduced 50% in patients who are on a diuretic, are volume depleted, or are very elderly because of risks of hypotension; may cause hyperkalemia in patients with chronic kidney disease or in those receiving potassium-sparing diuretics, aldosterone antagonists, ARB, or direct renin inhibitors; can cause acute kidney failure in patients with severe bilateral renal artery stenosis or severe stenosis in artery to solitary kidney; do not use in pregnancy or in patients with a history of angioedema
		Captopril (Capoten)	25–150	2 or 3	
		Enalapril (Vasotec)	5–40	1 or 2	
		Fosinopril (Monopril)	10–40	1	
		Lisinopril (Prinivil, Zestril)	10–40	1	
		Moexipril (Univasc)	7.5–30	1 or 2	
		Perindopril (Aceon)	4–16	1	
		Quinapril (Accupril)	10–80	1 or 2	
		Ramipril (Altace)	2.5–10	1 or 2	
		Trandolapril (Mavik)	1–4	1	
ARBs		Candesartan (Atacand)	8–32	1 or 2	Starting dose may be reduced 50% in patients who are on a diuretic, are volume depleted, or are very elderly because of risks of hypotension; may cause hyperkalemia in patients with chronic kidney disease or in those receiving potassium-sparing diuretics, aldosterone antagonists, ACE inhibitors, or direct renin inhibitor; can cause acute kidney failure in patients with severe bilateral renal artery stenosis or severe stenosis in artery to solitary kidney; do not cause a dry cough like ACE inhibitors may; do not use in pregnancy
		Eprosartan (Teveten)	600–800	1 or 2	
		Irbesartan (Avapro)	150–300	1	
		Losartan (Cozaar)	50–100	1 or 2	
		Olmesartan (Benicar)	20–40	1	
		Telmisartan (Micardis)	20–80	1	
		Valsartan (Diovan)	80–320	1	
Calcium channel blockers	Dihydropyridines	Amlodipine (Norvasc)	2.5–10	1	Short-acting dihydropyridines should be avoided, especially immediate-release nifedipine and nicardipine; dihydropyridines are more potent peripheral vasodilators than nondihydropyridines and may cause more reflex sympathetic discharge (tachycardia), dizziness, headache, flushing, and peripheral edema; have additional benefits in Raynaud's syndrome
		Felodipine (Plendil)	5–20	1	
		Isradipine (DynaCirc)	5–10	2	
		Isradipine SR (DynaCirc SR)	5–20	1	
		Nicardipine SR (Cardene SR)	60–120	2	
		Nifedipine long-acting (Adalat CC, Procardia XL)	30–90	1	
		Nisoldipine (Sular)	10–40	1	

(continued)

TABLE 15-5 Primary Antihypertensive Agents (continued)

Class	Subclass	Drug (Brand Name)	Usual Dose Range (mg/day)	Daily Frequency	Comments
β -Blockers	Nondihydropyridines	Diltiazem SR (Cardizem SR)	180–360	2	Extended-release and sustained-release products are preferred for hypertension; these agents block slow channels in the heart and reduce heart rate; may produce heart block, especially in combination with β -blockers; these products are not AB rated as interchangeable on a equipotent mg-per-mg basis because of different release mechanisms and different bioavailability parameters; Cardizem LA, Covera HS, and Verelan PM have delayed drug release for several hours after dosing; when dosed in the evening can provide chronotherapeutic drug delivery starting shortly before patients awake from sleep; have additional benefits in patients with atrial tachyarrhythmia
		Diltiazem SR (Cardizem CD, Cartia XT, Dilacor XR, Diltia XT, Tiazac, Taztia XT)	120–480	1	
		Diltiazem ER (Cardizem LA)	120–540	1 (morning or evening)	
		Verapamil SR (Calan SR, Isoptin SR, Verelan)	180–480	1 or 2	
		Verapamil ER (Covera HS)	180–420	1 (in the evening)	
		Verapamil oral drug absorption system ER (Verelan PM)	100–400	1 (in the evening)	
	Cardioselective	Atenolol (Tenormin)	25–100	1	Abrupt discontinuation may cause re-bound hypertension; inhibit β_1 -receptors at low to moderate dose, higher doses also block β_2 -receptors; may exacerbate asthma when selectivity is lost; have additional benefits in patients with atrial tachyarrhythmia or preoperative hypertension
		Betaxolol (Kerlone)	5–20	1	
		Bisoprolol (Zebeta)	2.5–10	1	
		Metoprolol tartrate (Lopressor)	100–400	2	
		Metoprolol succinate (Toprol XL)	50–200	1	
	Nonselective	Nadolol (Corgard)	40–120	1	Abrupt discontinuation may cause rebound hypertension; inhibit β_1 - and β_2 -receptors at all doses; can exacerbate asthma; have additional benefits in patients with essential tremor, migraine headache, thyrotoxicosis
		Propranolol (Inderal)	160–480	2	
		Propranolol long-acting (Inderal LA, InnoPran XL)	80–320	1	
		Timolol (Blocadren)	10–40	1	
	Intrinsic sympathomimetic activity	Acebutolol (Sectral)	200–800	2	Abrupt discontinuation may cause rebound hypertension; partially stimulate β -receptors while blocking against additional stimulation; no clear advantage for these agents; contraindicated in patients with coronary disease or post-myocardial infarction
		Carteolol (Cartrol)	2.5–10	1	
		Penbutolol (Levitol)	10–40	1	
		Pindolol (Visken)	10–60	2	
	Mixed α - and β -blockers	Carvedilol (Coreg)	12.5–50	2	Abrupt discontinuation may cause rebound hypertension; additional α -blockade produces more orthostatic hypotension
		Carvedilol phosphate (Coreg CR)	20–80	1	
		Labetalol (Normodyne, Trandate)	200–800	2	

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ER, extended-release; SR, sustained-release.

patients without a compelling indication. Other antihypertensive drug classes are considered alternative drug classes that may be used in select patients after primary agents (Table 15–6).

CLINICAL CONTROVERSY

Prehypertension is a BP classification that identifies patients who do not have hypertension, but are at risk for developing it. The Trial of Preventing Hypertension (TROPHY) showed that treating patients with prehypertension with the ARB candesartan decreased progression to stage 1 hypertension.²⁶ However, it is not known whether managing prehypertension with antihypertensive drug therapy, in addition to lifestyle modifications, decreases CV events or whether this treatment approach is cost-effective.

7 Thiazide-Type Diuretics as Traditional First-Line Therapy for Most Patients

JNC7 guidelines recommend thiazide-type diuretics whenever possible, as first-line therapy for most patients, which is consistent with the traditional pharmacotherapy of hypertension.¹ However, AHA guidelines do not recommend thiazide-type diuretics as preferred over an ACE inhibitor, ARB, or CCB for first-line therapy. Figure 15–2 displays the algorithm for the treatment of hypertension. This recommendation is specifically for patients without compelling indications and is based on best available evidence demonstrating reductions in CV morbidity and mortality.

Landmark placebo-controlled clinical trials—SHEP (Systolic Hypertension in the Elderly Program),⁹ STOP (Swedish Trial in Old Patients),¹⁰ and MRC (Medical Research Council)¹¹—showed significant reductions in stroke, MI, all-cause CV disease, and mortality with thiazide-type diuretic-based therapy versus placebo. These trials allowed for β -blockers as add-on therapy for BP control. Newer agents (ACE inhibitors, ARBs, and CCBs) were not available at the time of these studies. However, subsequent clinical trials have compared these newer antihypertensive agents to thiazide-type diuretics.^{27–32} These data show similar effects, but most trials used a prospective open-label, blinded end point study methodology that is not double-blinded and limited their ability to prove equivalence of newer drugs to diuretics. Other prospective trials have compared different primary antihypertensive agents to each other.^{29,33,34} Although these studies used head-to-head comparisons, they did not use a thiazide-type diuretic as their comparator treatment. Consequently, their results cannot be easily used to justify an antihypertensive drug class other than a thiazide-type diuretic as first-line therapy.

The ALLHAT Study³⁰ The result of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was the deciding evidence that the JNC7 used to justify thiazide-type diuretics as first-line therapy.³⁰ It was designed to test the hypothesis that newer antihypertensive agents (an α -blocker, ACE inhibitor, or dihydropyridine CCB) would be superior to thiazide-type diuretic-based therapy. The primary objective was to compare the combined end point of fatal coronary heart disease and nonfatal MI. Other hypertension-related complications (e.g., heart failure,

TABLE 15-6 Alternative Antihypertensive Agents

Class	Drug (Brand Name)	Usual Dose Range (mg/day)	Daily Frequency	Comments
α_1 -Blockers	Doxazosin (Cardura)	1–8	1	First dose should be given at bedtime; counsel patients to rise from a sitting or laying position slowly to minimize risk of orthostatic hypotension; have additional benefits in men with benign prostatic hyperplasia
	Prazosin (Minipress)	2–20	2 or 3	
	Terazosin (Hytrin)	1–20	1 or 2	
Direct renin inhibitor	Aliskiren (Tekturna)	150–300	1	May cause hyperkalemia in patients with chronic kidney disease and diabetes or in those receiving a potassium-sparing diuretic, aldosterone antagonist, ACE inhibitor, or ARB; may cause acute kidney failure in patients with severe bilateral renal artery stenosis or severe stenosis in artery to solitary kidney; do not use in pregnancy
Central α_2 -agonists	Clonidine (Catapres)	0.1–0.8	2	Abrupt discontinuation may cause rebound hypertension; most effective if used with a diuretic to diminish fluid retention; clonidine patch is replaced once per week; not recommended in very elderly
	Clonidine patch (Catapres-TTS)	0.1–0.3	1 weekly	
	Methyldopa (Aldomet)	250–1000	2	
Peripheral adrenergic antagonist	Reserpine (generic only)	0.05–0.25		A very useful agent that has been used in many of the major clinical trials; should be used with a diuretic to diminish fluid retention
Direct arterial vasodilators	Minoxidil (Loniten)	10–40	1 or 2	Should be used with diuretic and β -blocker to diminish fluid retention and reflex tachycardia
	Hydralazine (Apresoline)	20–100	2 to 4	

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

stroke) were evaluated as secondary end points. This was the largest hypertension trial ever conducted and included 42,418 patients ages 55 and older with hypertension and one additional CV risk factor. This prospective, double-blind trial randomized patients to chlorthalidone-, amlodipine-, doxazosin-, or lisinopril-based therapy for a mean of 4.9 years.

The doxazosin arm was terminated early when a significantly higher risk of heart failure versus chlorthalidone was observed.³⁵ The other arms were continued as scheduled and no significant differences in the primary end point were seen between the chlorthalidone and lisinopril or amlodipine treatment groups. However, chlorthalidone had statistically fewer secondary end points than amlodipine (heart failure) and lisinopril (combined CV disease, heart failure, and stroke). The study conclusions were that chlorthalidone-based therapy was superior in preventing one or more major forms of CV disease and was less expensive than amlodipine or lisinopril-based therapy.

ALLHAT was designed as a superiority study with the hypothesis that amlodipine, doxazosin, and lisinopril would be better than chlorthalidone.³⁶ It did not prove this hypothesis because the primary end point was no different between chlorthalidone, amlodipine, and lisinopril. Many subgroup analyses of specific populations (e.g., black patients, chronic kidney disease, diabetes) from the ALLHAT have been conducted to assess response in certain unique patient populations.^{37–39} Surprisingly, none of these analyses demonstrated superior CV event reductions with lisinopril or amlodipine versus chlorthalidone. Overall, thiazide-type diuretics remain unsurpassed in their ability to reduce CV morbidity and mortality in most patients.

Most patients require two or more agents to control BP. Therefore, a thiazide-type diuretic should be one of these agents unless contraindicated.

8 Other First-Line Treatment Options for Most Patients

Clinical trials data cumulatively demonstrate that ACE inhibitor-, CCB-, or ARB-based antihypertensive therapy reduces CV events. These agents may be used in patients without compelling indications, similarly to thiazide-type diuretics, as first-line therapy. The Blood Pressure Lowering Treatment Trialists' Collaboration evaluated the incidence of major CV events and death among different antihypertensive drug classes from 29 major randomized trials in 162,341 patients.⁴⁰ In placebo-controlled trials, the incidences of major CV events were significantly lower with ACE inhibitor- and CCB-based regimens than with placebo. Although there were differ-

ences in the incidences of certain CV events in some comparisons (e.g., stroke was lower with diuretic- or CCB-based regimens versus ACE inhibitor-based regimens), there were no differences in total major CV events when ACE inhibitors, CCBs, or diuretics were compared to each other. In studies evaluating ARB-based therapy to control regimens, the incidence of major CV events was lower with ARB-based regimens. However, the control regimens used in these comparisons included both active antihypertensive drug therapies and placebo.

Data from meta-analyses may not be as influential as data from well-designed, prospective, randomized, controlled trials (e.g., the ALLHAT). However, they provide clinically useful data that support using ACE inhibitor-, CCB-, or ARB-based treatment for hypertension as first-line therapy. Clinicians can use meta-analyses data as supporting evidence when selecting an alternative first-line antihypertensive regimen for hypertension in most patients, in addition to the 2007 AHA recommendations.⁴¹

Other major consensus guidelines recommend multiple first-line options for treating hypertension in most patients. The 2007 European Society of Hypertension–European Society of Cardiology guidelines and the 2006 United Kingdom's National Institute for Health and the Clinical Excellence guidelines list more than one drug therapy option as an acceptable first-line treatment approach.^{42,43} The European Society of Hypertension–European Society of Cardiology guidelines are founded on the principle that CV risk reduction is a function of BP control that is largely independent of specific antihypertensives.⁴² The United Kingdom guidelines stratify patients based on age and race; they recommend an ACE inhibitor first-line for patients younger than age 55 years, and either a CCB or thiazide-type diuretic first-line for patients age 55 years or older and for black patients.⁴³

9 β -Blockers versus Other First-Line Drug Therapies

Clinical trials data cumulatively suggests that β -blockers may not reduce CV events to the extent that ACE inhibitors, CCBs, or ARBs do. These data are from three meta-analyses of clinical trials evaluating β -blocker-based therapy for hypertension.^{44–47} Overall, these analyses demonstrated fewer reductions in CV events with β -blocker-based antihypertensive therapy compared mostly with ACE inhibitor- and CCB-based therapy. Although comparative data with ARB-based therapy are more limited, a similar trend was observed.

Meta-analyses data evaluating β -blockers and their ability to reduce CV events have limitations. Most studies that were included used atenolol as the β -blocker studied. Thus it is possible that atenolol is the only β -blocker that does not reduce risk of CV events as well as the other primary antihypertensive drug classes. However,

it is acceptable to extrapolate these findings to the β -blocker drug class in general. Interestingly, the 2006 United Kingdom guidelines recommend a β -blocker only after other primary antihypertensive agents (thiazide-type diuretics, CCBs, ACE inhibitors, or ARBs) have been used. These findings also call in question the validity of results from prominent prospective, controlled clinical trials evaluating antihypertensive drug therapy that use β -blocker–based therapy, especially atenolol, as the primary comparator.^{29,34,47}

β -Blocker therapy in patients without compelling indications still has a prominent role in the management of hypertension. It is important for clinicians to remember that β -blocker–based antihypertensive therapy does not increase risk of CV events; β -blocker–based therapy reduces risk of CV events compared to no antihypertensive therapy. Using a β -blocker as a primary antihypertensive agent is optimal when a thiazide-type diuretic, ACE inhibitor, ARB, or CCB cannot be used as the primary agent. Additionally, using a β -blocker in a young patient with hypertension that is thought to have high adrenergic drive, as evidenced by an elevated heart rate, may still be clinically reasonable.⁴⁶ β -Blockers still have an important role as an alternative add-on agent to reduce BP in patients with hypertension but without compelling indications.

10 Patients with Compelling Indications¹

The JNC7 report identifies six compelling indications. Compelling indications represent specific comorbid conditions where evidence from clinical trials supports using specific antihypertensive classes to treat both the compelling indication and hypertension (see Fig. 15–3). Data from these clinical trials demonstrate a reduction in CV morbidity and/or mortality that justifies use in patients with hypertension and with such a compelling indication. Some compelling indications include recommendations that are provided by other national treatment guidelines, or from newer clinical trials, which are complementary to the JNC7 guidelines.

Left Ventricular Dysfunction: Systolic Heart Failure⁴⁸ Five drug classes are listed as compelling indications for heart failure. These recommendations specifically refer to left ventricular dysfunction (also known as systolic heart failure), where the primary physiologic abnormality is decreased cardiac output. ACE inhibitor with diuretic therapy is recommended as the first-line regimen of choice. ACE inhibitor therapy is recommended based on numerous outcome studies showing reduced CV morbidity and mortality⁴⁸; diuretics are also a part of this first-line regimen because they provide symptomatic relief of edema by inducing diuresis. Loop diuretics are often needed, especially in patients with more advanced disease. Patients with left ventricular dysfunction have a BP goal of less than 120/80 mm Hg, so multiple drug therapies are typically needed.

Evidence from clinical trials shows that ACE inhibitors significantly modify disease progression by reducing morbidity and mortality. Although left ventricular dysfunction was the primary disease in these studies, ACE inhibitor therapy will also control BP. ACE inhibitors should be started with low-doses in patients with heart failure, especially those in acute exacerbation. Heart failure induces a compensatory high renin condition, and starting ACE inhibitors under these conditions can cause a pronounced first-dose effect and possible orthostatic hypotension.

β -Blocker therapy is appropriate to further modify disease in left ventricular dysfunction, and is a component of this first-line regimen (standard therapy) for these patients. In patients on an initial regimen of diuretics and ACE inhibitors, β blockers reduce CV morbidity and mortality.^{49,50} It is of paramount importance that β -blockers be dosed appropriately because of the risk of inducing an acute exacerbation of heart failure. They must be started in very low doses, doses much lower than that used to treat hypertension, and titrated slowly to high-doses based on tolerability. Bisoprolol,

carvedilol, and metoprolol succinate are the only β -blockers proven to be beneficial in left ventricular dysfunction.⁴⁸

After diuretics, ACE inhibitors, and β -blockers (collectively considered standard therapy), other agents may be added to further reduce CV morbidity and mortality, and reduce BP if needed. Early data suggested that ARBs may be better than ACE inhibitors in left ventricular dysfunction.⁵¹ However, when directly compared in a well-designed prospective trial, ACE inhibitors were found to be better.⁵² ARBs are acceptable as an alternative therapy for patients who cannot tolerate ACE inhibitors, and possibly as add-on therapy to those already on a standard three-drug regimen based on data from the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) studies.^{53,54}

The addition of aldosterone antagonists can reduce CV morbidity and mortality in left ventricular dysfunction.^{55,56} Spironolactone has been studied in severe left ventricular dysfunction and has shown benefit in addition to diuretic and ACE inhibitor therapy.⁵⁵ Eplerenone has been studied in patients with symptomatic left ventricular dysfunction within 3 to 14 days after an acute MI in addition to standard therapy.⁵⁶ An aldosterone antagonist may be considered in addition to a diuretic, ACE inhibitor or ARB, and β -blocker. It is not currently recommended to use both an aldosterone inhibitor and an ARB as add-on therapy to a standard therapy, because of the potential increase in risk of severe hyperkalemia.⁴⁸

Post-Myocardial Infarction⁵⁷ β -Blocker (those without intrinsic sympathomimetic activity [ISA]) and ACE inhibitor therapy are recommended in the AHA/American College of Cardiology and JNC7 guidelines.^{1,2,57} β -Blockers decrease cardiac adrenergic stimulation and reduce the risk of a subsequent MI or sudden cardiac death, as demonstrated in clinical trials. ACE inhibitors improve cardiac remodeling, cardiac function, and reduce CV events post-MI. These two drug classes, with β -blockers first, are considered the first drugs of choice for patients who have experienced a MI. One study, the Valsartan in Acute Myocardial Infarction Trial (VALLIANT), demonstrated that ARB therapy is similar to ACE inhibitor therapy in patients post-MI with left ventricular dysfunction.⁵⁸ However, ARBs are considered alternatives to ACE inhibitors in post-MI patients with left ventricular dysfunction. These patients have coronary artery disease, and have a BP goal of less than 130/80 mm Hg. Framingham risk scoring is not needed.

Eplerenone reduces CV morbidity and mortality in patients soon after an acute MI (within 3 to 14 days).⁵⁶ However, this supporting evidence was in patients with symptoms of acute left ventricular dysfunction. Considering that this drug has the propensity to cause significant hyperkalemia and the patient population studied, eplerenone should only be used in selected patients following a MI with very diligent monitoring of potassium.

Coronary Artery Disease^{57,59} Chronic stable angina and acute coronary syndrome (unstable angina and acute MI) are forms of coronary disease (also called coronary artery disease or ischemic heart disease). This compelling indication is also referred to as high coronary disease risk and high CV disease risk in the JNC7 report.¹ These are the most common forms of hypertension-associated target-organ disease. β -Blocker therapy has the most evidence demonstrating benefits in these patients. β -Blockers (those without ISA) are first-line therapy in chronic stable angina and have the ability to reduce BP, improve myocardial oxygen consumption and decrease demand. These patients have coronary artery disease, and have a BP goal of less than 130/80 mm Hg. Framingham risk scoring is not needed.

Long-acting CCBs are either alternatives (the nondihydropyridine CCBs diltiazem and verapamil) or add-on therapy (dihydropyridine CCBs) to β -blockers in chronic stable angina.⁵⁹ The International Verapamil-Trandolapril Study (INVEST) demonstrated no difference in CV risk reduction when β -blocker–based therapy was compared to

nondihydropyridine CCB-based therapy in this population.⁶⁰ Nonetheless, the preponderance of data are with β -blockers and they remain therapy of choice.^{1,2,57,59}

For acute coronary syndromes (ST-elevation MI and unstable angina/non-ST-segment MI), first-line therapy should consist of a β -blocker and ACE inhibitor.^{61,62} This regimen will lower BP, control acute ischemia, and reduce CV risk.

CCBs (especially nondihydropyridine CCBs) and β -blockers provide antiischemic effects; they lower BP and reduce myocardial oxygen demand in patients with hypertension and coronary disease. However, cardiac stimulation may occur with dihydropyridine CCBs or β -blockers with ISA, making these agents less desirable. Consequently, β -blockers with ISA should be avoided, nondihydropyridine CCBs should be alternatives to β -blockers, and dihydropyridines should be add-on therapy to β -blockers.

Once ischemic symptoms are controlled with β -blocker and/or CCB therapy, other antihypertensive drugs can be added to provide additional CV risk reduction. Clinical trials have demonstrated that the addition of an ACE inhibitor, or alternatively an ARB further reduces risk CV events in patients with chronic stable angina.⁶³ Thiazide-type diuretics can be added thereafter to provide additional BP lowering and to further reduce CV risk. Neither ACE inhibitors, nor thiazide-type diuretics provide anti-ischemic effects.

There has been concern that overtreating high BP in patients with coronary artery disease may bring about more harm than good (termed the *J-curve phenomenon*). Coronary blood flow occurs during diastole and the rate of flow is directly influenced by the DBP. Therefore, excessively reducing DBP may compromise coronary perfusion, especially in patients with fixed coronary artery stenosis, and lead to myocardial infarction. This concern has been theoretical based on retrospective analyses, and prospective studies have not found a J-curve until DBPs were very low (<60 mm Hg).

Diabetes Mellitus^{1,64–67} The primary cause of mortality in diabetes is CV disease, and hypertension management is a very important risk-reduction strategy. The BP goal in diabetes is less than 130/80 mm Hg. Diabetes is considered a coronary artery disease risk equivalent and Framingham risk scoring is not needed. Five antihypertensive agents have evidence supporting their compelling indications in diabetes (see Fig. 15–3). All of these agents have been shown to reduce CV events in patients with diabetes. However, risk reduction may not be equal when comparing these agents.

① All patients with diabetes and hypertension should be treated with either an ACE inhibitor or an ARB.⁶⁴ Pharmacologically, both of these agents should provide nephroprotection as a result of vasodilation in the efferent arteriole of the kidney. Moreover, ACE inhibitors have overwhelming data demonstrating CV risk reduction in patients with established forms of heart disease. Evidence from outcome studies have demonstrated reductions in both CV risk (mostly with ACE inhibitors) and reduction in risk of progressive kidney dysfunction (mostly with ARBs) in patients with diabetes.⁶⁴ There is controversy surrounding which agent is better because data support both drug classes. Nonetheless, either drug class should be used to control BP as one of the drugs in the antihypertensive regimen for patients with diabetes because multiple agents are often needed to attain goal BP values.

A thiazide-type diuretic is recommended as the second agent to lower BP and provide additional CV risk-reduction. A subgroup analysis of patients with diabetes from the ALLHAT trial showed no difference in long term risk of CV events in the chlorthalidone and lisinopril treatment groups.³⁸ Therefore, some argue that thiazide-type diuretics, used in low-doses, are equally effective in patients with hypertension and diabetes. Nonetheless, the entire body of evidence evaluating pharmacotherapy in patients with hypertension and diabetes, and consensus guidelines, support an ACE inhibitor or ARB first-line, with a thiazide-type diuretic as add-on therapy.^{1,64,65}

CCBs are useful add-on agents for BP control in patients with diabetes. Several studies have compared an ACE inhibitor with either a dihydropyridine CCB or a β -blocker. In the studies comparing a dihydropyridine with an ACE inhibitor, the ACE inhibitor group had significantly lower rates of CV end points, including MIs and all CV events.⁶⁷ These data do not suggest that CCBs are harmful in diabetic patients, but indicate that they are not as protective as ACE inhibitors. Although data are limited, nondihydropyridine CCBs (diltiazem and verapamil) appear to have more renal protective effects than the dihydropyridines.⁶⁵

β -Blockers reduce CV risk in patients with diabetes. These agents should be used when needed as add-on therapy with other standard agents, or to treat another compelling indication (e.g., post-MI). β -Blockers have been shown in at least one study to be as effective as ACE inhibitors in protection against morbidity and mortality in patients with diabetes.⁶⁶

β -Blockers (especially nonselective agents) may mask the signs and symptoms of hypoglycemia in patients with tightly controlled diabetes because most of the symptoms of hypoglycemia (i.e., tremor, tachycardia, and palpitations) are mediated through the sympathetic nervous system. Sweating, a cholinergically mediated symptom of hypoglycemia, should still occur during a hypoglycemic episode despite β -blocker therapy. Patients may also have a delay in hypoglycemia recovery time because compensatory recovery mechanisms need the catecholamine inputs that are antagonized by β -blocker therapy. Finally, unopposed α -receptor stimulation during the acute hypoglycemic recovery phase (as a consequence of endogenous epinephrine release intended to reverse hypoglycemia) may result in acutely elevated BP because of vasoconstriction. Despite these potential problems, β -blockers can be safely used in patients with diabetes.

Based on the weight of all evidence, ACE inhibitors or ARBs are preferred first-line agents for treating patients with hypertension and diabetes. The need for combination therapy should be anticipated, and thiazide-type diuretics should be the second agent added. Based on scientific evidence, β -blockers and CCBs are useful evidence-based agents in this population, but are considered add-on therapies to the aforementioned agents.

Chronic Kidney Disease⁶⁸ Patients with hypertension may develop damage to either the renal tissue (parenchyma) or the renal arteries. Chronic kidney disease initially presents as microalbuminuria (30 to 299 mcg/mg albumin-to-creatinine ratio on a spot urine sample or ≥ 30 mg albumin in a 24-hour urine collection) that can progress to overt kidney failure. The rate of kidney function deterioration is accelerated when both hypertension and diabetes are present. Once patients have an estimated GFR of less than 60 mL/min/1.73 m² or albuminuria, they have significant chronic kidney disease and the risk of CV disease and progression to severe chronic kidney disease increases.¹ Strict BP control to a goal of less than 130/80 mm Hg can slow the decline in kidney function. Although this strict BP goal is recommended in significant chronic kidney disease, long-term benefits of this lower BP goal have mostly been demonstrated in patients with both significant chronic kidney disease and diabetes.⁶⁹ This strict control often requires two or more antihypertensive agents.

In addition to lowering BP, ACE inhibitors and ARBs reduce intraglomerular pressure, which can theoretically provide additional benefits by further reducing the decline in kidney function. ACE inhibitors and ARBs have been shown to reduce progression of chronic kidney disease in diabetes⁶⁴ and in those without diabetes.^{65,70} It is difficult to differentiate whether the kidney protection benefits are from RAAS blockade or BP lowering. A recent meta-analysis failed to demonstrate any unique long-term kidney-protective effects of RAAS-blocking drugs compared with other antihypertensive drugs.⁷¹ Moreover, a subgroup analysis of patients from the ALLHAT stratified by different baseline GFR values also did not show a difference in long-term outcomes with chlorthalidone versus

lisinopril.³⁷ Nonetheless, consensus guidelines recommend either an ACE inhibitor or ARB as first-line therapy to control BP and preserve kidney function in chronic kidney disease.

Some data indicate that the combination of an ACE inhibitor with an ARB may be more effective than either agent alone.⁷² However, routine use of this combination in all patients with chronic kidney disease is controversial. Because these patients typically require multiple antihypertensive agents, diuretics and a third antihypertensive drug class (e.g., β -blocker, CCB) are often needed.

CLINICAL CONTROVERSY

Thiazide-type diuretics traditionally have been viewed as less effective than loop diuretics in patients with severe chronic kidney disease. Some clinicians routinely replace thiazide-type diuretics with a loop diuretic in patients who have estimated creatinine clearances below 30 mL/min. However, limited data demonstrate that the antihypertensive effects of hydrochlorothiazide are equal to that of furosemide in patients with chronic renal failure and hypertension.⁷³

Patients may rarely experience acute kidney failure when given an ACE inhibitor or ARB. The potential to produce acute kidney failure is particularly problematic in patients with bilateral renal artery stenosis or a solitary functioning kidney with stenosis. Patients with renal artery stenosis are usually older, and the condition is more common in patients with diabetes and in those who smoke. Patients with renal artery stenosis do not necessarily have evidence of kidney disease unless sophisticated tests are performed. Evaluating kidney function shortly after starting the drug can minimize this risk.

Recurrent Stroke Prevention Ischemic stroke is considered target-organ damage caused by hypertension. Attaining goal BP values in patients who have experienced a stroke, or a transient ischemic attack, is considered a primary modality to reduce risk of a second stroke. In general, these patients have noncoronary atherosclerotic vascular disease, are considered a coronary artery disease risk equivalent, and have a BP goal of less than 130/80 mm Hg. However, BP lowering should only be attempted after patients have stabilized following an acute cerebrovascular event. One clinical trial, PROGRESS (Perindopril Protection Against Recurrent Stroke Study), showed that the incidence of recurrent stroke in patients with a history of ischemic stroke can be reduced when a thiazide-type diuretic is used in combination with an ACE inhibitor.³¹ Reduction in recurrent stroke was seen with this combination therapy, even in those who had BP values less than 140/90 mm Hg. Recurrent stroke was not reduced with ACE inhibitor monotherapy in the PROGRESS, it was only reduced when the thiazide-type diuretic was added.

Reductions in risk of recurrent stroke have also been seen with ARBs.⁷⁴ In another clinical trial, the MOSES (Morbidity and Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention), patients with a history of stroke or transient ischemic attack had a lower risk of a recurrent stroke when treated with ARB-based therapy compared to dihydropyridine CCB-based therapy. Therefore, both an ACE inhibitor with a thiazide-type diuretic,^{1,75} or ARB-based therapy are evidence-based antihypertensive regimens for patients with a history of cerebrovascular disease, specifically ischemic stroke or transient ischemic attack, to prevent recurrent stroke. These recommendations do not apply to patients with a history of hemorrhagic stroke.

Alternative Drug Treatments

It is necessary to use other agents such as α -blockers, central α_2 -agonists, a direct renin inhibitor, adrenergic inhibitors, and vasodila-

tors in some patients. Although these agents are potent, many of them have a much greater incidence of adverse effects. Moreover, they do not have compelling outcomes data showing reduced morbidity and mortality in hypertension. They are generally reserved for patients with resistant hypertension, and should only be used as add-on therapy with other primary antihypertensive agents.

Special Populations¹

Selection of drug therapy should follow the guidelines provided by the JNC7, which are summarized in Figures 15–2 and 15–3. These should be maintained as the guiding principles of drug therapy. However, there are some patient populations where the approach to drug therapy may be slightly different or necessitate tailored dosing strategies. In some cases this is because other agents have unique properties that benefit a coexisting condition, but may not be based on evidence from outcomes studies in hypertension.

Hypertension in Older People Hypertension often presents as isolated systolic hypertension in the elderly. Epidemiologic data indicate that CV morbidity and mortality are more closely related to SBP than to DBP in patients ages 50 years and older, so this population is at high risk for hypertension-related target-organ damage.¹ Although several placebo-controlled trials have specifically demonstrated risk reduction in this form of hypertension, many older people with hypertension are either not treated, or treated yet not controlled.²¹

The SHEP was a landmark, double-blind, placebo-controlled trial that evaluated chlorthalidone-based treatment (with atenolol or reserpine as add-on therapy) for isolated systolic hypertension.⁹ A 36% reduction in total stroke, a 27% reduction in coronary artery disease, and 55% reduction in heart failure were demonstrated versus placebo. The Syst-Eur (Systolic Hypertension in Europe) was another placebo-controlled trial that evaluated treatment with a long-acting dihydropyridine CCB.¹² Treatment resulted in a 42% reduction in stroke, 26% reduction in coronary artery disease, and 29% reduction in heart failure. These data clearly demonstrate reductions in CV morbidity and mortality in older patients with isolated systolic hypertension, especially with thiazide-type diuretics and long-acting dihydropyridine CCBs.

The very-elderly population (age ≥ 80 years) has been underrepresented in clinical trials, including the SHEP and Syst-Eur studies. This population often is not treated to goal either because of a fear of lowering BP too much or because of limited data demonstrating benefit. The best available data in the very elderly comes from meta-analyses.^{76,77} Although these data do not show reductions in mortality, they consistently show fewer strokes with antihypertensive drug therapy. However, care should be taken that BP not be excessively lowered in this population, as it this is associated with increased risk of mortality.⁷⁸ The HYVET (Hypertension in the Very Elderly Trial), a prospective controlled clinical trial was recently stopped early due to significant reductions in stroke and total mortality with antihypertensive treatment in the very elderly versus placebo.⁷⁹

Thiazide-type diuretics or β -blockers have been compared with either ACE inhibitors or CCBs in elderly patients with either systolic or diastolic hypertension or both.⁸⁰ In the Swedish Trial in Old Patients with Hypertension-2 (STOP-2) study, no significant differences were seen between conventional drugs and either ACE inhibitors or CCBs. However, there were significantly fewer MIs and cases of heart failure in the ACE inhibitor group compared with the CCB group. These data suggest that overall treatment may be more important than specific antihypertensive agents in this population.

Elderly patients are more sensitive to volume depletion and sympathetic inhibition than younger individuals. This may lead to orthostatic hypotension (see Patients at Risk for Orthostatic Hypotension below). In the elderly, this can increase the risk of falls

as a consequence of the associated dizziness and risk of fainting. Centrally acting agents and α -blockers should generally be avoided or used with caution in the elderly because they are frequently associated with dizziness and postural hypotension. Diuretics and ACE inhibitors provide significant benefits and can safely be used in the elderly, but smaller-than-usual initial doses might be needed.

The JNC7 and AHA goal BP recommendations are independent of age.^{1,2} Age-adjusted goals are inappropriate. Moreover, treatment of hypertension in older patients should follow the same principles that are outlined for general care of hypertension. However, initial drug doses may be lower, and dosage titrations should occur over a longer period of time to minimize the risk of hypotension. An interim goal of a SBP of below 160 mm Hg may be necessary for those with very high initial SBP, but the ultimate goal should still be less than 140 mm Hg, less than 130 mm Hg, or less than 120 mm Hg, depending on CV risk and comorbid conditions of the patient.

12 Patients at Risk for Orthostatic Hypotension *Orthostatic hypotension* is a significant drop in BP when standing and can be associated with dizziness and/or fainting. It is defined as a SBP decrease of greater than 20 mm Hg or DBP decrease of greater than 10 mm Hg when changing from supine to standing.¹ Older patients (especially those with isolated systolic hypotension), patients with diabetes, severe volume depletion, baroreflex dysfunction, autonomic insufficiency, and use of venodilators (α -blockers, mixed α/β -blockers, nitrates, and phosphodiesterase inhibitors) all increase risk of orthostatic hypotension. In patients with these risks, antihypertensive agents should be started in low doses, especially diuretics, ACE inhibitors, and ARBs.

Hypertension in Children and Adolescents⁸¹ Detecting hypertension in children requires special attention to BP measurement, and is defined as SBP and/or DBP that is greater than 95th percentile for sex, age, and height on at least three occasions.⁸¹ BP between the 90th and 95th percentile, or equal to or greater than 120/80 mm Hg in adolescents, is considered prehypertension. Hypertensive children often have a family history of high BP, and many are overweight, predisposing them to insulin resistance and associated CV disease. Unlike hypertension in adults, secondary hypertension is more common in children and adolescents. An appropriate workup for secondary causes is essential if elevated BP is identified. Kidney disease (e.g., pyelonephritis, glomerulonephritis) is the most common cause of secondary hypertension in children. Coarctation of the aorta can also produce secondary hypertension. Medical or surgical management of the underlying disorder usually normalizes BP.

Nonpharmacologic treatment, particularly weight loss in those who are overweight, is the cornerstone of therapy for essential hypertension in children.⁸¹ The goal is to reduce the BP to below the 95th percentile for sex, age, and height, or below the 90th percentile if concurrent conditions, such as chronic kidney disease, diabetes, or target-organ damage, are present. ACE inhibitors, ARBs, β -blockers, CCBs, and thiazide-type diuretics are all acceptable choices in children. ACE inhibitors, ARBs, and direct renin inhibitors are contraindicated in sexually active girls because of potential teratogenic effect, and in those who might have bilateral renal artery stenosis or unilateral stenosis in a solitary kidney. As with adults, consideration for initial agents should be based on the presence of compelling indications or concurrent conditions that may warrant their use (e.g., ACE inhibitor or ARB for those with diabetes or microalbuminuria).

Pregnancy^{1,82} Hypertension during pregnancy is a major cause of maternal and neonatal morbidity and mortality. Hypertension during pregnancy is categorized as preeclampsia, eclampsia, gestational, chronic, and superimposition of preeclampsia on chronic hypertension. Preeclampsia, defined as a elevated BP greater than or equal to 140/90 mm Hg that appears after 20 weeks gestation accompanied by new-onset proteinuria (≥ 300 mg/24 hours), can lead to life-threaten-

ing complications for both mother and fetus. Eclampsia, the onset of convulsions in preeclampsia, is a medical emergency. Gestational hypertension is defined as new-onset hypertension arising after midpregnancy in the absence of proteinuria, and chronic hypertension is elevated BP that is noted before the pregnancy began. It is controversial whether treating elevated BP in patients with chronic hypertension in pregnancy is beneficial. However, women with chronic hypertension prior to pregnancy are at increased risk of a number of complications, including superimposed preeclampsia, preterm delivery, fetal growth restriction or demise, placental abruption, heart failure, and acute kidney failure.⁸²

Definitive treatment of preeclampsia is delivery. Delivery is indicated if pending or frank eclampsia is present. Otherwise, management consists of restricting activity, bedrest, and close monitoring. Salt restriction, or any other measures that contract blood volume, should not be employed. Antihypertensive agents are used prior to induction of labor if DBP is greater than 105 to 110 mm Hg with a target DBP of 95 to 105 mm Hg. Intravenous hydralazine is most commonly used, and intravenous labetalol is also effective. Immediate-release oral nifedipine has been used, but it is not approved by the Food and Drug Administration (FDA) for hypertension and untoward fetal and maternal effects (hypotension with fetal distress) have been reported.

Many agents can be used to treat chronic hypertension in pregnancy (Table 15-7). Unfortunately, there is little consensus and few data regarding the most appropriate therapy in pregnancy. Methyl-dopa is still considered the drug of choice.¹ Data indicate that uteroplacental blood flow and fetal hemodynamics are stable with methyldopa. Moreover, it is viewed as very safe, based on long-term followup data (7.5 years) that has not demonstrated adverse effects on childhood development. β -Blockers, labetalol and CCBs are also reasonable alternatives. ACE inhibitors and ARBs are known teratogens and are absolutely contraindicated.⁸³ Aliskiren also should not be used in pregnancy.

African Americans^{1,84} Hypertension affects African American patients at a disproportionately higher rate, and hypertension-related target-organ damage is more prevalent than in other populations. Reasons for these differences are not fully understood, but may be related to differences in electrolyte homeostasis, GFR, sodium excretion and transport mechanisms, plasma renin activity, and BP response to plasma volume expansion.

African Americans have an increased need for combination therapy to attain and maintain BP goals.⁸⁴ The Hypertension in African American Working Group of the International Society on Hypertension in Blacks has published treatment guidelines that are similar to the JNC7.⁸⁴ Lifestyle modifications are recommended to

TABLE 15-7 Treatment of Chronic Hypertension in Pregnancy	
Drug/Class	Comments
Methyldopa	Preferred agent based on long-term followup data supporting safety
β -Blockers	Generally safe, but intrauterine growth retardation reported
Labetalol	Increasingly preferred over methyldopa because of fewer side effects
Clonidine	Limited data available
Calcium channel blockers	Limited data available; no increase in major teratogenicity with exposure
Diuretics	Not first-line agents but probably safe in low doses if used chronically prior to conception
Angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and direct renin inhibitors	Contraindicated; major teratogenicity reported with exposure (fetal toxicity and death)

augment drug therapy. They also support thiazide-type diuretics as first-line for most patients and selecting specific drug therapy to treat compelling indications, if present. These guidelines aggressively promote combination therapy. They recommend starting with two drugs in patients with SBP values ≥ 15 mm Hg from goal. This aggressive approach is reasonable considering that overall goal BP attainment rates are low in African Americans.

BP-lowering effects of antihypertensive classes varies in African Americans. Thiazide diuretics and CCBs seem to be particularly effective at lowering BP in African Americans. When either of these two classes (especially thiazides) is used in combination with a β -blocker, ACE inhibitor, or ARB, antihypertensive response is significantly increased. This may be a result of the low renin pattern of hypertension, which can result in less BP lowering with β -blockers, ACE inhibitors, or ARBs when used as monotherapy compared to the effect in white patients. Interestingly, African Americans have a higher risk of angioedema and cough from ACE inhibitors than do whites.⁸⁴

Despite potential differences in antihypertensive effects, drug therapy selection should be based on evidence. Thiazide-type diuretics are first-line agents based on the preponderance of evidence. A subgroup analysis of African American patients from the ALLHAT also supports the first-line role of thiazide-type diuretics in treating African American patients with hypertension.³⁹ These agents just so happen to also be very effective at controlling BP in this population. ACE inhibitors, ARBs, and CCBs may also be used as first-line options. Other drug therapies should be used if a compelling indication is present, even if the antihypertensive effect may not be as great as with another drug class (e.g., a β -blocker is first-line therapy for BP control in an African American patient who is post-MI).

Other Concomitant Conditions

Most patients with hypertension have some other coexisting condition(s) that may influence selection or use of drug therapy. The influence of concomitant conditions should only be complementary to, and never in replacement of, drug therapy choices indicated by compelling indications. Under some circumstances, these are helpful in deciding on a particular antihypertensive agent when more than one antihypertensive class is recommended. In some cases, an agent should be avoided because it may aggravate a concomitant disorder. In other cases, an antihypertensive can be used to treat hypertension, a compelling indication, and another concomitant condition.

Pulmonary Disease and Peripheral Arterial Disease⁸⁵ β -Blockers, especially nonselective agents, have been generally avoided in patients with hypertension and reactive airway disease (asthma or chronic obstructive pulmonary disease with a reversible obstructive component) because of a fear of inducing bronchospasm. This precaution is more of a myth than a fact. Data suggests that cardioselective β -blockers can safely be used in patients with asthma or chronic obstructive pulmonary disease.⁸⁶ Consequently, cardioselective β -blockers should be used to treat a compelling indication (i.e., post-MI, coronary disease, or heart failure) in patients with reactive airway disease.

Peripheral arterial disease, noncoronary atherosclerotic vascular disease, is a coronary artery disease risk equivalent. The 2007 AHA guidelines now recommend a BP goal of less than 130/80 mm Hg in this population. ACE inhibitors may be ideal in patients with symptomatic lower-extremity peripheral arterial disease who also have hypertension, as they decrease CV events in these patients.⁸⁵ CCBs may also be beneficial because of their vasodilatory effects on the peripheral arteries. β -Blockers have traditionally been considered problematic in patients with peripheral arterial disease because of possible decreased peripheral blood flow secondary to unopposed stimulation of α -receptors that results in vasoconstriction. However, β -blockers are not contraindicated in peripheral arterial disease and have not been shown to adversely affect walking capability.⁸⁵

Dyslipidemia Dyslipidemia is considered a major CV risk factor. Controlling dyslipidemia is important to the overall care of patients with hypertension. Thiazide-type diuretics and β -blockers without ISA may adversely affect serum cholesterol values, although these effects generally are transient and of no clinical consequence.⁸⁷ α -Blockers have favorable effects (decreased low-density lipoprotein cholesterol and increased high-density lipoprotein cholesterol). However, because data from the ALLHAT show that α -blocker therapy does not reduce CV risk as much as thiazide-type diuretic therapy, this benefit is not clinically applicable.³⁵

Metabolic Syndrome^{13,88,89} Metabolic syndrome is a cluster of multiple cardiometabolic risk factors. It was most recently defined as the presence of three of the following five criteria: abdominal obesity (waist circumference >40 inches in men, >35 inches in women), elevated triglycerides (≥ 150 mg/dL or receiving drug treatment for elevated triglycerides), low high-density lipoprotein cholesterol (<40 mg/dL in men, <50 mg/dL in women or receiving drug treatment for low high-density lipoprotein), elevated BP ($\geq 130/\geq 85$ mm Hg or receiving drug treatment for high BP), and elevated fasting blood glucose (≥ 100 mg/dL or receiving drug treatment for elevated glucose).¹³

Regardless of the debate regarding whether or not metabolic syndrome is a true “disease,” it is widely accepted that patients with metabolic syndrome are at significant increased risk of developing CV disease and/or type 2 diabetes. Using an ACE inhibitor or ARB to treat patients with hypertension and the metabolic syndrome, especially patients with elevated fasting glucose but not yet type 2 diabetes, may be beneficial. A recent meta-analysis demonstrated that ARBs and ACE inhibitors are less likely than β -blockers or thiazide-diuretics to be associated with progression to new-onset type 2 diabetes.⁸⁹ However, studies specifically evaluating the most effective antihypertensive regimen in patients with metabolic syndrome have not been done. In addition, an ALLHAT subgroup analysis of patients with impaired fasting glucose showed that CV events were reduced more with chlorthalidone compared to lisinopril.³⁸ Thus, thiazides-type diuretics can be used in patients with metabolic syndrome, similar to ACE inhibitors, ARBs, or CCBs. In patients with elevated fasting glucose, or any patient at risk for developing type 2 diabetes, close monitoring of serum potassium should occur when treated with thiazide-type diuretics. If hypokalemia develops, or even subclinical hypokalemia (serum potassium within the normal range, but at the low end of the normal range), in thiazide treated patients, the risk of developing type 2 diabetes significantly increases.⁹⁰ Therefore, treatment of thiazide-induced hypokalemia, or even subclinical hypokalemia, should be considered to maintain serum potassium in the mid to high end of the normal range (e.g., 4.0–5.0 mEq/L). This may reverse thiazide-induced glucose intolerance or possibly prevent onset of type 2 diabetes. This can be accomplished though the addition of an ACE inhibitor, ARB, or potassium sparing diuretic, or with potassium supplementation for cases of more severe hypokalemia.

Erectile Dysfunction⁹¹ Most antihypertensive agents are associated with erectile dysfunction in men. However, it is not clear if erectile dysfunction associated with antihypertensive treatment is solely a result of drug therapy or is a symptom of underlying CV disease. Traditionally, β -blockers have been labeled as agents that significantly cause sexual dysfunction, and many practitioners have avoided prescribing them as a result. However, data supporting this notion are limited. A systematic review of 15 studies involving 35,000 patients assessing β -blocker use for MI, heart failure, and hypertension found only a very slight increased risk erectile dysfunction.⁹² In addition, prospective long-term data from the TOMHS (Treatment of Mild Hypertension Study) show no difference in the incidence of erectile dysfunction between diuretics and

β -blockers versus ACE inhibitors and CCBs.⁹³ Centrally acting agents are associated with higher rates of sexual dysfunction and should be avoided in men with erectile dysfunction.

Hypertensive men frequently have atherosclerotic vascular disease, which frequently results in erectile dysfunction. Consequently, erectile dysfunction may be mostly associated with chronic arterial changes resulting from elevated BP and lack of control may increase the risk of erectile dysfunction. These changes are even more pronounced in hypertensive men with diabetes.

Erectile dysfunction in hypertension may be an important marker for CV disease. A study of men prospectively screened for erectile dysfunction after being referred for nuclear stress test imaging showed that erectile dysfunction was a stronger predictor of severe coronary heart disease than traditional risk factors (age, smoking, hypertension, diabetes, and dyslipidemia).⁹⁴

Individual Antihypertensive Agents^{1,7}

Diuretics^{9-11,30} Diuretics, preferably a thiazide, are first-line agents for hypertension.^{1,2} The best available evidence justifying this recommendation is from ALLHAT.³⁰ Moreover, when combination therapy is needed in hypertension to control BP, a diuretic is recommended to be one of the agents used.¹ There are four subclasses of diuretics that are used in the treatment of hypertension: thiazides, loops, potassium-sparing agents, and aldosterone antagonists (see Table 15-5). Potassium-sparing diuretics are weak antihypertensive agents but provide an additive effect when used in combination with a thiazide or loop diuretic. Moreover, they counteract the potassium- and magnesium-losing properties of the other diuretic agents and possible glucose intolerance. Aldosterone antagonists (spironolactone and eplerenone) may be technically considered potassium-sparing agents, but are more potent antihypertensives. However, they are viewed by the JNC7 as an independent class because of evidence supporting compelling indications.

The exact hypotensive mechanisms of action of diuretics are multifaceted. The drop in BP seen when diuretics are first started is caused by an initial diuresis. Diuresis causes reductions in plasma and stroke volume, which decreases cardiac output and BP. This initial drop in cardiac output causes a compensatory increase in peripheral vascular resistance. With chronic diuretic therapy, extracellular fluid and plasma volume return to near pretreatment values. However, peripheral vascular resistance decreases to values that are lower than the pretreatment baseline. This reduction in peripheral vascular resistance is responsible for chronic antihypertensive effects.

Thiazide-type diuretics have additional actions that may further explain their antihypertensive effects. Thiazides mobilize sodium and water from arteriolar walls. This effect would lessen the amount of physical encroachment on the lumen of the vessel created by excessive accumulation of intracellular fluid. As the diameter of the lumen relaxes and increases, there is less resistance to the flow of blood and peripheral vascular resistance further drops. High dietary sodium intake can blunt this effect and a low salt intake can enhance this effect. Thiazides are also postulated to cause direct relaxation of vascular smooth muscle.

Thiazides are the preferred type of diuretic for treating hypertension. In patients requiring diuresis to treat concurrent edema, such as in heart failure, a loop diuretic should be considered. Diuretics should ideally be dosed in the morning if given once daily, and in the morning and afternoon when dosed twice daily to minimize risk of nocturnal diuresis. However, with chronic use, thiazide-type diuretics, potassium sparing diuretics, and aldosterone antagonists rarely cause a pronounced diuresis.

The major pharmacokinetic differences between the various thiazide-type diuretics are serum half-life and duration of diuretic effect. The clinical relevance of these differences is unknown because the

serum half-life of most antihypertensive agents does not correlate with the hypotensive duration of action. Moreover, diuretics lower BP primarily through extrarenal mechanisms. Hydrochlorothiazide and chlorthalidone are the two most frequently used thiazide diuretics in landmark clinical trials that have demonstrated reduced morbidity and mortality. These agents are not equipotent on a milligram-per-milligram basis; chlorthalidone is 1.5 to 2.0 times more potent than hydrochlorothiazide.⁹⁵ This is attributed to a longer half-life (45 to 60 hours vs. 8 to 15 hours) and longer duration of effect (48 to 72 hours vs. 16 to 24 hours) with chlorthalidone. These differences in BP lowering do not appear to result in differences in CV outcomes. A small meta-analysis of five outcome-based clinical trials evaluating CV events suggests there is no difference in long-term CV outcomes with chlorthalidone compared with other thiazide-type diuretics, including hydrochlorothiazide.⁹⁶ It is well accepted that CV benefits in hypertension apply to all thiazide-type diuretics, and benefits are considered a class effect.²

Diuretics are very effective in lowering BP when used in combination with most other antihypertensives. This additive response is explained by two independent pharmacodynamic effects. First, when two drugs cause the same overall pharmacologic effect (BP lowering) through different mechanisms of action, their combination usually results in an additive or synergistic effect. This is especially relevant when a β -blocker, ACE inhibitor, or ARB is indicated in an African American, but does not elicit sufficient antihypertensive effect. Adding a diuretic in this situation can often significantly lower BP. Second, a compensatory increase in sodium and fluid retention may be seen with antihypertensive agents. This problem is counteracted with the concurrent use of a diuretic.

Side effects of thiazide-type diuretics include hypokalemia, hypomagnesemia, hypercalcemia, hyperuricemia, hyperglycemia, dyslipidemia, and sexual dysfunction. Many of these side effects were identified when high-doses of thiazides were used in the past (e.g., hydrochlorothiazide 100 mg/day). Current guidelines recommend limiting the dose of hydrochlorothiazide or chlorthalidone to 12.5 to 25 mg/day, which markedly reduces the risk for most metabolic side effects. Loop diuretics may cause the same side effects, although the effect on serum lipids and glucose is not as significant, and hypocalcemia may occur.

Hypokalemia and hypomagnesemia may cause muscle fatigue or cramps. However, serious cardiac arrhythmias can occur in patients with severe hypokalemia and hypomagnesemia. Patients at greatest risk for this are patients with left ventricular hypertrophy, coronary disease, post-MI, a history of arrhythmia, or those concurrently receiving digoxin. Low-dose therapy (i.e., 25 mg hydrochlorothiazide or 12.5 mg chlorthalidone daily) rarely causes significant electrolyte disturbances. Efforts should be made to keep potassium in the therapeutic range by careful monitoring.

Diuretic-induced hyperuricemia can precipitate gout. This side effect may be especially problematic in patients with a previous history of gout and with thiazide-type diuretics. However, acute gout is unlikely in patients with no previous history of gout. If gout does occur in a patient who requires diuretic therapy, allopurinol can be given to prevent gout and will not compromise the antihypertensive effects of the diuretic. High doses of thiazide-type and loop diuretics may increase fasting glucose and serum cholesterol values. Diligent monitoring and treatment of diuretic-induced hypokalemia, even if subclinical, will lessen the associated increase in fasting glucose, and perhaps onset of type 2 diabetes.⁹⁰

Potassium-sparing diuretics can cause hyperkalemia, especially in patients with chronic kidney disease or diabetes and in patients receiving concurrent treatment with an ACE inhibitor, nonsteroidal antiinflammatory drugs, or potassium supplements. Hyperkalemia is especially problematic for the newest aldosterone antagonist eplerenone. This agent is a very selective aldosterone antagonist, and

its propensity to cause hyperkalemia is greater than with the other potassium sparing agents, and even spironolactone. Because of this increased risk of hyperkalemia, eplerenone is contraindicated in patients with impaired kidney function or type 2 diabetes with proteinuria (see Table 15–5). Although spironolactone may cause gynecomastia in up to 10% of patients, this occurs rarely with eplerenone.

Diuretics can be used safely with most other agents. However, concurrent administration with lithium may result in increased lithium serum concentrations. This interaction can predispose patients to lithium toxicity.

ACE Inhibitors^{27,32,80} ACE inhibitors are a first-line agents for hypertension.^{1,2} The ALLHAT demonstrated less heart failure and stroke with chlorthalidone than with lisinopril.³⁰ However, other outcome studies have demonstrated similar, if not better outcomes with ACE inhibitors than with thiazide diuretics.^{27,32}

ACE facilitates production of angiotensin II which has a major role in arterial BP regulation as depicted in Fig. 15–1. ACE is distributed in many tissues and is present in several different cell types, but its principal location is in endothelial cells. Thus the major site for angiotensin II production is in the blood vessels, not the kidney. ACE inhibitors block the ACE (also termed *bradykinase*), thus inhibiting conversion of angiotensin I to angiotensin II. Angiotensin II is a potent vasoconstrictor that also stimulates aldosterone secretion, causing an increase in sodium and water reabsorption with accompanying potassium loss. By blocking the ACE, vasodilation and a decrease in aldosterone occur. ACE inhibitors also block degradation of bradykinin and stimulate the synthesis of other vasodilating substances (prostaglandin E₂ and prostacyclin). The observation that ACE inhibitors lower BP in patients with normal plasma renin activity suggests that bradykinin and perhaps tissue production of ACE are important in hypertension. Increased bradykinin enhances the BP-lowering effects of ACE inhibitors, but also is responsible for the side effect of dry cough. ACE inhibitors effectively prevent or regress left ventricular hypertrophy by reducing the direct stimulation by angiotensin II on myocardial cells.

There are many evidence-based uses for ACE inhibitors (see Fig. 15–3). ACE inhibitors reduce CV morbidity and mortality in patients with left ventricular dysfunction,⁴⁸ and decrease progression of chronic kidney disease.⁶⁵ They should be first-line as disease modifying therapy in all of these patients unless absolutely contraindicated. ACE inhibitors, or ARBs in certain patients, are first-line in patients with diabetes and hypertension because of demonstrated CV disease and kidney benefits. A regimen including an ACE inhibitor with a thiazide-type diuretic is considered first-line in recurrent stroke prevention base on proven benefits from the PROGRESS trial showing reduced risk of secondary stroke.³¹ In combination with β -blocker therapy, evidence shows that ACE inhibitors further reduce CV risk in coronary disease, and in patients post-MI.^{57,59,61,62} These benefits of ACE inhibitors occur in patients with atherosclerotic vascular even in the absence of left ventricular systolic dysfunction or heart failure, and have the potential to reduce the development of new-onset type 2 diabetes.⁶³

There are 10 ACE inhibitors on the U.S. market (see Table 15–5). All except captopril, which has a much shorter half-life than the others, can be dosed once daily; captopril is dosed two or three times daily. In some patients, especially when higher doses are used, twice daily dosing is needed to maintain 24-hour effects with enalapril, benazepril, moexipril, quinapril, and ramipril. The absorption of captopril, but not other ACE inhibitors, is reduced when given with food.

ACE inhibitors are well tolerated,⁹⁸ but are not absent of side effects. ACE inhibitors decrease aldosterone and can increase serum potassium concentrations. Although this increase is usually small, and beneficial in thiazide-treated patients, hyperkalemia is possible. Patients with

chronic kidney disease or those on concomitant nonsteroidal antiinflammatory drugs, potassium supplements, or potassium-sparing diuretics are at risk for hyperkalemia. Judicious monitoring of serum potassium and creatinine values within 4 weeks of starting or increasing the dose of an ACE inhibitor can often identify these abnormalities before they evolve into serious hyperkalemia.

A worrisome adverse effect of ACE inhibitor is acute kidney failure. Fortunately, this serious adverse effect is rare, occurring in less than 1% of patients. Preexisting kidney disease increases the risk of this side effect. Bilateral renal artery stenosis or unilateral stenosis of a solitary functioning kidney render patients dependent on the vasoconstrictive effect of angiotensin II on the efferent arteriole of the kidney, thus explaining why these patients are particularly susceptible to acute kidney failure from ACE inhibitors. Slowly titrating the dose of ACE inhibitor and judicious kidney function monitoring can minimize risk and allow for early detection of those with renal artery stenosis.

It is important to note that GFR decreases in patients treated with ACE inhibitors or ARBs.⁶⁵ This is attributed to the inhibition of angiotensin II vasoconstriction on the efferent arteriole. This decrease in GFR often increases serum creatinine, and small increases should be anticipated when monitoring patients on ACE inhibitors. Modest elevations of either up to a 35% (for baseline creatinine values less than or equal to 3 mg/dL) or absolute increases less than 1 mg/dL, do not warrant changes.⁶⁵ If larger increases occur, ACE inhibitor therapy should be stopped or the dose reduced.

Angioedema is a serious potential complication of ACE inhibitor therapy. It occurs in less than 1% of the population, and is more likely in African Americans and smokers. Symptoms include lip and tongue swelling and possibly difficulty breathing. Drug discontinuation is needed for ACE inhibitor-associated angioedema. However, angioedema associated with laryngeal edema and/or pulmonary symptoms occasionally occurs and requires treatment with epinephrine, corticosteroids, antihistamines and/or emergent intubations to support respiration. A history of angioedema, even if not from an ACE inhibitor, precludes use of another ACE inhibitor (it is a contraindication). Cross-reactivity between ACE inhibitors and ARBs is small, but has been reported.^{53,99} An ARB can be used in a patient with a history of ACE inhibitor-induced angioedema when there is a compelling indication for an ARB with careful monitoring for a repeat occurrence of angioedema.

A persistent dry cough develops in up to 20% of patients, and is pharmacologically explained by the inhibition of bradykinin breakdown. This cough does not cause clinical illness, but is annoying to patients. It should be clearly differentiated from a wet cough because of pulmonary edema, which may be a sign of uncontrolled heart failure versus an ACE inhibitor-induced cough.

ACE inhibitors, in addition to ARBs, are absolutely contraindicated in pregnancy.^{1,83} Female patients of child-bearing age should be counseled regarding effective forms of birth control as ACE inhibitors are associated major congenital malformations when exposed in the first trimester and fetopathy (group of conditions that includes renal failure, renal dysplasia, hypotension, oligohydramnios, pulmonary hypotension, hypocalvaria, and death) when exposed in the second and third trimester.⁸³ Similar to diuretics, ACE inhibitors can increase lithium serum concentrations in patients on lithium therapy. Concurrent use of an ACE with a potassium-sparing diuretic (including aldosterone antagonists), potassium supplements, or an ARB may result in excessive increases in potassium.

Starting doses of ACE inhibitors should be low, with even lower doses in patients at risk for orthostatic hypotension, or severe renal dysfunction (e.g., elderly, chronic kidney disease). Acute hypotension may occur at the onset of ACE inhibitor therapy. Patients who are sodium or volume depleted, in heart failure exacerbation, very elderly, or on concurrent vasodilators or diuretics are at high risk

for this effect. It is important to start with half the normal dose of an ACE inhibitor for all patients with these risk factors, and use slow dose titration.

Angiotensin Receptor Blockers ARBs are first-line agents for hypertension.^{1,2} Angiotensin II is generated by two enzymatic pathways: the RAAS, which involves ACE, and an alternative pathway that uses other enzymes such as chymases (also known as “tissue ACE”). ACE inhibitors inhibit only the effects of angiotensin II produced through the RAAS, whereas ARBs inhibit angiotensin II from all pathways. It is unclear how these differences affect tissue concentrations of ACE. ACE inhibitors only partially block the effects of angiotensin II, though the clinical significance of this is not known.

ARBs directly block the angiotensin II receptor subtype 1 receptor that mediates the known effects of angiotensin II in humans: vasoconstriction, aldosterone release, sympathetic activation, antidiuretic hormone release, and constriction of the efferent arterioles of the glomerulus. Because they do not block the angiotensin II receptor subtype 2 receptor, the beneficial effects of angiotensin II receptor subtype 2 stimulation (vasodilation, tissue repair, and inhibition of cell growth) remain intact when ARBs are used. Unlike ACE inhibitors, ARBs do not block the breakdown of bradykinin. Therefore, some of the beneficial effects of bradykinin, such as vasodilation (which can enhance treatment of left ventricular dysfunction), regression of myocyte hypertrophy and fibrosis, and increased levels of tissue plasminogen activator, are not present with ARB therapy.

ARBs have outcomes data showing long-term reductions in progression of target-organ damage in patients with hypertension and certain compelling indications. In patients with type 2 diabetes and nephropathy, progression of nephropathy has been shown to be significantly reduced with ARB therapy.⁶⁴ Some benefits appear to be independent of BP lowering, suggesting that the pharmacologic effects of ARBs on the efferent arteriole may result in progression of kidney disease. For patients with left ventricular dysfunction, the CHARM studies showed that ARB therapy reduces risk of CV events when added to a stable regimen of a diuretic, ACE inhibitor, and β -blocker, or as alternative therapy in ACE-intolerant patients.^{53,54} Importantly, the ELITE (Evaluation of Losartan in the Elderly) studies show that losartan is not superior to captopril in left ventricular dysfunction when compared head-to-head.^{51,52} One outcome study, the VALLIANT, also showed that an ARBs can reduce CV events in patients post-MI with left ventricular dysfunction, but would be used mostly as an alternative to an ACE inhibitor for this use.⁵⁸

ARBs have been compared head-to-head with CCBs. The MOSES demonstrated that eprosartan reduces the occurrence of recurrent stroke more than nitrendipine does in patients with a past medical history of cerebrovascular disease.⁷⁴ Using nitrendipine was a reasonable comparator because the Syst-Eur had already demonstrated that nitrendipine reduces the occurrence of CV events, particularly stroke, in older patients with isolated systolic hypertension.¹² These data support the common notion that ARBs may have cerebroprotective effects that may explain CV event reductions. Another outcome study, the VALUE (Valsartan Long-term Use Evaluation) trial, showed that valsartan-based therapy is equivalent to amlodipine-based therapy for the primary composite outcome of first CV event in patients with hypertension and additional CV risk factors.³³ However, occurrence of certain components of the primary end point (stroke and MI) and new-onset type 2 diabetes was lower in the valsartan group. Although patients treated with amlodipine had slightly lower mean BP values than valsartan treated patients, there was no difference in the primary end point.

Data from pooled analyses and direct comparisons have demonstrated that ARBs have a fairly flat dose–response curve, suggesting that increasing the dose above low or moderate doses is unlikely to result in a large degree of BP lowering.⁹⁸ The addition of low doses

of a thiazide-type diuretic to an ARB significantly increases antihypertensive efficacy. Similar to ACE inhibitors, most ARBs have long enough half-lives to allow for once-daily dosing. However, candesartan, eprosartan, losartan, and valsartan have the shortest half-lives and may require twice-daily dosing for sustained BP lowering.

ARBs have the lowest incidence of side effects compared to other antihypertensive agents.⁹⁸ Because they do not affect bradykinin, they do not have the potential to illicit a dry cough like ACE inhibitors. Although these drugs have been termed “ACE inhibitors without the cough,” pharmacologic differences highlight that they could have very different effects on vascular smooth muscle and myocardial tissue that can correlate to different effects on target-organ damage and CV risk reduction when compared with ACE inhibitors. It is possible that their effects may be superior to ACE inhibitors in patients with type 2 diabetic nephropathy, but may be inferior to ACE inhibitors in patients with more advanced heart disease (e.g., heart failure, post-MI). Unfortunately, there are no direct comparisons looking at long-term effects in patients with just hypertension. Regardless, their role in patients with type 2 diabetic nephropathy is well established and they also are very reasonable alternatives in patients requiring an ACE inhibitor but who experience intolerable side effects.

CLINICAL CONTROVERSY

Data demonstrates that risk of CV events is further reduced when an ARB is added to an ACE inhibitor in patients with left ventricular dysfunction. Other data support this combination in patients with severe forms of nephrotic syndrome. However, using the combination of an ACE with an ARB has not been well studied as a standard treatment regimen in hypertension and incurs a significantly higher risk of side effects (e.g., hyperkalemia).¹⁰⁰

Like ACE inhibitors, ARBs may cause renal insufficiency, hyperkalemia, and orthostatic hypotension. The same precautions that apply to ACE inhibitors for patients with suspected bilateral renal artery stenosis, those on drugs that can raise potassium, and those on drugs that increase risk of hypotension apply to ARBs. ARBs can be used with caution in patients with a history of angioedema, but unlike ACE inhibitors are not contraindicated. Angioedema is also less likely to occur than with ACE inhibitors, but cross-reactivity has been reported.^{53,99} An ARB should only be used in a patient with a history of ACE inhibitor-induced angioedema when there is a compelling indication for an ARB with careful monitoring for a repeat occurrence of angioedema. ARBs should not be used in pregnancy.⁸³

Calcium Channel Blockers^{12,27} CCBs, both dihydropyridine CCBs and nondihydropyridine CCBs, are first-line agents for hypertension.^{1,2} They have compelling indications in coronary disease and in diabetes. However, with these compelling indications, they are essentially in addition to, or in replacement of, other antihypertensive drug classes.

Previous data indicated that dihydropyridine CCBs may not provide as much protection against CV events when compared with conventional therapy (diuretics and β -blockers) or ACE inhibitors in uncomplicated hypertension.²⁷ However, newer data shows that CCBs are likely to be as effective at lowering CV events as other agents. In ALLHAT there was no difference in the primary outcome between chlorthalidone and amlodipine, and only the secondary outcome of heart failure was higher with amlodipine.³⁰ A subgroup analysis of ALLHAT directly compared amlodipine to lisinopril and demonstrated that there was no difference in the primary outcome.¹⁰¹ As discussed previously, the VALUE study also showed no difference in the primary outcome of first CV event in high-risk patients between valsartan and amlodipine.³³

There may be differences in CV event reduction between dihydropyridine CCBs and nondihydropyridine CCBs. In patients with hypertension and diabetes, dihydropyridine CCBs appear to be less cardioprotective than ACE inhibitors.⁶⁴ Studies with the nondihydropyridine CCBs (diltiazem and verapamil) are limited, but the NORDIL (Nordic Diltiazem) study found diltiazem to be equivalent to diuretics and β -blockers in reducing CV events.²⁷ It is possible that these differences (beneficial with diltiazem and neutral with dihydropyridines) may relate to the sympathetic stimulation that can occur with dihydropyridines.

Dihydropyridine CCBs are very effective in older patients with isolated systolic hypertension. The Syst-Eur demonstrated that a long-acting dihydropyridine CCB reduced the risk of CV events markedly in isolated systolic hypertension.¹² A long-acting dihydropyridine CCB should be strongly considered in isolated systolic hypertension.

Contraction of cardiac and smooth muscle cells requires an increase in free intracellular calcium concentrations from the extracellular fluid. When cardiac or vascular smooth muscle is stimulated, voltage-sensitive channels in the cell membrane are opened, allowing calcium to enter the cells. The influx of extracellular calcium into the cell releases stored calcium from the sarcoplasmic reticulum. As intracellular free calcium concentration increases, it binds to a protein, calmodulin, which then activates myosin kinase enabling myosin to interact with actin to induce contraction. CCBs work by inhibiting influx of calcium across the cell membrane. There are two types of voltage-gated calcium channels: a high-voltage channel (L type) and a low-voltage channel (T type). Currently available CCBs only block the L-type channel, which leads to coronary and peripheral vasodilation.

The two subclasses of CCBs, dihydropyridines and nondihydropyridines (see Table 15–5) are pharmacologically very different from each other. Antihypertensive effectiveness is similar with both subclasses, but they differ in other pharmacodynamic effects. Nondihydropyridines decrease heart rate and slow atrioventricular nodal conduction. Similar to β -blockers, these drugs may also treat supraventricular tachyarrhythmias (e.g., atrial fibrillation). Verapamil produces negative inotropic and chronotropic effects that are responsible for its propensity to precipitate or cause systolic heart failure in high-risk patients. Diltiazem also has these effects but to a lesser extent than verapamil. All CCBs (except amlodipine and felodipine) have negative inotropic effects. Dihydropyridines may cause a baroreceptor-mediated reflex tachycardia because of their potent peripheral vasodilating effects. This effect appears to be more pronounced with the first generation dihydropyridines (e.g., nifedipine) and is significantly diminished with the newer agents (e.g., amlodipine) and when given in sustained-release dosage forms. Dihydropyridines do not alter conduction through the atrioventricular node and thus are not effective agents in supraventricular tachyarrhythmias.

Among dihydropyridines, short-acting nifedipine may rarely cause an increase in the frequency, intensity, and duration of angina in association with acute hypotension. This effect is most likely due to a reflex sympathetic stimulation, and is likely obviated by using sustained-release formulations of nifedipine. For this reason, all other dihydropyridines have an intrinsically long-half-life or are provided in sustained release formulations. Immediate-release nifedipine has been associated with an increased incidence of adverse CV effects, is not approved for treatment of hypertension, and should not be used to treat hypertension. Other side effects with dihydropyridines include dizziness, flushing, headache, gingival hyperplasia, and peripheral edema. Side effects caused by vasodilation, such as dizziness, flushing, headache, and peripheral edema, occur more frequently with all dihydropyridines than with the nondihydropyridines because they are less-potent vasodilators.

Diltiazem and verapamil can cause cardiac conduction abnormalities such as bradycardia or atrioventricular block. These prob-

lems occur mostly with high-doses or when used in patients with preexisting abnormalities in the cardiac conduction system. Heart failure has been reported in otherwise healthy patients as a consequence of negative inotropic effects. Both drugs can cause anorexia, nausea, peripheral edema, and hypotension. Verapamil causes constipation in approximately 7% of patients. This side effect also occurs with diltiazem, but to a lesser extent.

Verapamil and to a lesser extent diltiazem, can cause drug interactions because of their ability to inhibit the cytochrome P450 3A4 isoenzyme system. This inhibition can increase serum concentrations of other drugs that are metabolized by this isoenzyme system (e.g., cyclosporine, digoxin, lovastatin, simvastatin, tacrolimus, theophylline). Verapamil and diltiazem should be given very cautiously with a β -blocker because there is an increased risk of heart block with these combinations. When a CCB is needed in combination with a β -blocker for BP lowering, a dihydropyridine should be selected, because it will not increase risk of heart block. The hepatic metabolism of CCBs, especially felodipine, nicardipine, nifedipine, and nisoldipine, may be inhibited by ingesting large quantities of grapefruit juice (≥ 1 quart daily).

Many different formulations of verapamil and diltiazem are currently available (see Table 15–5). Although certain sustained-release verapamil and diltiazem products may contain the same active drug (e.g., Calan SR and Verelan), they are usually not AB rated by the FDA as interchangeable on a mg-per-mg basis because of different biopharmaceutical release mechanisms. However, the clinical significance of these differences is likely negligible.

Two sustained-release verapamil products (Covera HS and Verelan PM) and one diltiazem product (Cardizem LA) are chronotherapeutically designed to target the circadian BP rhythm. These agents are primarily dosed in the evening (with the exception of Cardizem LA which may be dosed in the morning or evening) so that drug is released during the early morning hours when BP first starts to increase. The rationale behind chronotherapy in hypertension is that blunting the early morning BP surge may result in greater reductions in CV events than conventional dosing of regular antihypertensive products in the morning. However, evidence from the CONVINCe (Controlled Onset Verapamil Investigation of Cardiovascular End Points) trial showed that chronotherapeutic verapamil was similar, but not better than, a thiazide-type diuretic/ β -blocker-based regimen with respect to CV events.²⁸

β -Blockers^{27,28,48,59,62} β -Blockers have been used in several large outcome trials in hypertension. However, in most of these trials, a thiazide-type diuretic was the primary agents with a β -blocker added on for additional BP lowering. Therefore, β -blockers are now only considered appropriate first-line agents to treat specific compelling indications (post-MI, coronary disease). They also are evidence-based as additional therapy for other compelling indications (heart failure and diabetes). Numerous trials have shown reduced CV risk when β -blockers are used following an MI, during an acute coronary syndrome, or in chronic stable angina. Although once considered contraindicated in heart failure, multiple studies have shown that carvedilol and metoprolol succinate reduce mortality in patients with left ventricular dysfunction who are treated with a diuretic and ACE inhibitor.

For patients with hypertension but without compelling indications, other primary agents (thiazide-type diuretics, ACE inhibitors, ARBs, and CCBs) should be used as the initial first-line agent before β -blockers. While this may be surprising to experienced clinicians, this recommendation is consistent with the 2007 AHA guidelines, the 2007 European Society of Hypertension guidelines, and the 2006 United Kingdom's National Institute for Health and the Clinical Excellence guidelines.^{2,92,93} It is based on meta-analyses data that suggest β -blocker-based therapy may not reduce CV events as well

as these other agents when used as the initial drug to treat patients with hypertension and without a compelling indication for a β -blocker.

Several mechanisms of action have been proposed for β -blockers, but none of them alone is consistently associated with a reduction in arterial BP. β -Blockers have negative chronotropic and inotropic cardiac effects that reduce cardiac output and explains some of the antihypertensive effect. However, cardiac output falls equally in patients treated with β -blockers regardless of BP lowering.

β -Adrenoceptors are located on the surface membranes of juxtaglomerular cells, and β -blockers inhibit these receptors and thus the release of renin. However, there is a weak association between plasma renin and antihypertensive efficacy of β -blocker therapy. Some patients with low plasma renin concentrations do respond to β -blockers. Therefore, additional mechanisms must also account for the antihypertensive effect of β -blockers. However, the ability of β -blockers to reduce plasma renin and thus angiotensin II concentrations may play a major role in their ability to reduce CV risk.

There are important pharmacodynamic and pharmacokinetic differences among β -blockers, but all agents provide a similar degree of BP lowering. There are two pharmacodynamic properties of the β -blockers that differentiate this class: cardioselectivity and ISA. β -Blockers that possess a greater affinity for β_1 -receptors than β_2 -receptors are *cardioselective*.

The β_1 - and β_2 -adrenoceptors are distributed throughout the body, but they concentrate differently in certain organs and tissues. There is a preponderance of β_1 -receptors in the heart and kidney, and a preponderance of β_2 -receptors in the lungs, liver, pancreas, and arteriolar smooth muscle. β_1 -Receptor stimulation increases heart rate, contractility, and renin release. β_2 -Receptor stimulation results in bronchodilation and vasodilation. Cardioselective β -blockers are not likely to provoke bronchospasm and vasoconstriction. Insulin secretion and glycogenolysis are mediated by β_2 -receptors. Blocking β_2 -receptors may reduce these processes and cause hyperglycemia or blunt recovery from hypoglycemia.

Cardioselective β -blockers (e.g., atenolol, metoprolol) have clinically significant advantages over nonselective β -blockers (e.g., propranolol, nadolol), and are generally preferred to treat hypertension. Cardioselective agents are safer than nonselective agents in patients with asthma or diabetes. However, cardioselectivity is a dose-dependent phenomenon; at higher doses, cardioselective agents lose their relative selectivity for β_1 -receptors and block β_2 -receptors as effectively as they block β_1 -receptors. The dose at which cardioselectivity is lost varies from patient to patient.

Some β -blockers (e.g., acebutolol, pindolol) have ISA and act as partial β -receptor agonists. When they bind to the β -receptor, they stimulate it, but far less than a pure β -agonist. If sympathetic tone is low, as it is during resting states, β -receptors are partially stimulated by ISA β -blockers. Therefore, resting heart rate, cardiac output, and peripheral blood flow are not reduced when these type of β -blockers are used. Theoretically, ISA agents would appear to have advantages over β -blockers in certain patients with heart failure, or sinus bradycardia. Unfortunately, they do not appear to reduce CV events as well as other β -blockers. In fact, they may increase risk post-MI or in those with coronary disease. Thus, agents with ISA are rarely needed and have little to no clinical utility.

Pharmacokinetic differences among β -blockers relate to first-pass metabolism, route of elimination, degree of lipophilicity, and serum half-lives. Propranolol and metoprolol undergo extensive first-pass metabolism, so the dose needed to attain β -blockade with either drug varies from patient to patient. Atenolol and nadolol have are renally excreted. The dose of these agents may need to be reduced in patients with moderate to severe chronic kidney disease.

β -Blockers, especially those with highly lipophilic properties, penetrate the central nervous system penetration and may cause

other effects. Propranolol is the most lipophilic drug and atenolol is the least lipophilic. It is unclear whether higher lipophilicity is associated with more central nervous system side effects (dizziness, drowsiness). However, the lipophilic properties can provide better effects for non-CV conditions such as migraine headache prevention, essential tremor, and thyrotoxicosis. BP lowering is equal among β -blockers regardless of lipophilicity.

CLINICAL CONTROVERSY

Many of the clinical trials included in the meta-analyses data that suggest β -blocker-based therapy may not reduce CV events as well as these other agents used atenolol dosed once daily.^{44–47} Atenolol has a half life of 6 to 7 hours and is nearly always dosed once daily, whereas immediate-release forms of carvedilol and metoprolol tartrate have 6- to 10- and 3- to 7-hour half-lives respectively, and are always dosed at least twice daily. Consequently, it is possible that these findings might only apply to atenolol and also that these findings may be a result of using atenolol once daily instead of twice daily.

Most side effects of β -blockers are an extension of their ability to antagonize β -adrenoceptors. β -Blockade in the myocardium can be associated with bradycardia, atrioventricular conduction abnormalities (e.g., second- or third-degree heart block), and the development of acute heart failure. The decreases in heart rate may actually benefit certain patients with atrial arrhythmias (atrial fibrillation, atrial flutter) and hypertension by both providing rate control and BP lowering. β -Blockers usually only produce heart failure if they are used in high initial doses in patients with preexisting left ventricular dysfunction or if started in these patients during an acute heart failure exacerbation. Blocking β_2 -receptors in arteriolar smooth muscle may cause cold extremities and may aggravate peripheral arterial disease or Raynaud's phenomenon as a result of decreased peripheral blood flow. In addition, there is an increase of sympathetic tone during periods of hypoglycemia that may result in an increase in BP because of unopposed α -receptor-mediated vasoconstriction.

Abrupt cessation of β -blocker therapy can produce unstable angina, MI, or even death in patients with coronary disease. Abrupt cessation may also lead to rebound hypertension (a sudden increase in BP to above pretreatment values). To avoid this, β -blockers should always be tapered gradually over 1 to 2 weeks before eventually discontinuing the drug. This acute withdrawal syndrome is believed to be secondary to progression of underlying coronary disease and hypersensitivity of β -adrenergic receptors as a result of upregulation. In patients without coronary disease, abrupt discontinuation may present as tachycardia, sweating, and generalized malaise, in addition to increased BP.

Like diuretics, β -blockers have been shown to increase serum cholesterol and glucose values, but these effects are transient and of questionable clinical significance. In patients with diabetes or dyslipidemia, the reduction in CV events was as great with β -blockers as with an ACE inhibitor in the United Kingdom Prospective Diabetes Study,⁶⁶ and far superior to placebo in the SHEP trial.⁹ In the GEMENI (Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertension) trial, patients with diabetes and hypertension who were randomized to metoprolol had an increase in hemoglobin A_{1c} values, whereas patients randomized to carvedilol did not.¹⁰² This suggests that mixed α - and β -blocking effects of carvedilol may be preferential to metoprolol in patients with uncontrolled diabetes. However, differences in hemoglobin A_{1c} values were too small to make this application clinically relevant in all patients with diabetes that need treatment with a β -blocker.

β -Blockers can slightly increase serum triglycerides and decrease high-density lipoprotein cholesterol. β -Blockers with α -blocking properties produce no changes in these lipid values. Because these are of questionable clinical significance, cardioselective agents, which have less overall side effects, remain the β -blockers of choice for most patients.

13 Alternative Agents The primary role of an alternative antihypertensive agent is to provide additional BP lowering in patients who are already treated with an agent from a drug class proven to reduce CV events (diuretics, ACE inhibitors, ARBs, CCBs, or even β -blockers).

α_1 -Blockers.³⁵ Prazosin, terazosin, and doxazosin are selective α_1 -receptor blockers. They work in the peripheral vasculature and inhibit the uptake of catecholamines in smooth muscle cells resulting in vasodilation and BP lowering.

Doxazosin was one of the original treatment arms of the ALLHAT. However, it was stopped prematurely when statistically more secondary end points of stroke, heart failure, and CV events were seen with doxazosin compared with chlorthalidone.³⁵ There were no differences in the primary end point of fatal coronary heart disease and nonfatal MI. These data suggest that thiazide-type diuretics are superior to α_1 -blockers in preventing CV events in patients with hypertension. Therefore, α_1 -blockers are alternative agents that should be used in combination with primary antihypertensive agents.

α_1 -Blockers can provide symptomatic benefits in men with benign prostatic hypertrophy. These agents block postsynaptic α_1 -adrenergic receptors located on the prostate capsule, causing relaxation and decreased resistance to urinary outflow. However, when used to lower BP, they should only be in addition to primary antihypertensive agents.

A potentially severe side effect of α_1 -blockers is a “first-dose” phenomenon that is characterized by transient dizziness or faintness, palpitations, and even syncope within 1 to 3 hours of the first dose. This adverse reaction can also happen after dose increases. These episodes are accompanied by orthostatic hypotension and can be obviated by taking the first dose and subsequent first increased doses at bedtime. Because orthostatic hypotension and dizziness may persist with chronic administration, these agents should be used cautiously in elderly patients. Even though antihypertensive effects are achieved through a peripheral α_1 -receptor antagonism, these agents cross the blood–brain barrier and may cause central nervous system side effects. α_1 -Blockers also may cause priapism. Sodium and water retention can occur with chronic administration. Consequently, these agents are most effective when given in combination with a diuretic to maintain antihypertensive efficacy and minimize potential edema.

Aliskiren.^{103,104} Aliskiren is the first oral agent within a new antihypertensive drug class that directly inhibits renin.¹⁰³ This drug blocks the RAAS at its point of activation, which results in reduced plasma renin activity and BP lowering. It has a 24-hour half-life, is primarily eliminated through biliary excretion unchanged, and provides 24-hour antihypertensive effects with once-daily dosing.

The exact role of this drug class in the management of hypertension is unclear. Aliskiren is approved as monotherapy or in combination therapy. However, because of the lack of long-term studies evaluating CV event reduction and significant drug cost compared to generic agents with outcomes data, it should clearly be used as an alternative therapy for the treatment of hypertension. Studies evaluating the ability of aliskiren to lower CV events and decrease progression of diabetic nephropathy are planned to start in 2007, but will not be completed for many years. Aliskiren provides BP reductions comparable to an ACE inhibitor, ARB, or CCB. It also has additive antihypertensive effects when used in combination with thiazides, ACE inhibitors, ARBs, or a

CCB, although its effectiveness in combination with maximum doses of ACE inhibitors has not been adequately studied.

Many of the cautions and adverse effects seen with ACE inhibitors and ARBs apply to direct renin inhibitors (i.e., aliskiren). Aliskiren should never be used in pregnancy because of the known teratogenic effects of using other drugs that block the RAAS system. Angioedema has also been reported in patients treated with aliskiren. Increases in serum creatinine and serum potassium values have been observed. The mechanisms of these adverse effects are likely similar to those with ACE inhibitors and ARBs. It is reasonable to use similar monitoring strategies by measuring serum creatinine and serum potassium in patients treated with aliskiren. This is particularly important in patients treated with the combination of aliskiren and an ACE inhibitor or an ARB who are at higher risk for hyperkalemia (e.g., chronic kidney disease).

Central α_2 -Agonists. Clonidine, guanabenz, guanfacine, and methyldopa lower BP primarily by stimulating α_2 -adrenergic receptors in the brain. This stimulation reduces sympathetic outflow from the vasomotor center in the brain and increases vagal tone. It is also believed that peripheral stimulation of presynaptic α_2 -receptors may further reduce sympathetic tone. Reduced sympathetic activity together with enhanced parasympathetic activity can decrease heart rate, cardiac output, total peripheral resistance, plasma renin activity, and baroreceptor reflexes. Clonidine is often used in resistant hypertension, and methyldopa is a first-line agent for pregnancy-induced hypertension.

Chronic use of centrally acting α_2 -agonists results in sodium and water retention. As with other centrally acting antihypertensives, depression can occur, especially with high doses. The incidence of orthostatic hypotension and dizziness is high, so they should be used very cautiously in the elderly. Lastly, clonidine has a relatively high incidence of anticholinergic side effects (sedation, dry mouth, constipation, urinary retention, and blurred vision). Thus it should generally be avoided for chronic antihypertensive therapy in the elderly.

Abrupt cessation of central α_2 -agonists may lead to rebound hypertension. This effect is thought to be secondary to a compensatory increase in norepinephrine release after abrupt discontinuation. In addition, other effects such as nervousness, agitation, headache, and tremor can also occur, which may be exacerbated by concomitant β -blocker use, particularly with clonidine. Thus, if clonidine is to be continued it should be tapered. In patients who are receiving concomitant β -blocker therapy, the β -blocker should be gradually discontinued first several days before gradual discontinuation of clonidine.

Methyldopa can cause hepatitis or hemolytic anemia, although this is rare. Transient elevations in serum hepatic transaminases are occasionally seen with methyldopa therapy but are clinically irrelevant unless they are greater than three times the upper limit of normal. Methyldopa should be quickly discontinued if persistent increases in serum hepatic transaminases or alkaline phosphatase are detected because this may indicate the onset of a fulminate life-threatening hepatitis. A Coombs-positive hemolytic anemia occurs in less than 1% of patients receiving methyldopa, although 20% of patients exhibit a positive direct Coombs test without anemia. For these reasons, methyldopa has limited use in routine management of hypertension except in pregnancy.

Reserpine. Reserpine lowers BP by depleting norepinephrine from sympathetic nerve endings, and blocking transport of norepinephrine into its storage granules. Norepinephrine release into the synapse following nerve stimulation is reduced and results in reduced sympathetic tone, peripheral vascular resistance, and BP. Reserpine also depletes catecholamines in the brain and the myocardium.

Reserpine has a slow onset of action and long-half life that allows for once-daily dosing. However, it may take 2 to 6 weeks before the

maximal antihypertensive effect is seen. Because reserpine can cause significant sodium and water retention, it should only be given in combination with a diuretic (preferably a thiazide). Reserpine's strong inhibition of sympathetic activity results in increased parasympathetic activity. This effect explains why side effects such as nasal stuffiness, increased gastric acid secretion, diarrhea, and bradycardia can occur. Depression has been reported, which is a consequence of central nervous system depletion of catecholamines and serotonin. The initial reports of depression with reserpine were in the 1950s and are inconsistent with current definitions of depression. Regardless, reserpine-induced depression is dose-related. Moreover, very high doses (above 1 mg daily) were frequently used in the 1950s, resulting in more depression. When reserpine is used in doses between 0.05 and 0.25 mg daily (recommended doses), the rate of depression is equal to that seen with β -blockers, diuretics, or placebo.⁹

Reserpine was used as a third-line agent in many of the landmark clinical trials that have documented the benefit in treating hypertension, including the VA Cooperative trials and most importantly, the SHEP trial.⁹ An analysis of the SHEP data found that reserpine was very well tolerated.

Direct Arterial Vasodilators. Hydralazine and minoxidil directly relax arteriolar smooth muscle resulting in vasodilation and BP lowering. Both agents cause potent reductions in perfusion pressure that activates the baroreceptor reflexes. Activation of baroreceptors results in a compensatory increase in sympathetic outflow, which leads to an increase in heart rate, cardiac output, and renin release. Consequently, tachyphylaxis can develop resulting in a loss of hypotensive effect with continued use. This compensatory baroreceptor response can be counteracted by concurrent use of a β -blocker.

All patients receiving hydralazine or minoxidil long-term for hypertension should first receive both a diuretic and a β -blocker. Direct arterial vasodilators can precipitate angina in patients with underlying coronary disease unless the baroreceptor reflex mechanism is completely blocked with a β -blocker. Nondihydropyridine CCBs can be used as an alternative to β -blockers in these patients, but a β -blocker is preferred. The side effect of sodium and water retention is significant with these drugs, and is minimized by using a diuretic concomitantly.

One side effect unique to hydralazine is a dose-dependent drug-induced lupus-like syndrome. Hydralazine is eliminated by hepatic *N*-acetyltransferase. This enzyme displays genetic polymorphism, and "slow acetylators" are especially prone to develop drug-induced lupus with hydralazine. This syndrome is more common in women and is reversible upon discontinuation. Drug-induced lupus may be avoided by using less than 200 mg of hydralazine daily. Other side effects of hydralazine include dermatitis, drug fever, peripheral neuropathy, hepatitis, and vascular headaches. For these reasons, hydralazine has limited usefulness in the treatment of hypertension. However, it is still especially useful in patients with severe chronic kidney disease and in kidney failure.

Because minoxidil is a more potent vasodilator than hydralazine, the compensatory increases in heart rate, cardiac output, renin release, and sodium retention are even more dramatic. Sodium and water retention can be so severe with minoxidil that heart failure can be precipitated. It is even more important to coadminister a β -blocker and a diuretic with minoxidil. A loop diuretic is often more effective than a thiazide in patients treated with minoxidil. A troublesome side effect of minoxidil is hypertrichosis (hirsutism), presenting as increased hair growth on the face, arms, back, and chest. This usually ceases when the drug is discontinued. Minoxidil is reserved for very-difficult-to-control hypertension and in patients requiring hydralazine who experience drug-induced lupus.

Other Agents. Guanethidine and guanadrel are postganglionic sympathetic inhibitors. Because of significant complications, these

drugs have little to no role in the management of hypertension. They deplete norepinephrine from postganglionic sympathetic nerve terminals and inhibit the release of norepinephrine in response to sympathetic nerve stimulation, resulting in reduced cardiac output and peripheral vascular resistance. Orthostatic hypotension is common because reflex-mediated vasoconstriction is blocked. Long-term norepinephrine depletion leads to postsynaptic receptor supersensitivity. Consequently, concomitant use of sympathomimetics or tricyclic antidepressants may provoke hypertensive crisis. Erectile dysfunction, diarrhea, and weight gain are also common.

Agents in Development.¹⁰⁴ Darusentan, clevidipine, and nebivolol are new agents under study that provide significant reductions in BP and may be approved for hypertension in the near future. Darusentan is an endothelin (A) selective endothelin receptor antagonist. There currently are no antihypertensive agents available that target the endothelin receptor. If this agent is approved, it will likely be used in patients with resistant hypertension. Nebivolol is a "third-generation" cardioselective β -blocker. It produces vasodilation and improves endothelial function via the L-arginine-nitric oxide pathway. Clevidipine is an ultrashort-acting, vascular-selective, dihydropyridine calcium antagonist. It is being developed for intravenous use in patients with hypertensive crisis.

PHARMACOECONOMIC CONSIDERATIONS

The cost of effectively treating hypertension is substantial. However, these costs can be offset by savings that would be realized by reducing CV morbidity and mortality. Cost related to treating target-organ damage (e.g., MI, end-stage kidney failure) can drastically increase healthcare costs. The cost per life-year saved from treating hypertension is estimated to be \$40,000 for younger adults and even less for older adults.¹⁰⁵ Treatments that cost less than \$50,000 per quality-adjusted life-year saved generally are considered favorable by health economists.

In a cost-minimization study that included the cost of drug acquisition, supplemental drugs, laboratory tests, clinic visits, and complications, the total costs of treating hypertension with either a diuretic, ACE-inhibitor, or CCB was under \$1,500.¹⁰⁶ Another cost-minimization analysis found that 86 middle-age or 29 elderly patients with hypertension would need to be treated to prevent 1 MI, stroke, or death.¹⁰⁷

A comparative analysis of 133,624 patients with hypertension ages 65 and older from a state prescription drug-assistance program demonstrated that 40% of patients were prescribed pharmacotherapy that was not necessarily recommended by the JNC7 guidelines recommendations.¹⁰⁸ If these 40% had drug-therapy modifications made to follow evidence-based treatment, a reduction in costs of \$11.6 million would have been realized in the 2001 calendar year based on discounted prices. This was projected to increase to \$20.5 million using usual Medicaid pricing limits.

Thus it is crucial to identify ways to control the cost of care without increasing the morbidity and mortality associated with uncontrolled hypertension. Using evidence-based pharmacotherapy will save costs not only by using the most effective agents. Thiazide-type diuretics are first-line treatment options in most patients without compelling indications, and are very inexpensive. Just using thiazides, either as monotherapy or in combination, is appropriate under almost all circumstances and aspects of hypertension management. When needed, using other generic primary antihypertensive agents that can be administered once daily should be considered.

HYPERTENSIVE URGENCIES AND EMERGENCIES^{1,7}

Both hypertensive urgencies and emergencies are characterized by the presence of very elevated BP—greater than 180/120 mm Hg.

However, the need for urgent or emergent antihypertensive therapy should be determined based on the presence of acute or immediately progressing target-organ injury, but not elevated BP alone. Urgencies are not associated with acute or immediately progressing target-organ injury, whereas emergencies are. Examples of acute target-organ injury include encephalopathy, intracranial hemorrhage, acute left ventricular failure with pulmonary edema, dissecting aortic aneurysm, unstable angina, and eclampsia or severe hypertension during pregnancy.

14 Hypertensive Urgency

A common error with treating hypertensive urgency is initiating overly aggressive antihypertensive therapy. This treatment likely has been caused by the classification terminology “urgency.” Hypertensive urgencies are ideally managed by adjusting maintenance therapy by adding a new antihypertensive and/or increasing the dose of a present medication. This is the preferred approach to these patients as it provides a more gradual reduction in BP. Very rapid reductions in BP to goal values should be discouraged because of potential risks. Because autoregulation of blood flow in patients with hypertension occurs at a much higher range of pressure than in normotensive persons, the inherent risks of reducing BP too precipitously include cerebrovascular accidents, MI, and acute kidney failure. Hypertensive urgency requires BP reductions with oral antihypertensive agents to stage 1 values over a period of several hours to several days. All patients with hypertensive urgency should be reevaluated within 7 days (preferably after 1 to 3 days).

Acute administration of a short-acting oral antihypertensive (captopril, clonidine or labetalol) followed by careful observation for several hours to assure a gradual reduction in BP is an option for hypertensive urgency. However, there are no data supporting this approach as being absolutely needed. Oral captopril is one of the agents of choice and can be used in doses of 25 to 50 mg at 1- to 2-hour intervals. The onset of action of oral captopril is 15 to 30 minutes, and a marked fall in BP is unlikely to occur if no hypotensive response is observed within 30 to 60 minutes. For patients with hypertensive rebound following withdrawal of clonidine, 0.2 mg clonidine can be given initially, followed by 0.2 mg hourly until the

DBP falls below 110 mm Hg or a total of 0.7 mg clonidine has been administered. A single dose may be all that is necessary. Labetalol can be given in a dose of 200 to 400 mg, followed by additional doses every 2 to 3 hours.

Oral or sublingual immediate-release nifedipine for acute BP lowering is dangerous. This approach produces a rapid reduction in BP. Use of immediate-release and should never be used for hypertensive urgencies because of reports of severe adverse events such as nifedipine as MIs and strokes.¹⁰⁹

Hypertensive Emergency

Hypertensive emergencies are those rare situations that require immediate BP reduction to limit new or progressing target-organ damage (see Arterial Blood Pressure: Classification above). Hypertensive emergencies require parenteral therapy, at least initially, with one of the agents listed in Table 15–8. The goal in hypertensive emergencies is not to lower BP to less than 140/90 mm Hg; rather, a reduction in mean arterial pressure of up to 25% within minutes to hours is the initial target. If then stable, BP can be reduced to 160/100–110 mm Hg within the next 2 to 6 hours. Precipitous drops in BP may lead to end-organ ischemia or infarction. If patients tolerate this reduction, additional gradual reductions toward goal BP values can be attempted after 24 to 48 hours. The exception to this guideline is for patients with an acute ischemic stroke where maintaining an elevated BP is needed for a much longer period of time.

The clinical situation should dictate which intravenous medication is used to treat hypertensive emergencies. Regardless, therapy should be provided in a hospital or emergency room setting with intraarterial BP monitoring. Table 15–8 lists special indications for agents that can be used. Some of these agents are discussed in further detail below.

Nitroprusside is widely considered the agent of choice for most cases, but can be problematic in patients with chronic kidney disease. It is a direct-acting vasodilator that decreases peripheral vascular resistance but does not increase cardiac output unless left ventricular failure is present. Nitroprusside can be given to treat most hypertensive emergencies, but in aortic dissection, propranolol should be given first to prevent reflex sympathetic activation. Nitroprusside is

TABLE 15-8 Parenteral Antihypertensive Agents for Hypertensive Emergency

Drug	Dose	Onset (min)	Duration (min)	Adverse Effects	Special Indications
Sodium nitroprusside	0.25–10 mcg/kg/min intravenous infusion (requires special delivery system)	Immediate	1–2	Nausea, vomiting, muscle twitching, sweating, thiocyanate and cyanide intoxication	Most hypertensive emergencies; caution with high intracranial pressure, azotemia, or in chronic kidney disease
Nicardipine hydrochloride	5–15 mg/h intravenous	5–10	15–30; may exceed 240	Tachycardia, headache, flushing, local phlebitis	Most hypertensive emergencies except acute heart failure; caution with coronary ischemia
Fenoldopam mesylate	0.1–0.3 mcg/kg/min intravenous infusion	<5	30	Tachycardia, headache, nausea, flushing	Most hypertensive emergencies; caution with glaucoma
Nitroglycerin	5–100 mcg/min intravenous infusion	2–5	5–10	Headache, vomiting, methemoglobinemia, tolerance with prolonged use	Coronary ischemia
Hydralazine hydrochloride	12–20 mg intravenous 10–50 mg intramuscular	10–20 20–30	60–240 240–360	Tachycardia, flushing, headache, vomiting, aggravation of angina	Eclampsia
Labetalol hydrochloride	20–80 mg intravenous bolus every 10 min; 0.5–2.0 mg/min intravenous infusion	5–10	180–360	Vomiting, scalp tingling, bronchoconstriction, dizziness, nausea, heart block, orthostatic hypotension	Most hypertensive emergencies except acute heart failure
Esmolol hydrochloride	250–500 mcg/kg/min intravenous bolus, then 50–100 mcg/kg/min intravenous infusion; may repeat bolus after 5 minutes or increase infusion to 300 mcg/min	1–2	10–20	Hypotension, nausea, asthma, first-degree heart block, heart failure	Aortic dissection; perioperative

metabolized to cyanide and then to thiocyanate, which is eliminated by the kidneys. Therefore, serum thiocyanate levels should be monitored when infusions are continued longer than 72 hours. Nitropruside should be discontinued if the concentration exceeds 12 mg/dL. The risk of thiocyanate accumulation and toxicity is increased in patients with impaired kidney function.

Intravenous nitroglycerin dilates both arterioles and venous capacitance vessels, thereby reducing both cardiac afterload and preload which can decrease myocardial oxygen demand. It also dilates collateral coronary blood vessels and improves perfusion to ischemic myocardium. These properties make intravenous nitroglycerin ideal for the management of hypertensive emergency in the presence of myocardial ischemia. Intravenous nitroglycerin is associated with tolerance when used over 24 to 48 hours, and can cause severe headache.

Fenoldopam and nicardipine are newer and more expensive alternative agents. Fenoldopam is a dopamine-1 agonist. It can improve renal blood flow and may be especially useful in patients with kidney insufficiency. Nicardipine provides arterial vasodilation, and can treat cardiac ischemia similar to nitroglycerin, but may provide more predictable reductions in BP.

The hypotensive response of hydralazine is less predictable than with other parenteral agents. Consequently, its major role is in the treatment of eclampsia or hypertensive encephalopathy associated with renal insufficiency.

hypotension. Modifying other CV risk factors (e.g., smoking, dyslipidemia, and diabetes) is also important.

15 COMBINATION ANTIHYPERTENSIVE THERAPY

Starting therapy with a combination of two drugs is recommended in patients who are far from their BP goal, for patients where goal achievement may be difficult (e.g., those with BP goals of less than 130/80 mm Hg, African Americans), and in patients with multiple compelling indications for different antihypertensive agents. Moreover, combination therapy is often needed to control BP and most patients require two or more agents.^{1,21,42,65}

Combination regimens for hypertension should ideally include a diuretic, preferably a thiazide-type. This method will provide additional BP lowering as most patients respond well to a combination regimen that includes a diuretic. Clinicians should anticipate the need for three drugs to control BP in patients with aggressive BP goals of <130/80 mm Hg.⁶⁵ Using low-dose combinations also provides greater reductions in BP compared to high doses of single agents, with fewer drug-related side effects.⁹⁸

Diuretics, when combined with several agents (especially an ACE inhibitor, ARB or β -blocker), can result in additive antihypertensive effects. BP lowering from certain antihypertensive agents can activate the RAAS as a compensatory mechanism to counteract BP changes, and regulate fluid loss. Most alternative antihypertensive agents (i.e., reserpine, arterial vasodilators, and centrally acting agents) need to be given with a diuretic to avoid sodium and water retention.

Many fixed-dose combination products are commercially available (Table 15–9). Most of these products contain a thiazide-type diuretic and have multiple dose strengths available. Individual dose titration is more complicated with fixed-dose combination products, but this strategy can reduce the number of daily tablets/capsules and can simplify regimens to improve adherence. This alone may increase the likelihood of achieving or maintaining goal BP values.

EVALUATION OF THERAPEUTIC OUTCOMES

ACHIEVING GOALS

The most important strategy to prevent CV morbidity and mortality in hypertension is BP control to goal values. Routine goal BP values should be attained in elderly patients and in those with isolated systolic hypertension, but actual BP lowering can occur at a very gradual pace over a period of several months to avoid orthostatic

TABLE 15-9 Fixed-Dose Combination Products

Combination	Drugs (Brand Name)	Strengths (mg/mg)	Daily Frequency
ACE inhibitor with a thiazide diuretic	Benazepril/hydrochlorothiazide (Lotensin HCT)	5/6.25, 10/12.5, 20/12.5, 20/25	1
	Captopril/hydrochlorothiazide (Capozide)	25/15, 25/25, 50/15, 50/25	1 to 3
	Enalapril/hydrochlorothiazide (Vaseretic)	5/12.5, 10/25	1
	Lisinopril/hydrochlorothiazide (Prinzide, Zestoretic)	10/12.5, 20/12.5, 20/25	1
	Moexipril/hydrochlorothiazide (Uniretic)	7.5/12.5, 15/25	1 or 2
	Quinapril/hydrochlorothiazide (Accuretic)	10/12.5, 20/12.5, 20/25	1
	Quinapril/hydrochlorothiazide (Accuretic)	10/12.5, 20/12.5, 20/25	1
ARB with a thiazide diuretic	Candesartan/hydrochlorothiazide (Atacand HCT)	600/12.5, 600/25	1
	Eprosartan/hydrochlorothiazide (Teveten HCT)	16/12.5, 32/12.5	1
	Irbesartan/hydrochlorothiazide (Avalide)	75/12.5, 150/12.5, 300/12.5	1
	Losartan/hydrochlorothiazide (Hyzaar)	50/12.5, 100/25	1
	Olmesartan/hydrochlorothiazide (Benicar HCT)	20/12.5, 40/12.5, 40/25	1
	Telmisartan/hydrochlorothiazide (Micardis HCT)	40/12.5, 80/12.5	1
	Valsartan/hydrochlorothiazide (Diovan HCT)	80/12.5, 160/12.5	1
β -Blocker with a thiazide diuretic	Atenolol/chlorthalidone (Tenoretic)	50/25, 100/25	1
	Bisoprolol/hydrochlorothiazide (Ziac)	2.5/6.25, 5/6.25, 10/6.25	1
	Propranolol/hydrochlorothiazide (Inderide)	40/25, 80/25	2
	Propranolol LA/hydrochlorothiazide (Inderide LA)	80/50, 120/50, 160/50	1
	Metoprolol/hydrochlorothiazide (Lopressor HCT)	50/25, 100/25	1 or 2
	Nadolol/bendroflumethiazide (Corzide)	40/5, 80/5	1
	Timolol/hydrochlorothiazide (Timolide)	10/25	1 or 2
ACE inhibitor with calcium channel blocker	Amlodipine/benazepril (Lotrel)	2.5/10, 5/10, 10/20	1
	Enalapril/pelodipine (Lexxel)	5/5	1
	Trandolapril/verapamil (Tarka)	2/180, 1/240, 2/240, 4/240	1 or 2
ARB with calcium channel blocker	Valsartan/amlodipine (Exforge)	5/160, 10/160, 5/320, 10/320	1
	Olmesartan/amlodipine (AZOR)	5/20, 10/20, 5/40, 10/40	1

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

TABLE 15-10 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
• Agents listed in Table 15-1
Associated conditions
• Obesity, excess alcohol intake
Secondary hypertension

16 RESISTANT HYPERTENSION

Resistant hypertension is the failure to achieve goal BP in patients who are adhering to full doses of an appropriate three-drug regimen that includes a diuretic.¹ Patients with newly diagnosed hypertension or who are not receiving drug therapy should not be considered to have resistant hypertension.¹¹⁰ Difficult-to-control hypertension is persistently elevated BP despite treatment with two or three drugs that does not meet the criteria for resistant hypertension (e.g., maximum doses that includes a diuretic).

Table 15-10 lists several causes of resistant hypertension. Volume overload is a common cause, thus highlighting the importance of diuretic therapy in the management of hypertension. In addition, nonadherence to drug therapy and lifestyle modifications plays an important role. Patients should be closely evaluated to see if any of these causes can be reversed. If nothing is identified, the principle of drug therapy selection from the JNC7 and AHA guidelines should still apply. Compelling indications, if present, should guide selection assuming these patients are on a diuretic.

Medications that have additive or synergistic effects when given in combination should ideally be used. In patients with severe chronic kidney disease (e.g., estimated GFR <30 mL/min 1.73 m²), a loop diuretic might be considered over a thiazide.

CLINICAL MONITORING

Routine ongoing monitoring to assess disease progression, the desired effects of antihypertensive therapy (efficacy), and undesired adverse side effects (toxicity) is needed in all patients treated with antihypertensive drug therapy.

Disease Progression

Patients should be monitored for signs and symptoms of progressive target-organ disease (see Table 15-1). A careful history for chest pain (or pressure), palpitations, dizziness, dyspnea, orthopnea, headache, sudden change in vision, one-sided weakness, slurred speech, and loss of balance should be taken to assess for the presence of hypertensive complications. Other clinical monitoring parameters that may be used to assess target-organ disease include fundoscopic changes on eye examination, left ventricular hypertrophy on electrocardiogram, proteinuria, and changes in kidney function. These parameters should be monitored periodically because any sign of deterioration requires immediate assessment and followup.

Efficacy

Clinic-based BP monitoring remains the standard for managing hypertension. BP response should be evaluated 2 to 4 weeks after initiating or making changes in therapy. Once goal BP values are attained, assuming no signs or symptoms of acute target-organ disease are present, BP monitoring can be done every 3 to 6 months.

More frequent evaluations are required in patients with a history of poor control, nonadherence, progressive target-organ damage, or symptoms of adverse drug effects.

Self-measurements of BP or automatic ambulatory BP monitoring can be useful clinically to establish effective 24-hour control. This type of monitoring may become the standard of care in the future, but the JNC7 and AHA recommends that ambulatory BP monitoring only be used in select situations such as suspected white coat hypertension. If patients are measuring their BP at home, it is important that they measure during the early morning hours for most days, and then at different times of the day on alternative days of the week. Additionally, patients should be instructed to measure BP two to three times each time they measure BP, and to document all values accurately.

Toxicity

Patients should be monitored routinely for adverse drug effects (Table 15-11). Monitoring should typically occur 2 to 4 weeks after starting a new agent or dose increases, and then every 6 to 12 months in stable patients. Additional monitoring may be needed for other concomitant diseases if present (e.g., diabetes, dyslipidemia, gout). Moreover, patients treated with an aldosterone antagonist (eplerenone or spironolactone), should have potassium concentrations and kidney function assessed within 3 days and again at 1 week after initiation to detect potential hyperkalemia.⁴⁸ The occurrence of an adverse drug event may require dosage reduction or substitution with an alternative antihypertensive agent.

ADHERENCE

Lack of persistence with hypertension treatment is a major problem in the United States and is associated with significant increases in costs as a result of development of complications. Because hypertension is a relatively asymptomatic disease, poor adherence is frequent, particularly in patients newly treated. It has been estimated that only up to 50% of patients with newly diagnosed hypertension are continuing treatment at 1 year.¹¹¹ Therefore, it is imperative to assess patient adherence on a regular basis.

Identification of nonadherence should be followed up with appropriate patient education, counseling, and intervention. Once-daily regimens are preferred in most patients to improve adherence. Although some may believe that aggressive treatment may negatively impact quality of life and thus adherence, several studies have found that most patients actually feel better once their BP is controlled. Patients on antihypertensive therapy should be questioned periodically about changes in their general health perception, energy level, physical functioning, and overall satisfaction with treatment. Lifestyle modifications should always be recommended to provide additional BP lowering and other potential health benefits. Persistence with lifestyle modifications should be continually encouraged in patients engaging in such endeavors.

TABLE 15-11 Select Monitoring for Antihypertensive Pharmacotherapy

Class	Parameters
Diuretics	Blood pressure, blood urea nitrogen (BUN)/serum creatinine, serum electrolytes (potassium, magnesium, sodium), uric acid (for thiazides)
Aldosterone antagonists	Blood pressure, BUN/serum creatinine, serum potassium
Angiotensin-converting enzyme inhibitors	Blood pressure, BUN/serum creatinine, serum potassium
Angiotensin receptor blockers	Blood pressure, BUN/serum creatinine, serum potassium
Calcium channel blockers	Blood pressure; heart rate
β -Blockers	Blood pressure, heart rate

CONCLUSIONS

Hypertension is a very common medical condition in the United States. Treatment of patients with hypertension should include both lifestyle modifications and pharmacotherapy. Outcome-based studies have definitively demonstrated that treating hypertension reduces the risk of CV events and subsequently reduces morbidity and mortality. Moreover, evidence evaluating individual drug classes has resulted in an evidence-based approach to selecting pharmacotherapy in an individual patient, which is outlined in the JNC7 and 2007 AHA guidelines. Diuretics, ACE inhibitors, ARBs, and CCBs are all first-line agents. However, diuretics, specifically thiazide-type diuretics, are unsurpassed in their ability to reduce risk of CV events in hypertension based on an extensive body of supportive evidence. If patients with hypertension have a comorbid condition that is considered a compelling indication, a different set of drugs may be recommended for first-line therapy. Data suggests that using a β -blocker as the primary agent to treat patients with hypertension, without the presence of a compelling indication, may not be as beneficial on reducing risk of CV events compared to diuretic-, ACE inhibitor-, ARB-, or CCB-based therapy. Therefore, β -blockers are not first-line therapy options unless an appropriate compelling indication is present.

An often overlooked concept in managing hypertension is to treat patients to a goal BP value. In addition to selecting the most appropriate agent, attaining a goal BP is also of paramount importance to ensure maximum reduction in risk for CV events is provided. A BP goal of less than 140/90 mm Hg is recommended for general prevention of CV events or disease; however, this goal is less than 130/80 mm Hg for patients with diabetes, significant chronic kidney disease, coronary artery disease, noncoronary atherosclerotic vascular disease or a Framingham risk score of 10% or greater, and is less than 120/80 mm Hg for patients with left ventricular dysfunction (i.e., systolic heart failure). Most patients with hypertension require more than one pharmacologic agent to attain goal BP values; therefore, combination therapy is often needed.

ABBREVIATIONS

ACE: angiotensin-converting enzyme

ARB: angiotensin II receptor blocker

AHA: American Heart Association

BP: blood pressure

CCB: calcium channel blocker

CV: cardiovascular

DBP: diastolic blood pressure

GFR: glomerular filtration rate

ISA: intrinsic sympathomimetic activity

JNC 7: Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

MI: myocardial infarction

RAAS: renin-angiotensin aldosterone system

SBP: systolic blood pressure

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